CLINICAL AND PHARMACOLOGICAL ASPECTS OF THE USE OF MORPHINE IN ADVANCED CANCER

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ABSTRACT

The pharmacology of morphine has been studied with particular reference to its use in chronic dosage in patients with advanced cancer and to explore the hypothesis that one of its metabolites, morphine-6-glucuronide, which is a highly potent analgesic in animal models, may play an important part in the analgesic action of morphine.

In this work two different assays for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) have been compared; radioimmunoassay (RIA) and high performance liquid chromatography (HPLC).

Basic pharmacokinetic parameters for morphine and morphine-6-glucuronide have been established in healthy volunteers. Changes in both morphine and M6G plasma concentrations were found to reflect changes in scores for drowsiness, relaxation and dry mouth after oral and intravenous administration.

In cancer patients receiving regular doses of oral morphine there was a mean absolute bioavailability of 34% which was not significantly different from that in healthy volunteers. No influence of impaired hepatic function due to metastases was seen on this or plasma clearance. A ratio of morphine:M6G of between 1:6 and 1:9 was found (compared to a ratio of 1:11 in healthy volunteers), and the ratio of morphine:M3G was 1:55.

The pharmacology of controlled release morphine tablets (MST-Continus) has been investigated. No difference in bioavailability relative to aqueous morphine solution was found and when changing from oral morphine solution to MST no advantage in using a loading dose of aqueous morphine when initiating treatment with controlled release tablets was found.

Morphine, M3G and M6G have been demonstrated in CSF, pleural fluid and ascitic fluid from cancer patients. Evidence for an enterohepatic circulation of morphine has been obtained by the demonstration of these substances in bile from cancer patients receiving regular morphine.

Patterns of use of morphine in patients with cancer pain have been studied by both a retrospective review of drug use in a continuing care unit and a postal questionnaire to a cross section of medical practitioners.

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Finally I am indebted to those patients who took part in these clinical studies during the final weeks of their life and without whom this work would not be possible.

ETHICS COMMITTEE APPROVAL

The work presented in this thesis contains a number of studies with morphine in both healthy volunteers and cancer patients. For each of these studies individual approval from the ethics committee of the Royal Marsden Hospital was obtained. In the case of the healthy volunteers, written informed consent was obtained together with permission from their general practitioner to take part in the study. All patients entered into these studies had the procedure carefully explained to them and consent was obtained before an independant witness and recorded in writing in accordance with the guidelines of the ethics committee.

PERSONAL CONTRIBUTION TO THE WORK IN THIS THESIS

The clinical pharmacology studies presented in this thesis were all performed personally with the exception of that described in Chapter 4.b, which was performed jointly with Dr P Poulain whilst he was a visiting research fellow at the Royal Marsden Hospital. In each of the other studies I have been responsible for the study design, obtaining ethical committee approval, recruitment and screening of volunteers and patients, administration of drugs and collection and preparation of clinical samples, measurement of pharmacodynamic and clinical parameters and storage and delivery of samples to the analytical laboratory.

Whilst the assay of the samples was performed by technical staff at the two analytical laboratories, I was responsible for the day to day supervision and quality control of the HPLC assay at St Bartholomew's Hospital and became fully acquainted with the analytical techniques.

The data interpretation and pharmacokinetic analyses were all performed personally.

The questionnaire study (Chapter 6.a) was conceived jointly with Sister Isabel White, Research Sister at the Royal Marsden Hospital, with whom I designed the questionnaire, defined the study population and arranged for the despatch and collection of the questionnaires.

The retrospective review (Chapter 6.b) is entirely my own work.

CHAPTER 1 INTRODUCTION

1.a Morphine

Pharmaceutical preparations

Clinical use

Pharmacokinetics

Pharmacodynamics

1.b Objectives

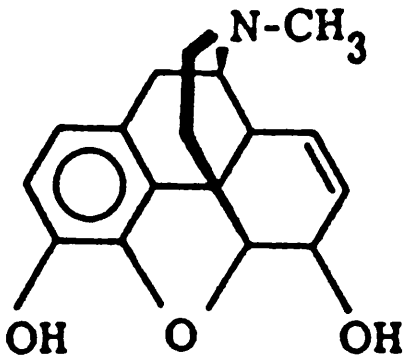
The relief of pain in patients with cancer is largely achieved by pharmacological methods. However, drug treatment alone is rarely sufficient by itself. Pain and suffering in the cancer patient are invariably compounded by anxiety, fear, depression, hopelessness and misunderstanding. Empathy, explanation and reassurance may have a profound pain-relieving effect, and anxiety and depression may require specific treatment.

Of the analgesics, the main group of drugs used in cancer pain are the opioids,and most patients with chronic cancer pain will eventually require a strong opioid analgesic to achieve pain control. Opium, the inspissated juice of the unripe seed capsules of the poppy Papaver Somniferum, has been used as an analgesic from the third century BC or perhaps earlier. Opium is known to contain at least 23 different alkaloids, of which morphine has the most marked analgesic activity. Isolation of morphine from opium was first achieved in 1805 by Serturner, a German pharmacist, and it is now regarded as the strong opioid agonist of choice for oral use (Saunders 1963, Twycross and Lack 1983, Hanks and Hoskin 1986).

In 1898 Dreser introduced a derivative of morphine produced by acetylation of the molecule in the 3 and 6 positions. Diacetylmorphine, or diamorphine, soon became established as an effective analgesic possibly more potent than morphine, but associated with a much greater tendency to cause physical dependence, tolerance and addiction. As a result the use of diamorphine has been restricted and it is available for medical use only in Britain and Belgium, and more recently in Canada.

1.(a)Morphine

Morphine is extracted from opium and is its principal alkaloid, constituting about 10% by weight. The chemical structure of morphine base is shown in Figure 1.a.1.



MORPHINE

1.a.1 Morphine sulphate in aqueous solution (chloroform water) is the usual preparation for oral use. The addition of ethylene diamine tetracetic acid and benzoic acid to the solution prolong the shelf-life from two weeks when made up in chloroform water alone to six months. This formulation has the advantage that elixir of any given strength can be prepared for an individual patient as necessary, maintaining a constant volume convenient for administration, usually 10mls. The limit of solubility is 400mg in 10mls. The principal disadvantage of the elixir is its characteristic bitter taste which is difficult to disguise.

Combination elixirs based on the traditional Brompton Cocktail are still available. Two such formulations containing morphine remain in recent past editions of the British National Formulary (BNF) composed of morphine 5 mg/5ml and cocaine 5 mg/5ml to which may be added chlorpromazine 62.5 mg/5ml. In the most recent edition of the BNF, whilst these formulations remain, their use is no longer recommended (British National Formulary No15, 1988).

1.a.2 Nepenthe was originally an alcoholic tincture of opium but is now formulated as an elixir containing anhydrous morphine 8.4 mg/ml of which only 500 microgrammes is as opium tincture (British National Formulary No11 1985). It is therefore essentially an alternative morphine elixir with no advantages over morphine sulphate. 1 ml of undiluted nepenthe (10mls of 10% solution) is equivalent to 12mg morphine sulphate by mouth. A parenteral preparation of nepenthe is also available.

1.a.3 Slow release morphine sulphate tablets (MST-Continus) are available in four strengths: 10mg (brown), 30mg (purple), 60mg (orange) and 100mg (grey) tablets. A higher strength tablet is planned.

1.a.4 For parenteral use, morphine sulphate injection is available in concentrations of 10, 15, 20 and 30 mg/ml. There is also a long-acting aqueous suspension containing 64 mg/ml for subcutaneous or intramuscular use (Duromorph), and a preservative-free injection for spinal use in strengths of 2.5 mg in 5 mls and 2mg in 10mls. Cyclimorph injection contains either 10 or 15 mg morphine tartrate with 50 mg cyclizine tartrate per ml.

1.a.5 Morphine may also be administered rectally and suppositories containing morphine sulphate or morphine hydrochloride are available commercially in strengths of 15 mg and 30 mg, but most hospital pharmacies are able to prepare a variety of other strengths according to need.

Two buccal morphine preparations are under development and early studies suggest that good absorption by this route is achieved (Bardgett et al 1983).

Clinical Use

1.a.6 General Aspects

Morphine is the strong opioid agonist of choice for treating cancer pain which is not controlled by weak opioids in full dosage. When confronted by patients taking other opioid analgesics which are ineffective then an appropriate equivalent dose of morphine must be chosen (Table 1.a.1). Dose escalation will often then be required, titrating the dose against pain relief, with no arbitrary upper limit whilst evidence of a dose-response effect is seen (Hanks and Twycross 1984).

Table 1.a.1

Alternative strong opioid drugs; analgesic equivalent doses and relative disadvantages compared to morphine

Drug	Usual dose (4-hrly unless stated)	Equivalent 4-hrly dose morphine	Disadvantage compared to morphine
Buprenorphine (Temgesic)	0.2mg 8-hrly	10mg	Partial agonist Ceiling effect for analgesia
Dextromoramide (Palfium)	5mg	10mg	Short duration in chronic use with increasing dose requirements
Dipipanone (Diconal with Cyclizine)	10mg	5mg	Fixed combination with cyclizine
Papaveretum (Omnopon)	10mg	7mg	Opium extract - active component is morphine
Pethidine	50mg	6mg	Duration 2-3hrs Toxic metabolite accumulates in chronic use
Methadone	5mg 8-hrly	5mg	Long half-life high protein binding may accumulate in chronic use

After Twycross and Lack (1983), Hanks and Haskin (1986, 1987)

However morphine is far from a panacea for cancer pain and is most effective when used in the context of careful pain assessment and monitoring with selection of specific tumouricidal treatment modalities where appropriate (e.g.radiotherapy for bone pain) and coanalgesic drugs (e.g. steroids, anti-inflammatory agents, psychotropic drugs etc.). Despite such strategies however there remains a small number of patients in whom pain control is unsatisfactory and escalation of opioid doses is not accompanied by any significant effect on their pain. Whilst in some cases this may be accounted for by the mechanism of pain, for example bone pain and nerve root pain are often poorly responsive to opioid drugs, in others true opioid - resistant pain may be present. The mechanism for this is unclear. It is possible that this reflects an individual variation in morphine pharmacokinetics, perhaps related to poor absorption, increased clearance or impaired production of active metabolites. Supportive evidence for a mechanism involving drug handling rather than drug resistance at opioid receptors in the central nervous system comes from case reports of patients in whom oral or parenteral morphine (or diamorphine) was ineffectual but morphine introduced directly into the CNS by the spinal route, either extra- or intra-dural has resulted in dramatic pain relief (Howard et al 1981).

The other principal use of morphine in advanced cancer is to relieve troublesome respiratory symptoms and in particular cough and dyspnoea due to parenchymal lung disease. This depressant effect of morphine on the respiratory centre has, in the past, been a source of concern in the light of the relatively large doses which may be required by some patients. It has been shown, however, that even in patients with longstanding chronic lung disease no evidence of

ventilatory failure could be demonstrated as measured by respiratory rate, peak flow and arterial blood gases, after stabilisation on doses of greater than 150mg morphine sulphate daily (Walsh 1984). This may reflect in part physical tolerance to the effects of morphine at the respiratory centre but also the principle that pain is the physiological antagonist of the respiratory depressant effects of opioid analgesics (Hanks and Twycross 1984).

Side effects of morphine may be predictable, such as constipation and drowsiness, or unpredictable such as nausea with or without vomiting, confusion, itching, sweating and dry mouth. Predictable side effects should be anticipated, constipation being avoided with regular laxatives and the possibility of drowsiness discussed with the patient and relatives in the expectation that this will resolve after a few days. Antiemetics are not recommended routinely since a significant number of patients will not require them (Hanks 1982), but if nausea does develop then haloperidol is probably the drug of choice.

1.a.7 Oral Administration

Oral morphine sulphate elixir remains the preparation of choice for oral use, given regularly at 4-hourly intervals. At initiation of treatment regular dose adjustments may be required until pain relief is achieved. If preferred, a double dose may be given on retiring to bed, in order to avoid the need to wake in the middle of the night for the dose due at this time. Slow release morphine sulphate tablets (MST-Continus) provide a means of maintaining plasma morphine

levels and those of its metabolites within the therapeutic range, using only twice daily administration. This may have considerable advantages to the ambulant patient whose morphine requirements are stable using regular 4-hourly elixir. Conversely, where morphine treatment is being initiated, or frequent dose adjustments are required, the long half-life of this preparation becomes a considerable disadvantage in monitoring the effects of changes in dose. This is reflected in the poor performance of MST as a post-operative analgesic (Hanks et al 1981, Banring et al 1986) compared to its efficacy in chronic use.

1.a.8 Rectal administration

Rectal administration provides a suitable alternative to oral administration where indicated. The regular use of a 4-hourly suppository is, however, not ideal and may be unacceptable to some patients. Where this route is to be considered, oxycodone suppositories may be preferable, requiring only 8-hourly administration. A 30mg oxycodone suppository appears equivalent to 20mg oral morphine sulphate (Twycross and Lack 1983).

1.a.9 Parenteral administration

Parenteral administration may be necessary where oral or rectal preparations cannot be used. Diamorphine, where available, has advantages over morphine for parenteral use as discussed below. However, morphine is effective parenterally and in most countries diamorphine is not available. The principal disadvantage of morphine lies in its relatively poor solubility so that concentrations greater than 30mg/ml cannot be used. For many patients this may therefore entail the administration of relatively large volumes of fluid given

subcutaneously or even intramuscularly. Blood levels following continuous subcutaneous infusion are similar to those after intravenous infusion (Waldmann et al 1984) and in most centres this is the preferred means of parenteral administration with increasingly sophisticated infusion pumps allowing considerable flexibility in their use (Jones and Hanks 1986).

The use of patient controlled analgesia using intravenous opioids is becoming increasingly popular (Leading article 1980, Graves et al 1983) and it appears effective in post-operative pain, providing immediate analgesia when required, without additional side-effects or serious complications, in particular respiratory depression. It is less well established in the treatment of chronic pain due to advanced cancer but effective analgesia can be provided by this means of administration, with the advantages of added flexibility when marked fluctuations in dose requirements occur.

1.a.10 Equivalent parenteral:oral dose ratios

When changing from the oral or rectal route to parenteral administration of morphine it is important to take into consideration the poor oral bioavailability of morphine and reduce the parenteral dose. There remains, however, controversy as to the appropriate dose change to be made. Conventionally, oral morphine has been considered to be one-sixth as potent as intramuscular morphine from the results of a double-blind, randomized, 4-way crossover study in patients with chronic cancer pain in which single doses of 30 and 60mg orally or 60 and 120mg orally were compared with 8 and 16mg intramuscularly. Predictably a smaller peak effect but prolonged duration of analgesia

was found with the oral route compared with the intramuscular, and a ratio of 1:6 for total analgesic effect and 1:12 for peak analgesic effect was found (Houde et al 1965). However, clinical experience in chronic dosage suggests that this ratio is not applicable and that a ratio of 1:3 or 1:2 is more appropriate (Twycross 1980, Twycross and Lack 1983), which is in keeping with pharmacokinetic data for the oral bioavailability of morphine. It has been suggested that the single dose data and clinical experience with chronic dosage are not incompatible and may merely reflect the wide confidence intervals which exist in such studies or the effect of 4-hourly analgesia compared to total or peak analgesia (Kaiko 1985). Clearly further well designed trials addressing this problem in the setting of chronic dosage are required, but at present a ratio of 1:2 appears to work satisfactorily in most patients.

1.a.11 Spinal Administration

Morphine and diamorphine achieve their analgesic effects by interaction with opioid receptors in the central nervous system and direct administration of the drug into the CNS bypassing the blood brain barrier would be expected to produce effective analgesia and perhaps reduce peripheral side effects. There has been considerable interest in recent years in the techniques of both epidural and intrathecal administration of opiates and there is good evidence that very small doses of 1.25 to 2.5mg intrathecal morphine or diamorphine will produce effective and long lasting analgesia. A study in post-operative patients given 2 mg diamorphine or 2.5 mg morphine intrathecally, and subsequently 1mg/kg morphine intravenously showed

CSF levels of morphine were 4000 times greater after intrathecal administration than after intravenous. A significant difference in the elimination half lives for morphine and diamorphine were seen, that for diamorphine being considerably shorter than for morphine (Paterson et al 1984). This may be explained by the much greater lipid solubility of diamorphine although degradation in CSF analogous to that in plasma is also to be expected. In contrast, following extradural injections a smaller CSF to plasma gradient is seen with significantly higher concentrations of morphine in the plasma. A dose of 5mg by extradural administration has been proposed as equivalent to 1mg intrathecally in producing analgesia for 12-18 hours (Moore et al 1984).

In opioid responsive pain, therefore, it would be anticipated that with much smaller doses, equivalent or better analgesia could be achieved by the spinal route, assuming a relationship between CSF drug levels and availability of the drug to receptors in brain and cord tissue. For both post-operative pain and chronic cancer pain there is increasing evidence to confirm the efficacy of spinal opiates (Watson et al 1984) but it is less clear whether this route of administration has significant advantages over oral or parenteral use. The introduction of an extradural or intrathecal cannula through which repeated injections may be given is a potentially hazardous procedure and should only be undertaken by skilled personnel in units experienced in their use. For routine use to be recommended for the treatment of chronic cancer pain significant advantages in terms of reduced side effects must therefore be demonstrated. Early experience found that rostral spread of high concentrations of opioid drug to the respiratory centres could result in marked respiratory depression occurring after intrathecal injection (Davies et al 1980, Leading article 1986). The

use of diamorphine with its shorter half life has been recommended as the drug of choice on this basis (Paterson et al 1984). Itching has also been reported as more common after intrathecal opiates (Justin and Reynolds 1982) though subsequently refuted (Leading Article 1986). The relative incidence of more common side effects such as sedation, nausea and vomiting and constipation remains unclear.

1.a.12 Buccal Administration

There is increasing interest in the use of morphine by the buccal route which has the advantage of avoiding the initial first pass metabolism responsible for the poor oral bioavailability of morphine. At present two preparations for buccal use are undergoing evaluation. They may provide a valuable alternative route of administration in the future for patients with advanced cancer unable to take oral medication.

1.a.13 Tolerance and Addiction

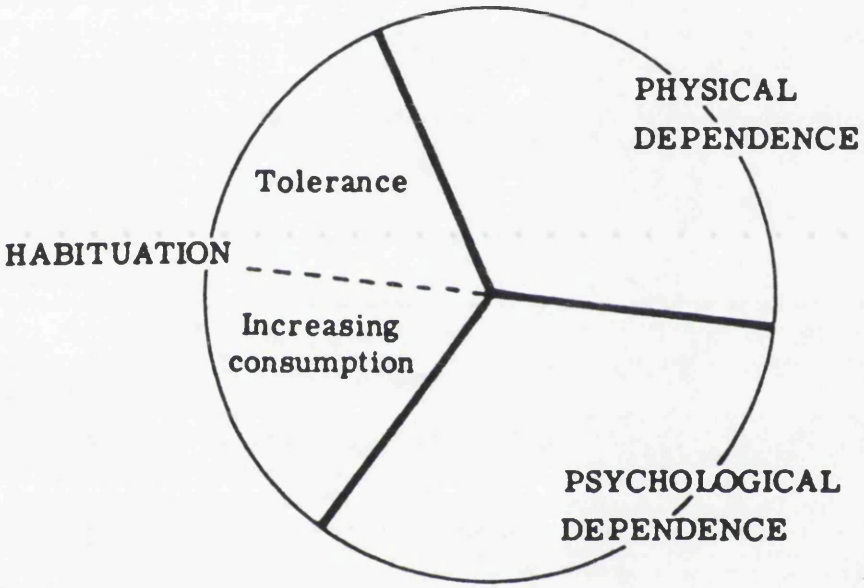
Addiction (or, more correctly, drug dependence), as defined by a behavioural pattern of drug use, characterised by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply and a high tendency to relapse after withdrawal (Jaffe 1985) is not seen in association with the use of regular strong opioid analgesics for cancer pain. The evidence for this comes not only from extensive clinical experience (Walsh 1985) but also from carefully documented cases where reducing doses of morphine, and even complete withdrawal has been demonstrated following definitive treatment such as radiotherapy or a local nerve block (Twycross and Lack 1983, Sawe et al 1983). In the wider context,

a large retrospective review of medical inpatients receiving narcotic analgesics found only 4 out of 11,882 cases of subsequent addiction, none of whom had a previous history of drug abuse, and only one of these was described as severe (Porter and Jick 1980).

In many patients receiving regular opioids, however, some degree of tolerance and physical dependence will be seen. Physical dependence may be distinguished from the wider issue of drug dependence or addiction by considering it as the component in which an altered physiological and/or psychological state is produced by the repeated administration of a drug, which necessitates continued administration of the drug to prevent the appearance of a withdrawal syndrome (Jaffe 1985). Tolerance refers to the need for increasing doses of a drug to produce the same effect and may be due to changes in pharmacokinetics such as enzyme induction, increased excretion, or adaptive changes in responding tissues, possibly mediated by changes in receptor numbers or sensitivity (Isbell 1972). The close interaction between tolerance, dependence and habituation resulting in the overall picture of drug dependence or addiction is shown in figure 1.a.2.

Figure 1.a.2

Components of Addiction



After Hanks and Hoskin (1986, 1987)

based on WHO Technical Report Series No. 287 (1964)
Evaluation of dependence-producing drugs.

Tolerance may be seen as an increase in dose requirements during the first few weeks of initiating morphine. However, as treatment proceeds and pain control is achieved a slower rate of rise in dose with long periods of dose stability is seen with even dose reduction and drug withdrawal becoming possible (Twycross and Lack 1983). Tolerance does not develop equally or at the same rate to all the effects of the opioids so that sedation, meiosis and constipation may be prominent despite a need for increased doses to maintain analgesia without clinically significant respiratory depression. These increases in dose are usually small and in the context of advanced cancer must be distinguished from the effects of progressive disease. There is little data on the influence of morphine pharmacokinetics on such changes in dose requirements. One study has measured hepatic enzyme activity with patients on increasing doses of morphine and found no evidence of enzyme autoinduction as the dose received by a patient increased (Sawe et al, 1983). However the influence of absorption, distribution, clearance and patterns of metabolites has not been investigated.

The precise reasons for addiction not occurring in most patients remains unclear. Risk factors such as particular personality types and sociological factors have been identified in occasional drug users who progress to addiction compared to those who do not (Segal 1978) and a complex interplay of many factors is seen. The unique position in our society of the patient dying from advanced cancer and the administration of the drug under controlled medical conditions may account for otherwise susceptible individuals not becoming addicts.

Florid withdrawal symptoms are not to be expected with gradual dose reduction, but inadvertent sudden discontinuation of

medication or introduction of a drug with opioid antagonist activity may provoke the typical syndrome of morphine withdrawal.

1.a.14 Morphine intolerance

In clinical practice there are occasions when intolerance to morphine may be encountered. This most commonly takes the form of intractable nausea and vomiting or excessive drowsiness and confusion.despite careful dose titration and appropriate prophylactic drugs such as anti-emetics. In such patients an alternative strong opioid drug such as phenazocine or methadone, which are themselves chemically related to morphine may be tolerated without such side-effects. There is little information as to the mechanism of such morphine intolerance but possible explanations include either a pharmacokinetic variation in these individuals or individual variation in response at the opioid receptor. The action of morphine on gastric emptying resulting in functional pyloric stenosis may be important (Twycross and Lack 1986).

Support for a pharmacokinetic basis for idiosyncratic intolerance comes from observations in patients who develop renal failure whilst receiving morphine when increased sensitivity and intolerance to morphine is seen. This often responds to a reduction in dose or discontinuation for a short period before resuming treatment at a lower dose level. Several studies have now documented accumulation of morphine glucuronides in renal failure, whilst morphine clearance remains normal, and a correlation between clinical deterioration and persisting high levels of metabolite, in particular morphine-6-glucuronide has been made (Osborne et al, 1986). A similar build up of active metabolite related to either increased production or reduced clearance in morphine intolerant individuals may be postulated.

1.a.15 General considerations.

There are a number of factors to be considered in the interpretation of the available pharmacokinetic data. Assay specificity is perhaps the single most important consideration in interpreting pharmacokinetic data in studies with morphine and this will be discussed in detail in chapter two. Most studies in which the pharmacokinetics of morphine have been described use single doses of morphine administered parenterally or orally to normal volunteers or morphine-naive patients who are usually immediately post-operative. It is possible that this reflects a very different situation to that encountered in the treatment of chronic cancer pain where morphine is given regularly over a period of weeks or months. The doses given in pharmacokinetic studies are rarely more than 10mg, in contrast to the wide range of doses employed for cancer pain when occasional patients may require daily doses of several grams to achieve pain control. Another important factor to consider when comparing normal volunteers or healthy post-operative patients with patients having advanced cancer is the influence of the disease upon drug handling. Hepatic and renal impairment are common in advanced malignancy and this may well influence the pharmacokinetics of drugs in these patients.

1.a.16 Absorption

Absorption of morphine from the gastrointestinal tract is virtually complete, occurring predominantly in the proximal small bowel (Brunk and Delle 1974). Morphine is a basic compound (pKa 9.85) and becomes un-ionised (lipid soluble and diffusible) as the pH rises in

this region. A similar pH dependance has been demonstrated at the buccal mucosa (AlSayed et al 1987) where morphine is also readily absorbed. Absorption through the rectal mucosa is rapid and blood levels similar to that after oral administration are achieved (Hanning et al 1985).

1.a.17 Distribution

Pharmacokinetic data derived from single dose studies in both rats and man suggest that a three-compartment model for the distribution of morphine is most likely (Stanski et al 1976, Dahlstrom and Paalzow 1978, Dahlstrom et al 1978, Stanski et al 1978, Aitkenhead et al 1984, Murphy and Hug 1981) with rapid distribution occurring from the plasma compartment. In plasma, some 30-40% of the morphine present is protein bound, predominantly to albumin (Olsen 1975).

The apparent volume of distribution is also large but with considerable variation. It is relatively smaller in the elderly (Owen et al 1983). In one study in cancer patients (Sawe et al 1981) the volume of distribution ranged from 0.95 to 3.75 l/kg.

A study in rats (Dahlstrom and Paalzow 1975) showed rapid distribution of morphine from plasma into brain after intravenous administration, with maximum levels at 15-20 minutes after injection and an even distribution throughout the brain. The ratio of morphine in plasma to that in brain reached a constant value of between 3.8 and 4.8 at about 4 hours after injection. After intramuscular injections of morphine in man maximum concentrations in CSF were reported at 3 hours after administration and at equilibrium were 90% of those in plasma. After epidural administration of morphine maximum levels in CSF were found to be 20-25 times the plasma peak levels and due to the more

rapid distribution of drug from the plasma compartment the ratio of CSF/plasma morphine rose to between 125 and 175 after 5 hours (Nordberg, 1984). However in another study no difference was found between CSF and plasma levels after epidural administration compared to intravenous administration of the same dose (Schenin et al, 1986).

In man there is little information on the pattern of morphine and its metabolites in the CSF after oral or parenteral administration of morphine. In one study serial CSF samples have been taken from an indwelling catheter in six patients following an intravenous dose of 10mg per 70kg of morphine (Kaiko et al 1978). Paired plasma samples were also taken. CSF morphine levels reached a peak at 1 hour followed by a steady decline and at 8 hours CSF morphine was the same as free plasma morphine. These data were fitted to both a two-compartment and three-compartment model in both of which the CSF concentrations fitted closely to the time course of morphine in the peripheral compartment. Measurements of analgesia, mood and pupil size were also taken in this study, with peak intensity of these effects being seen at 30 - 100 minutes after administration again closely following the time course of morphine in a peripheral compartment of the pharmacokinetic model.

Tissue concentrations of morphine have been measured in two post-mortem studies in man. In 14 cases of fatal morphine poisoning in addicts, morphine was present in blood, muscle, liver and urine, levels in muscle being similar to those in blood and those in liver up to 5 times blood levels (Felby et al 1974). The other study was in a 35-year old woman who received severe gunshot wounds to the abdomen and during the 48 hours before death received 37mg morphine. Morphine concentrations were 0.67µg/ml in blood, 0.04µg/g in brain, 0.11µg/g in liver, 0.21µg/g in lung and 0.44µg/g in bile as measured by

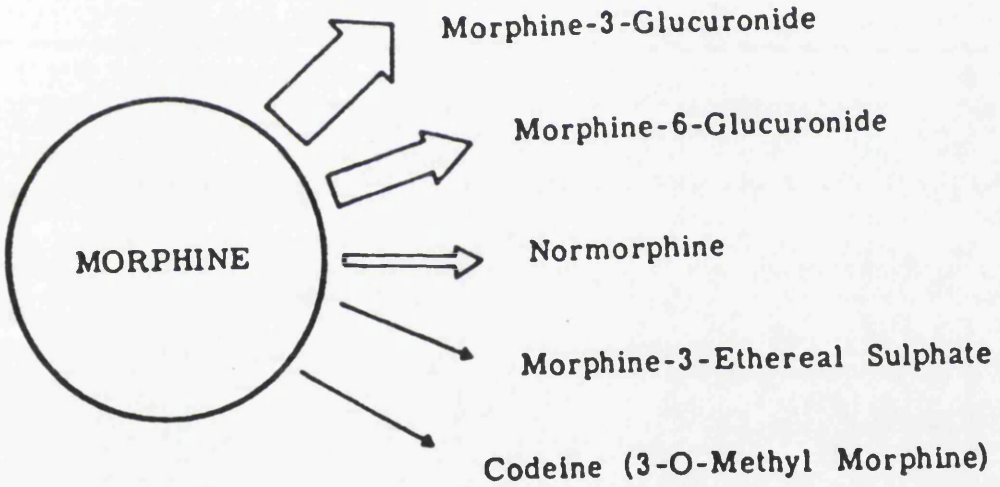
radioimmunoassay (Cravey and Reed, 1977).

1.a.18 Metabolism

Morphine undergoes extensive biotransformation by predominantly synthetic and oxidative reactions , details of which are shown in Figure 1.a.3. (Boerner et al 1975, Dahlstrom et al 1976, Yeh et al 1977, Sawe et al 1983, 1985)

Figure 1.a.3

Principal metabolites of morphine



Extensive presystemic elimination is thought to account for the poor bioavailability of morphine after oral administration, ranging from 15% to 64% in one study in cancer patients (Sawe et al,1981). In dogs dose related presystemic elimination has been demonstrated (Garrett and Jackson, 1979), but there is no evidence for such a mechanism in man. The main metabolites found in plasma following administration of morphine are morphine 3 glucuronide (M3G) and morphine 6 glucuronide (M6G). During long term treatment the conjugation of morphine with glucuronic acid is proportional to the dose, with no evidence of saturation of the system or autoinduction as the dose is increased (Sawe et al,1983)

In the past there has been controversy over whether the liver or kidney is the main site of morphine metabolism in man. Data from animal studies show conclusively that both in vitro (Dahlstrom et al 1976) and in vivo (Dahlstrom and Paalzow 1978) conjugation of morphine with glucuronic acid occurs in the liver, with clearance of morphine in isolated perfused liver experiments closely approximating the calculated hepatic clearance occurring in vivo. In a rat model, the first pass fraction eliminated after oral administration is 85%. This is significantly higher than after intraportal administration of morphine, suggesting that in rats the small bowel mucosa also plays an important part in metabolism, calculated to be 46% of first pass elimination.

In man there is also good evidence to support hepatic metabolism. In vitro work on human liver obtained immediately after death has demonstrated the ability of hepatic microsomes to glucuronidate morphine (Sawe et al 1982). A study in six cancer patients submitted to laparotomy at which liver biopsies were obtained, followed by in

vivo pharmacokinetic profiles after administration of single doses of morphine showed a clear correlation between UDP-glucuronyl transferase activity in the liver biopsy specimens and morphine-3-glucuronide/morphine ratios in plasma (Sawe et al 1985). A study in 8 patients with advanced alcoholic liver disease has shown a decrease in total body clearance of morphine from a mean of 33.5 ml/min in 6 normal subjects to a mean of 21 ml/min with a corresponding prolongation of mean terminal half-life from 111 mins to 201 mins(Mazoit et al, 1987). Anotherstudy in 6 patients with hepatic cirrhosis and encephalopathy has shown an increased absolute bioavailability of morphine after a single oral dose of 10mg compared with a single IV dose of 4mg. A mean bioavailability of 100% was found (Hasselstrom et al, 1986). In 6 patients with septic shock a significant reduction in hepatic blood flow (287 mls/min compared to 870 mls/min in six normal controls) was associated with prolongation of the mean terminal half life of morphine after a single IV dose of 0.075 mg/kg from 5.9hrs in the normal controls to 13.2 hrs in the shocked patients (McNab et al, 1986). Further indirect clinical evidence for the role of the gut or liver in morphine metabolism lies in the observed difference between oral and parenteral use. In the study mentioned above (Sawe et al 1981) oral bioavailability varied from 15-49% in five patients with normal liver function but was 64% in one icteric patient.

Data which appear to conflict with the predominant role of the liver in morphine metabolism were produced in one study of patients with hepatic cirrhosis and impaired liver function as measured by indocyanin green disposition. No difference in the disposition and elimination of morphine compared with healthy volunteers could be demonstrated following a single intravenous dose (Patwardham et al

1981).

Extrahepatic metabolism has also been demonstrated in animal models. Isolated rabbit kidney proximal tubules have been shown to glucuronidate morphine in vitro (Schali and Roch-Ramel 1982). In two chronically cannulated cows, the hepatic extraction ratio for morphine fell from 0.7 at portal vein plasma concentrations of over 2000 nmol/l to zero at about 200 nmol/l (McQuay et al 1984). Most patients with advanced cancer receiving morphine will have blood concentrations below that at which hepatic extraction was seen in these cow experiments (Neumann et al 1982).

In man in vitro evidence for extrahepatic metabolism comes from the demonstration of UDP glucuronyl transferase in microsomal fractions prepared from gut and kidney of human foetuses, with the capacity to glucuronidate morphine. In the same study however, hepatic enzyme activity was appproximately ten times higher than that in gut (Pacifici and Rane,1982).

In vivo evidence for renal metabolism is based mainly upon observations in patients with impaired renal function. A retrospective analysis of patients with advanced cancer suggested that those with impaired renal function (serum creatinine greater than 180 micromoles/l) required lower doses of morphine (median 5 mg 4-hourly) than those with impaired hepatic function who required a median of 20 mg 4-hourly (Regnard and Twycross 1984). However the ranges of dose requirements in each group were large and no statistical analysis has been used to determine the validity of these observations. A study performed in patients undergoing renal transplantation in which a single intravenous dose of morphine was given following induction of anaesthesia showed elevated morphine levels compared to a control

group. Of greater significance was a plateau phase during which morphine levels remained constant followed by a steady fall at a time which correlated with the recovery of renal function in the transplanted kidney (Moore et al 1984). Further evidence that hepatic extraction may not be important has been suggested by the finding of a relative bioavailability for oral morphine of over 100% in another study by the same authors (McQuay et al 1983).

The findings in these two latter studies have been criticised on the basis that both used a radioimmunoassay subsequently shown to cross react significantly with M6G (Hanks and Aherne 1985). M6G may accumulate in plasma and may therefore have contributed significantly to the apparent concentrations of what was thought to be unconjugated morphine in these studies, leading to misinterpretation of the data. Three subsequent studies have now been performed in patients with renal failure, including anephric patients, using highly specific assay techniques. None of these studies show impaired elimination of morphine but do show accummulation of glucuronides (Aitkenhead et al 1984, Woolner et al 1986, Sawe and Odar Cederlof 1987), consistent with the explanation of a cross-reacting assay to account for the earlier findings of Moore et al (1984).

The weight of evidence in man therefore at present seems to be in favour of hepatic metabolism as the principal route of morphine elimination. Animal data suggest that undoubtedly both the small bowel and kidney can also metabolise morphine and the relative roles of these and other sites of extrahepatic metabolism have yet to be defined. It may well be that in chronic high dosage these sites have considerable significance particularly where hepatic impairment may be present. Whilst the effects of hepatic function on a single dose of morphine

have been investigated (Hasselstrom et al 1986, Mazoit et al 1987) there is no information on the influence of liver function in the patient receiving chronic oral doses of morphine as in the patient with advanced cancer.

1.a.19 Excretion

The main route of excretion for morphine is through the kidney by glomerular filtration and possibly to a minor extent by tubular excretion (Boerner et al 1975). Estimates of the proportion of unchanged morphine excreted in urine range from 2 to 12% (mean 7%) of an administered dose, and this is independent of dose. Morphine glucuronides are the major excretory metabolites accounting for 60-70% of an administered dose, with smaller amounts of normorphine and normorphine conjugates being detectable. Seventy to eighty per cent of an administered dose is excreted within 48 hours of administration, with most of this appearing within the first 24 hours (Berkowitz1976) In dogs a dose related reduction in morphine and morphine metabolite excretion in the urine above 7.2mg/kg given intravenously has been demonstrated. Lower doses (0.41 - 0.47 mg/kg) had an inhibitory effect on urine flow but had no influence on drug clearance (Garrett and Jackson 1979). No evidence for such dose dependent metabolism has been shown in man.

In rats, biliary excretion and enterohepatic circulation of morphine has been clearly demonstrated (Walsh and Levine 1975, Dahlstrom and Paalzow 1978). Following subcutaneous administration, half of the administered dose was excreted in the bile, predominantly as morphine glucuronide. Using labelled ^{14}C-morphine it has been shown that when present as the glucuronide it is poorly absorbed from small

bowel but rapidly reabsorbed from large bowel, reflecting different rates of hydrolysis. Hydrolysis and thus absorption was also reduced following administration of lincomycin, suggesting that bacterial glucuronidase is important in this process.

The evidence for significant enterohepatic circulation in man is less compelling, although morphine has been detected in the faeces after non-oral administration in both normal volunteers and addicts (Boerner et al 1975) the amount varying from 10% to less than 1% of the administered dose. The influence of antibiotics on this has not been evaluated. The presence of morphine in bile has been inferred by an indirect method using intramuscular ^{14}C-labelled morphine followed by duodenal intubation in one subject in whom it was estimated that 7.4% of the injected dose appeared in the gastrointestinal tract (Elliot et al 1954). One study has analysed bile collected via a T-tube in a post-surgical patient requiring 15mg morphine 4-hourly for three days and found no free morphine and only 0.7µg/ml morphine conjugate (Oberst 1942). At post mortem after 37mg morphine given over 48hrs, a concentration in bile of 0.44µg/ml has been reported using analysis by radioimmunoassay (Cravey and Reed 1977).

Enterohepatic circulation could have an important contribution to the plasma morphine levels in chronic administration and in the use of slow release morphine sulphate (MST Continus). Two peaks of plasma morphine concentration have been described following administration of MST. The first, occurring in the initial hour is probably defined by the rate of absorption from the bowel, but the second at 4-5 hours has been attributed to enterohepatic circulation (Leslie et al 1980).

There is no evidence that significant excretion of morphine or its metabolites occurs by other routes in man.

1.a.20 Pharmacokinetic parameters.

Tables 1.a.2, 1.a.3 and 1.a.4 detail the major studies from which the present knowledge of basic pharmacokinetic parameters of morphine are derived together with their values.

An important factor in evaluating the results presented is the assay used as has been discussed above. It is likely that early studies using radioimmunoassay are unreliable in terms of the absolute amounts of morphine measured due to their poor specificity. This is discussed further in Chapter 2.

Key to Tables 1.a.2 - 1.a.4

Subjects	V	Volunteers
	P:P-O	Post-operative patients
	P:CA	Cancer patients
	P:CR	Patients with hepatic cirrhosis
	P:RF	Patients with renal failure
	P:NB	New-born babies
	P:INF	Infants

C_{max} Peak blood concentration

t_{max} Time to peak blood concentration

$t_{½}$ Elimination half-life

V_d Volume of distribution

F Bioavailability

(In Table 1.a.4(R) denotes Relative Bioavailability to oral solution and (A) denotes Absolute Bioavailability; in all other tables F denotes Absolute Bioavailability.)

Assay	G	Gas Liquid Chromatography
	R	Radioimmunoassay
	H	High performance liquid chromatography

Table 1.a.2
Published pharmacokinetic parameters of morphine:
I Single IV/IM dose

(i)Normal renal and hepatic function

Author	Subjects	Dose	V_d	Clearance	$t_{1/2}$	Assay
		(mg)	(l/kg)	(ml/kg/min)	(hrs)	
Stanski et al (1976)	10 P:P-O	1mg/kg	1.0	5.6	2.3	R
Berkowitz et al (1976)	31 P:P-O	10mg/ 70kg	-	-	0.83	R
Stanski et al (1978)	6 P:P-O	10mg	4.7	12.4	4.5	R
Stanski et al (1978)	8 V	10mg	3.2	14.7	2.9	R
Sawe et al (1981)	7 P:CA	4mg	2.1	9.2	3.1	G
Murphy et al (1981)	10 P:P-O	0.05-0.2mg/kg	3.4	23.0	1.7	R
Dahlstrom et al (1982)	8 P:P-O	10-20mg	6.2	20.5	3.8	G
Majaverian et al (1982)	7 V	0.1-	2.2	8.0	3.4	R
Owen et al (1983)	(a)13 V (23-28yrs)	10mg/ 70kg	2.1	33.7	1.0	G
	(b)7 V (60-69yrs)		1.2	27.7	0.7	H
Sawe et al (1985)	6 P:CA	4mg	4.0	28.0	1.7	H
Persson et al (1986)	10 P:P-O	Infusion 0.6-5.0 µg/kg/min	2.2	20.6	1.5	G
Lynn and Slattery (1987)	(a)7 P:NB	Infusion 20-100 µg/kg/hr	3.38	6.29	6.81	H
	(b)4 P:INF		5.15	23.8	3.91	

(ii) Impaired hepatic function

Author	Subjects	Dose	V_d	Clearance	t	Assay
		(mg)	(l/kg)	(ml/kg/min)	(hr)	
Patwardham et al (1981)	(a)6 P:CR	0.15 mg/kg	2.3	14.6	2.2	G
	(b)6 V		2.9	16.2	2.5	
Hasselstrom et al (1986)	6 P:CR	4mg	4.3	11.3	4.4	H
Mazoit et al (1987)	(a)8 P:CR	0.1 mg/kg	5.16	33.5	1.85	R
	(b)6 V		5.84	21.0	3.35	

(iii) Impaired renal function

Aitkenhead et al (1984)	(a)11 P:P-O	0.125 mg/kg	2.8	11.5	3.5	H
	(b)9 P:RF		1.8	10.3	3.2	
Woolner et al (1986)	(a)3 V	10-14.7 mg	4.0	21.3	2.17	G
	(b)4 P:RF		3.0	27.8	1.21	
Chauvin et al (1987)	(a)7 P:P-O	0.2 mg/kg	3.7	21.3	3.1	R
	(b)9 P:RF		2.8	17.1	3.1	
Sawe and Odar-Cederlof (1987)	7 P:RF	4 mg	4.4	21.1	2.4	H

Table 1.a.3
Published pharmacokinetic parameters of morphine:
II Oral Solution, single doses

Author	Subjects	Dose (mg)	C_{max} (ng/ml)	t_{max} (hr)	$t_{1/2}$ (hr)	F (%)	Assay
Sawe et al (1981)	7 P:CA	20-30	-	3.4	3.4	38.2 (15.2-63.6)	G
Hanks et al (1981)	8 P:PO	20	73.1	2.9	-	-	R
McQuay et al (1983)	5 P:PO	10		1.5	-	100	R
Sawe et al (1985)	6 P:CA	20-25	-	-	3.3	47.1 (29.9-69.3)	H
Savarese et al (1986)	13 V	15 (12 doses)	22.0	0.77			H/R
Hasselstrom et al (1986)	6 P:CR	10	-	-	6.4	100	H
Sloan et al (1987)	15 P:CA	60-400	55.0	1.2	-	-	H
Khojasteh et al (1987)	23 P:CA	133 (mean)	22.1	0.98	1.82		H

Table 1.a.4
Published pharmacokinetic parameters for morphine
III Controlled release tablet (MST) and buccal administration

Author	Subjects	Dose (mg)	C_{max} (ng/ml)	t_{max} (hr)	F (%)	Assay
(i) MST						
Leslie et al (1979)	6 V	20	-	-	-	G
Hanks et al (1981)	12 P:PO	20	55.0	3.3	86.4(R)	R
McQuay et al (1983)	5 P:PO	10		3.0	120 (R)	R
Vater et al (1984)	11 V	20	14.8	2.4	18.3 (A)	H/R
Savarese et al (1986)	13 V	30	20.3	2.3	85.5 (R)	H/R
Sloan et al (1987)	15 P:CA	60-400	65.0 (mean)	3.6	90.4 (R)	H
(ii) Buccal						
Bardgett et al (1983)	2 V 2 P:PO	7.4 13.3	16-18 36-47	1.0 1.0	- >100 (R)	H
Bell et al (1985)	20 P:PO	13.3	36.0	1.0	146 (R)	H
Fisher et al (1987)	11 V 5 P:PO	25	10.8	4.75	19 (A)	H

1.a.21 Clinical Effects of Morphine

The clinical effects of morphine in man are well recognised and include an inhibitory action on the central nervous system accounting for analgesia, respiratory depression and somnolence; an excitatory action on the CNS accounting for miosis, vomiting and convulsions; a stimulant action on peripheral smooth muscle accounting for constipation, bronchoconstriction and increased bladder and uterine tone; and a number of other associated peripheral effects including itching, sweating and dry mouth.

Some of these pharmacological actions of morphine can be directly related to effects on opioid receptors.

1.a.22 Opioid receptors

Considerable interest has emerged in recent years over the relation between the clinical effects of opioid drugs and the discovery of endogenous opioids and opioid receptors. Three main classes of opioid receptors have been elucidated through experiments with specific agonists and antagonists in animals (Martin et al 1976). These are the mu, kappa , and sigma receptors each mediating different effects in experimental systems as shown in table 1.a.5. Further subclassifications of these groups have been proposed and an additional group, the delta receptor has also been described.

Morphine is a pure opioid agonist with a predominant action at the mu receptor but also binds to kappa and sigma receptors.

Table 1.a.5

Putative effects mediated by main classes of opioid receptor

Mu	Kappa	Sigma
Supraspinal analgesia	Spinal analgesia	Dysphoria
Euphoria	Sedation	Hallucinations
Miosis	Miosis	Delusions
Respiratory depression	Respiratory depression	Respiratory stimulation
Physical dependence		Vasomotor stimulation

(adapted from Martin et al, 1976)

These receptors are found in several areas of the brain, particularly in the periaqueductal grey matter and throughout the spinal cord. From animal studies it is also possible that there is some differentiation of nociceptive stimuli between receptor types, with mu receptors being selective for heat stimulus and kappa receptors selective for pressure stimulus (Upton et al 1982).

Opioid receptors have also been demonstrated outside the central nervous system. In the gastrointestinal tract of rats a selective peripherally acting opioid antagonist, quaternary naltrexone, will reverse morphine-induced gastrointestinal slowing without any effect on analgesia, suggesting that the peripheral effects of morphine may be mediated through such receptors (Manara et al 1986).

The relative role of central and peripheral receptors in the actions of morphine in man remains unclear, as does their putative physiological role in relation to endogenous opioids.

1.a.23 Active Metabolites

The active substance binding to the opioid receptor has in the past been assumed to be morphine itself. There is, however, now some evidence to suggest that metabolites of morphine may be important in producing its effects.

Morphine-3-glucuronide, the major metabolite of morphine, has long been regarded as inactive with no significant analgesic activity after subcutaneous or intracerebral injection in mice (Shimomura et al 1971), or in isolated tissue preparations (Schulz and Goldstein 1972, Kataoka et al 1977). It has however been detected in the CSF in rodents

(Yoshimura et al 1973) and in man (Sawe 1986) after systemic administration of morphine and a single report suggests that when injected directly into the cerebral ventricles it may have some analgesic activity (Sasajima 1970). An alternative explanation would be that prior deglucuronidation (Schulz and Goldstein 1972) of the M3G accounts for the associated analgesic activity.

Other metabolites of morphine are morphine-6-glucuronide, morphine-3,6-diglucuronide, normorphine, normorphine-6-glucuronide, codeine, and morphine ethereal sulphate (Boerner et al 1975, Yeh et al 1977). All of these metabolites have been believed to be produced in insignificant quantities and to make no contribution to the analgesic action of morphine.

Morphine-6-glucuronide, normorphine, codeine, and morphine ethereal sulphate all have analgesic activity (Lasagna and de Kornfeld 1958, Shimomura et al 1971).

Morphine-6-glucuronide is the most potent: when injected into the cerebral ventricles of rats it is 45 times as potent as morphine, and three to four times as potent by subcutaneous injection (Shimomura et al 1971). Morphine-6-glucuronide has been thought to be produced in very small quantities after single doses of morphine in man (Boerner et al 1975), but on chronic dosing the average ratio of morphine-6-glucuronide to morphine in plasma is reported as being almost four to one (Sawe et al 1981). Morphine-6-glucuronide, like the 3-glucuronide is highly polar but appears to cross the blood brain barrier (Yoshimura et al 1973, Sawe 1986). Thus this metabolite may be of considerable significance when morphine is used chronically.

Evidence for a possible role for the glucuronides in the pharmacodynamics of morphine comes from the observations in patients

with renal failure receiving morphine. In this situation accumulation of both morphine-3-glucuronide and morphine-6-glucuronide has been demonstrated with normal clearance of morphine. This accumulation of metabolites has been correlated with periods of confusion and respiratory depression and provides circumstantial evidence to suggest that impaired metabolite clearance, in particular of morphine-6-glucuronide, may be at least partially responsible for the effects of morphine in this situation (Osborne et al,1986). It seems likely also that morphine-6-glucuronide contributes significantly to the overall analgesic effect of morphine when given in repeated dosage by mouth. The other metabolites of morphine which are active, notably normorphine and morphine ethereal-6-sulphate, have not been detected in significant quantities in man even after prolonged high dosage (Sawe et al 1983).

The importance of metabolite activity may become particularly relevant when considering chronic oral use such as occurs in patients with advanced cancer. Clinical experience suggests that morphine is relatively more potent when given in repeated dosage, and that the oral to parenteral potency ratio is in the region of 1:2 or 1:3 (Twycross and Lack 1983), which is clearly different from the single dose ratios of 1:6 or 1:8 (Houde et al 1965). It may well be that accumulation of M6G, and perhaps other active metabolites also, in chronic oral use, can account for this discrepancy.

Two other mechanisms whereby morphine may become more effective on repeated dosage have also been suggested: that the presystemic metabolism of morphine is saturable, as is the case in dogs (Garrett and Jackson 1979); or that enterohepatic circulation may contribute significantly to the maintenance of plasma and tissue levels of unconjugated morphine. The first suggestion is probably wrong in man;

the systemic availability of oral morphine appears to be unchanged whatever the dose or duration of treatment (Sawe et al 1983). Enterohepatic circulation of morphine has been demonstrated in rodents (Walsh and Levine 1975, Dahlstrom and Paalzow 1978),as described earlier, but there is no unequivocal evidence for it in man.

1.b Objectives of the work presented in this thesis

1. To develop and validate a sensitive, specific and reliable assay for morphine, M6G and M3G.

2. To determine basic pharmacokinetic parameters for morphine, M6G and M3G in normal volunteers and to correlate these with the pharmacodynamics of morphine and M6G.

3. To investigate the pharmacokinetics of morphine and M6G in patients with advanced cancer receiving regular long term treatment with morphine.

4. To assess the clinical use of morphine in patients with advanced cancer and to investigate factors influencing dose requirements.

CHAPTER 2 METHODS

2.a Review of morphine assay methods

2.b HPLC assay for morphine and morphine metabolites

2.c RIA for morphine

2.d RIA for morphine metabolites

2.e Comparison of RIA with HPLC

2.f Method of blood sampling

Review of Morphine Assay Methods

A fundamental limitation of pharmacokinetic studies with morphine has until recently been the inability of standard assay techniques to reliably distinguish morphine from its metabolites. This is a particular problem in chronic use because of the accumulation of the glucuronide conjugates M3G and M6G to a concentration many times greater than that of unconjugated morphine. Only a small degree of non-specificity is required in the assay for the concentrations of unconjugated morphine to be considerably overestimated. Recent developments in assay techniques now enable reliable and specific measurements of morphine in tissue fluids to be obtained.

2.a.1 Early Methods

Early studies into the metabolism of morphine used colorimetric methods of analysis using the principle of an organic base (morphine) forming a soluble complex with an organic acid. The best dye was found to be methyl orange, but other compounds used include bromothymol blue, bromocresol purple and bromocresol green. However these methods are non-specific and relied on extensive purification processes involving extraction, adsorption or precipitation. This requires relatively large samples and despite such processes the isolates were rarely free from interfering materials, and cross-reaction with metabolites is inevitable.

Other methods studied at this time which proved unreliable and had poor specificity included nephelometry, polarography, iodometry and gravimetry.

2.a.2 Radioisotope tracer studies

The synthesis of ^{14}C labelled derivatives of morphine enabled more accurate studies on the fate of morphine and its metabolites. Evidence for N-demethylation and O-dealkylation was first established using such methods, as were studies in the routes of absorption and excretion of morphine both in animals and in man (Oberst 1942, Elliot et al, 1954). The main limitations of this work with radiolabelled morphine lie in the difficulty in adapting this technique for quantitative measurements and the constraints of applying indirect measures of metabolism reliant upon detection of $^{14}CO_2$ cleaved from the parent molecule.

2.a.3 Fluorometric assay

Several attempts to measure morphine using photometry were described in the 1950's but these methods failed to achieve the sensitivity required to be useful for measurements in biological systems.

A fluorometric assay was subsequently developed based on the conversion of morphine, which is only weakly fluorescent to pseudomorphine which is highly fluorescent, using oxidation by potassium ferricyanide (Kupferberg et al 1964). Extensive extraction of samples was again required when biological materials were being analysed, and whilst enabling sensitive measurements of morphine down to concentrations of 0.04µg/ml this method again lacked specificity, cross-reacting with metabolites and morphine derivatives including dihydromorphine and monoacetylmorphine.

2.a.4 Gas Liquid Chromatography (GLC)

GLC is for many substances the assay method of choice for sensitive and specific analyses, using a mobile gas phase and a stationary liquid phase between which partition of the substance of interest occurs. Several methods of GLC have been described for the measurement of morphine. Direct gas liquid chromatography of polar substances such as morphine is not possible at the low levels required in biological studies and it is therefore necessary to produce a volatile derivative usually by reaction with acid anhydrides. Analysis is therefore preceded by an extensive extraction process in which up to eight washings of the samples may be performed. Incubation with β-glucuronidase is also performed to hydrolyse morphine conjugates where these are of interest. Detection of morphine after chromatography uses electron capture with mass spectrometry.

Experience with GLC for morphine has shown this to be a specific method, although unable to measure separately morphine metabolites. The principal drawbacks of this method however lie in the need for meticulous extraction techniques using reagents of high purity and the fact that this becomes a time-consuming and labour intensive process. Despite this, until the recent development of high performance liquid chromatography (HPLC), GLC has been the best specific assay for morphine and several important studies have used a GLC assay (Fry et al 1974 ,Sawe et al 1981, Woolner et al,1986).

2.a.5 Radioimmunoassay (RIA).

RIA relies upon the production of an antiserum to bind the

substance of interest, the ratio of bound to free substance as measured by radioactivity in the two separated fractions then being used to determine the concentration present in a sample. This method has considerable advantages over chromatography techniques in being capable of analysing samples without an extensive extraction and with rapid turnover of samples.

The first RIA for morphine was described in 1970 (Spector and Parker, 1970) using antiserum raised in rabbits to a 3-carboxymethyl-morphine-BSA conjugate. Early reports showed that this assay produced comparable results to the fluorescent assay available at the time (Kupferberg, 1964). The assay was unable however to distinguish between morphine, codeine or diamorphine and extensive cross-reaction with morphine-3-glucuronide would also be expected. Subsequently an antiserum to 6-succinyl morphine-BSA conjugate was produced (Wainer et al, 1973), leaving the 3- position of the morphine molecule free to act as an antigenic determinant. As a result only 0.2% cross-reactivity with morphine-3-glucuronide was present although cross-reaction with morphine, codeine and diamorphine also occurred.

More recently the importance of cross-reactivity with morphine-6-glucuronide (M6G) has been recognised. This is considerable when an antiserum is raised to a 6-position conjugate, with cross-reaction being >100% with a goat antiserum raised to a 6-succinyl morphine-BSA conjugate in one report (Aherne and Littleton, 1985). Since ratios of plasma concentrations of M6G : morphine have been estimated at between 2.5 and 3.9 : 1 (Sawe et al,1983,1985), this degree of cross-reactivity results in considerable over estimation of plasma morphine. Failure to recognise the significance of this cross-reaction has resulted in a

number of misleading reports using results based on nonspecific radioimmunoassays (RIA's). In particular, recent studies in patients with impaired renal function and undergoing renal transplantation were initially thought to demonstrate accumulation of morphine with impaired renal function. More recent studies with a specific HPLC assay have shown this to be erroneous and that due to cross reaction with the nonspecific RIA, accumulating glucuronides were measured as free morphine and this was misinterpreted as morphine accumulation. In fact morphine clearance is unchanged in renal function.

Because of these problems, a more specific antiserum has been sought in the further development of RIA for morphine estimations. By raising antiserum to conjugates based on the cyclic N position of the morphine molecule, the problem of cross-reactivity with the two major metabolites of morphine, M3G and M6G, is overcome (Aherne and Littleton, 1985). There remains a theoretical cross-reaction with normorphine but significant levels of this metabolite in man have not been detected using a specific HPLC assay (Sawe et al 1983, Joel personal communication). Thus the antiserum raised to N-succinyl morphine-BSA conjugate has been shown to have only 0.011% cross-reactivity with M3G and 0.013% with M6G, and validation of this assay with HPLC shows good correlation for morphine levels in plasma (see Chapter 2.e and Savarese et al, 1986)

The availability of both specific antisera and cross-reacting antisera has recently been exploited to develop the technique of differential radioimmunoassay (Hand et al, 1987). Morphine is measured using the specific antiserum, the total concentration of M3G and morphine by a cross-reacting antiserum raised to a 3-position conjugate and the total concentration of M6G and morphine by a cross-reacting

antiserum raised to a 6-position conjugate. The individual concentrations of M3G and M6G are then deduced by subtraction using the value for morphine concentration obtained with the specific antiserum. Good correlation with spiked standards was obtained but no comparison between this method and HPLC has been reported.

2.a.6 High Performance Liquid Chromatography (HPLC).

The development of high performance liquid chromatography (HPLC) has enabled sensitive and specific analysis of morphine and its main metabolites, M6G and M3G, and whilst not without its problems, has become the optimal assay system for morphine estimation. HPLC is based on the same principles as GLC using a liquid mobile phase and a solid stationary phase. For ionizable compounds such as morphine, ion-pair reverse phase chromatography has emerged as the best method. Ion-pair chromatography refers to that in which the compound of interest is present in an aqueous mobile phase, the pH of which is adjusted so that the compound is charged. A "pairing ion " is then added to the mobile phase of opposite charge to the compound of interest so that an "ion-pair" is formed. This is then separated from the mobile phase using a reverse phase column and eluted in an organic phase. Reversed phase partition is when the mobile phase is more polar than the stationary phase, in contrast to normal partition when the stationary phase is more polar than the mobile phase. In the HPLC assay for morphine described later in this chapter the ion-pairing agent is dodecyl sulphate which forms an ion-pair with morphine in acidic conditions.

The principle problems encountered with HPLC for morphine and its metabolites are related to the detection of the separated substances

after chromatographic separation. M3G is readily detected at low concentrations by fluorescence but both morphine and M6G are only weakly fluorescent. One approach to overcome this problem has been to oxidise the morphine and convert it to its fluorescent dimer pseudomorphine (Jane and Taylor 1975) and this has been successful in morphine determinations from urine. An HPLC method has been described for morphine, M3G and M6G using detection solely by UV fluorescence at 210nm with sensitivity down to 5ng of morphine and M3G being claimed (Svensson et al 1982). Other workers however have found fluorescence to be insufficiently sensitive to measure nanogram quantities of morphine and have as a result used the technique of electrochemical detection (White 1979), with which specific determination of morphine in concentrations of less than 1ng/ml has been claimed (Wallace et al 1980, Todd et al 1982). More recently Svensson has described a modification of his original HPLC assay incorporating electrochemical detection with which measurement of morphine, M6G and normorphine in concentrations down to 1nmol/l (0.29ng/ml) is possible (Svensson 1986). The major refinement in this assay was the use of two electrodes in the electrochemical detector coupled in series enabling removal of more readily oxidisable components at a low potential on the first electrode and then measurement of morphine, M6G and normorphine at a higher potential on the second electrode. This results in a lower background current and lower noise level.

2.b. HPLC FOR MORPHINE AND MORPHINE METABOLITES

The HPLC assay used in the following studies was based on that described by Svensson (Svensson et al 1982, Svensson 1986) using reversed phase ion pair HPLC with UV detection of M3G and electrochemical detection of morphine and M6G. The assay is preceded by extraction of the plasma samples through two SEP-PAK cartridges.

2.b.1 Extraction technique

Apparatus: Vacuum pump (Vac-Elute)

SEP-PAK C18 cartridge (Waters Associates)

pH meter (Gallenkamp)

Reagents

Eluent: 10mM sodium dihydrogen phosphate ($Na\ H_2\ PO_4$)

10% acetonitrile (CH_3CN)

Orthophosphoric acid to adjust pH to 2.1

Deionised double-distilled water.

Methanol

5mM Ammonium Sulphate (pH adjusted to 9.3)

5M Ammonium Sulphate (pH adjusted to 9.3)

Extraction

The first SEP-PAK cartridge is washed in turn with the following, ensuring that the cartridge is not allowed to dry out between washings:

a) 5ml methanol

b) 3ml eluent

c) 5ml distilled water

d) 1ml sample in 3mls 5M ammonium sulphate

e) 20ml of 5mM ammonium sulphate

f) 0.5ml distilled water

g) 3ml eluent

The final 3ml eluted is collected in a plastic tube and the second SEP-PAK cartridge then washed in the same way with the following:

a) 5mls methanol

b) 3mls eluent

c) 5mls distilled water

d) 3ml sample from first cartridge in 3mls 5M ammonium sulphate

e) 20mls of 5mM ammonium sulphate

f) 0.5ml distilled water

g) 3mls eluent

The final 3mls eluted from the second cartridge is then used as the sample for the HPLC. This is stored in a polypropylene plastic tube at -20^{o}C prior to analysis.

2.b.2 Chromatography

Equipment

Ultrasonic degasser (Kery Ultrasonics Ltd)

Autosampler (Gilson model 231)

Spectroflow 400 pump (Kratos)

U-bondapak C18 column (Waters associates)

Waters Z-module radial compression system

FS970 LC Fluorometer (Schoeffel Instruments Inc)

Electrochemical detector (Esa Coulochem model 5100A)

Analytic cell for detector (Esa Coulochem model 5011)

Conditioning cell for detector (Esa Coulochem model 5021)

Trio Trivector integrator

Pye Unicam CDP4 integrator (Philips)

Chart recorder

Reagents

Mobile Phase

5mM Sodium dihydrogen phosphate (NaH_2PO_4)

1mM sodium dodecyl sulphate ($NaC_{12}\ SO_4$)

28% acetonitrile (CH_3CN)

Prepared with ultrasonic degassing and pH then adjusted to 2.1 using orthophosphoric acid.

Sample

500 µl sample prepared from washing of plasma sample through two SEP-PAK cartridges as described above.

Standards

Morphine Sulphate (Evans Chemical Ltd)

Morphine-3-glucuronide (Sigma Chemicals)

Morphine-6-glucuronide (Salford Ultrafine Chemicals Ltd)

Procedure

Plasma samples are prepared by extraction as described above and stored in polypropylene tubes at -20°C. The earlier use of polyethylene tubes for storage was found to be associated with an interfering peak on the chromatogram. Standards are made up in plasma and extracted as above.

A 500 µl sample is injected by autosampler into the system. The time of each sample run has varied from 15 to 40 minutes depending upon the flow rate used and problems of new interfering peaks in individual samples being superimposed upon subsequent sample runs. For most samples a run time of 15-20 minutes has been used, using a flow rate of 1.5ml/minute.

Batches of 12-20 samples are run at a time. With each batch a full set of standards for morphine, M3G and M6G are run together with five control samples of spiked bank plasma. Weekly current-voltage curves were performed to optimise the potential at which the electrochemical detector cells were used.

The final chromatogram is produced both by computerised integrator and by a manual chart recorder. The latter was found necessary to check on readings from the computer when peaks were close together or where variations in the baseline resulted in misinterpretation by the computer.

An example of the chromatogram for M and M6G using the Trio Trivector integrator is shown in Figure 2.b.1(a), and for M3G using the Pye unicam integrator in Figure 2.b.1(b).

Interpretation of Chromatogram

Peak height has been used to measure magnitude of effect. Standard curves are constructed using the least squares method. Examples of these for morphine, M3G and M6G as shown in Figures 2.b.2(a) - 2.b.2(c) respectively.

From the standard curve, concentrations in ng/ml are calculated from peak heights obtained in samples. Both construction of the standard curve and subsequent calculation of sample concentrations were carried out on a BBC microcomputer using a standard program available in the Clinical Pharmacology Department, St Bartholomew's Hospital.

Figure 2.b.1(a)
Chromatogram for morphine and M6G using electrochemical detection

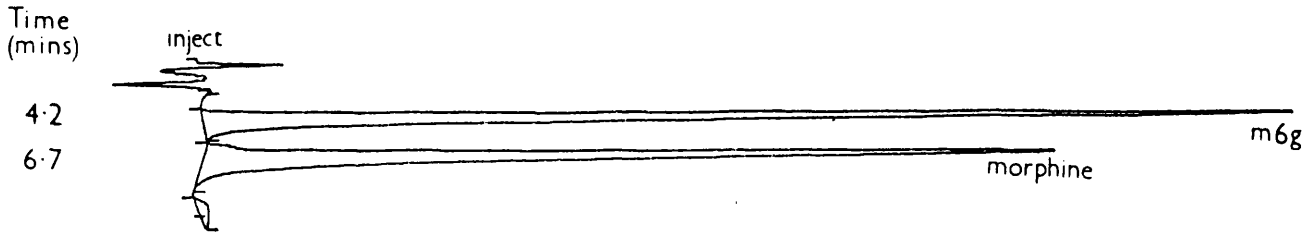


Figure 2.b.1(b)
Chromatogram for M3G using UV fluorescence

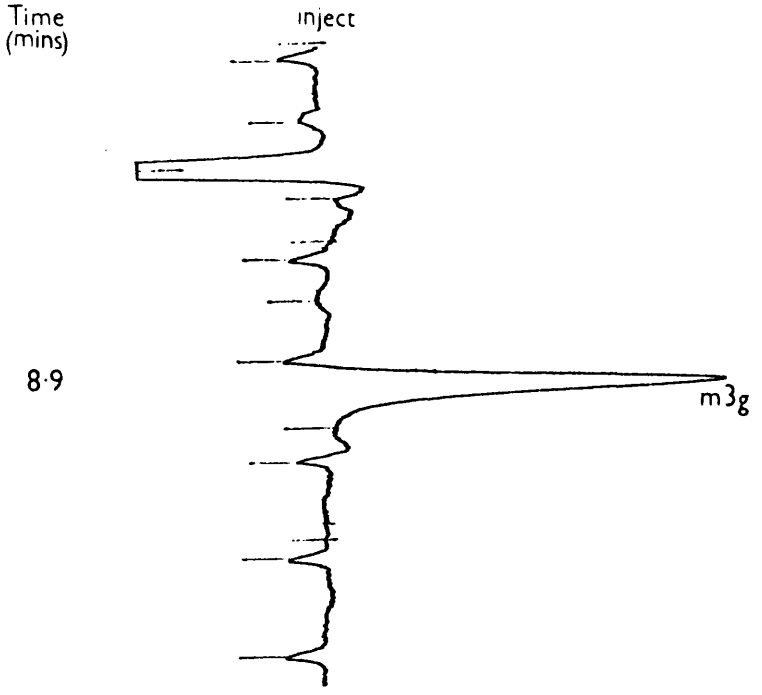


Figure 2.b.2 (a)
Standard curve for morphine

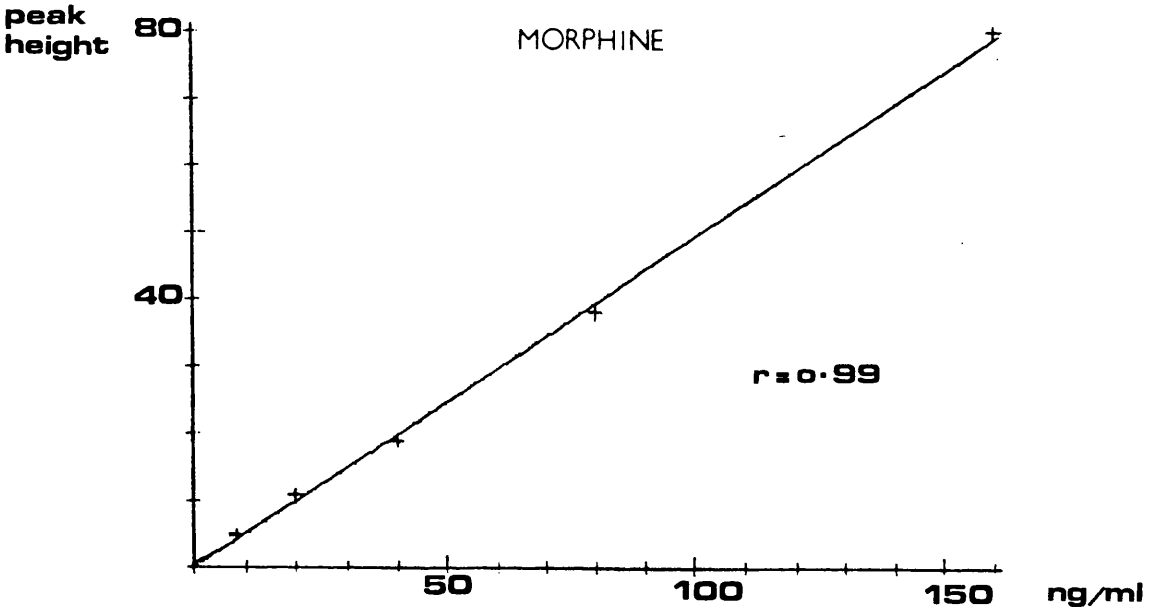


Figure 2.b.2 (b)
Standard curve for M3G

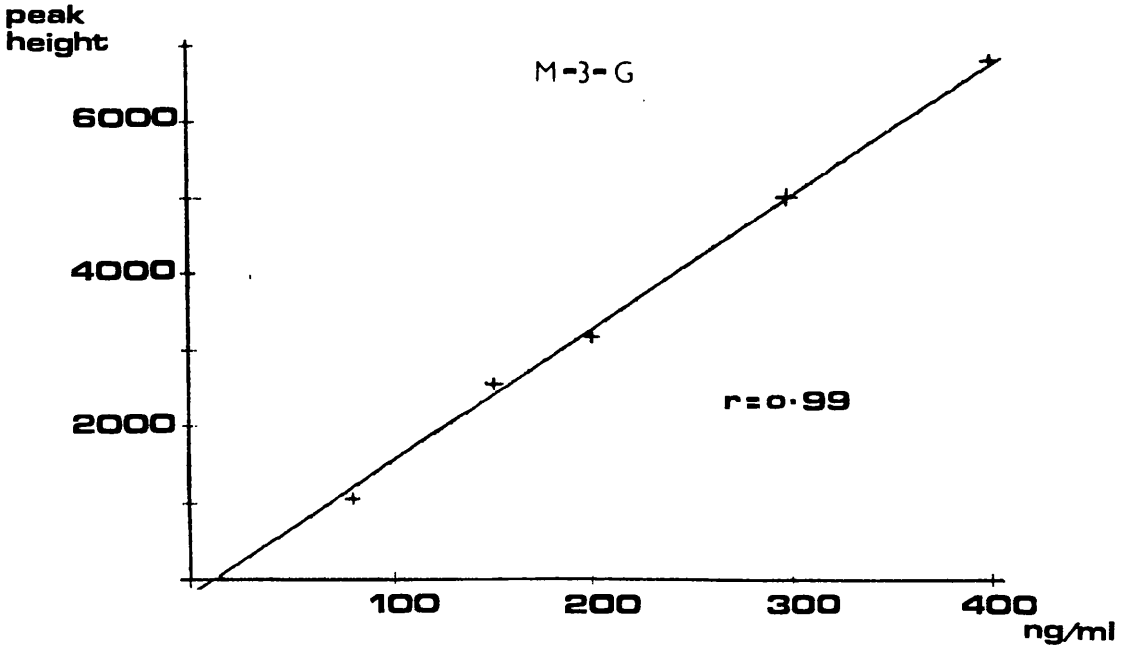
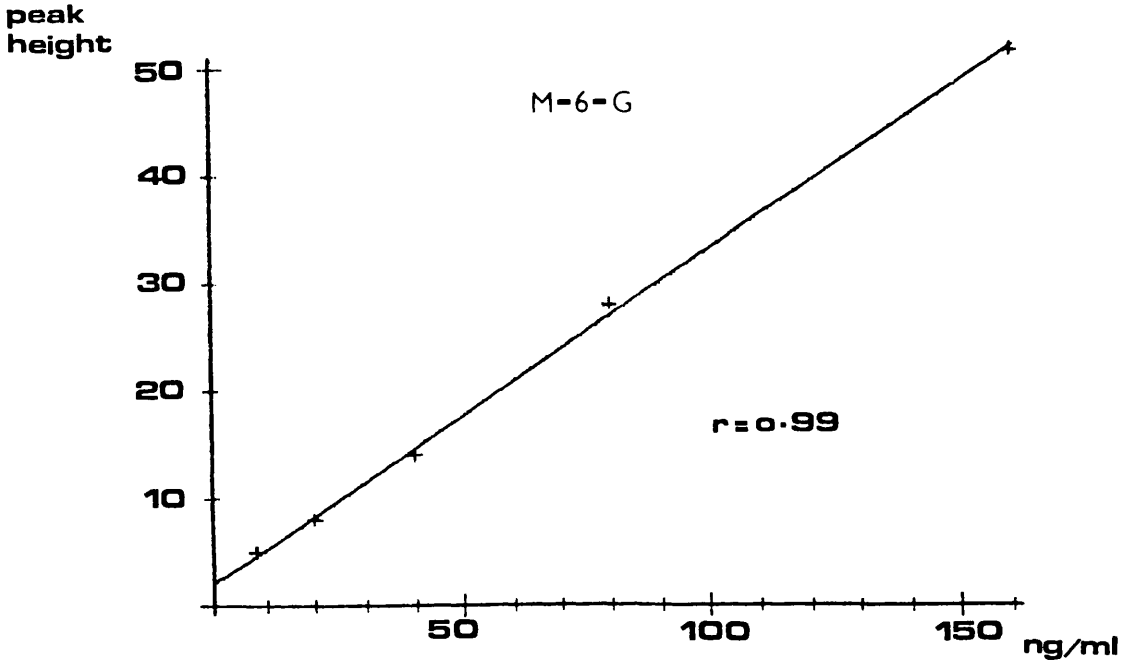


Figure 2.b.2 (c)
Standard curve for M6G



2.c.3 Development of Assay

During the period in which these projects were undertaken further development work on the assay has also been carried out. Despite this considerable problems have been encountered in its day to day use, primarily related to the use of electrochemical detection at extremes of its range of sensitivity in order to detect nanogram quantities of morphine and M6G.

Some of these problems are illustrated in the following examples:

a) Interfering peaks have been a common, but in many cases unpredictable complication, occurring in one of two positions:

(i) At the end of the chromatogram resulting in interference with the following sample unless a suitable time is allowed to wash out the interfering substance. This is illustrated in figure 2.b.3 where using a reduced flow rate of 1ml/minute to minimise baseline deflection a late peak at 18 minutes is seen. One result of this has been that lengthy run times for each sample have been frequently required.

(ii) A persistent peak was encountered adjacent to or superimposed upon the peak for morphine as illustrated in Figure 2.b.4. This was traced to the use of polyethylene plastic tubes in the storage of the specimens and these peaks resolved once these were changed to polypropylene tubes.

Figure 2.b.3
Late interfering peak

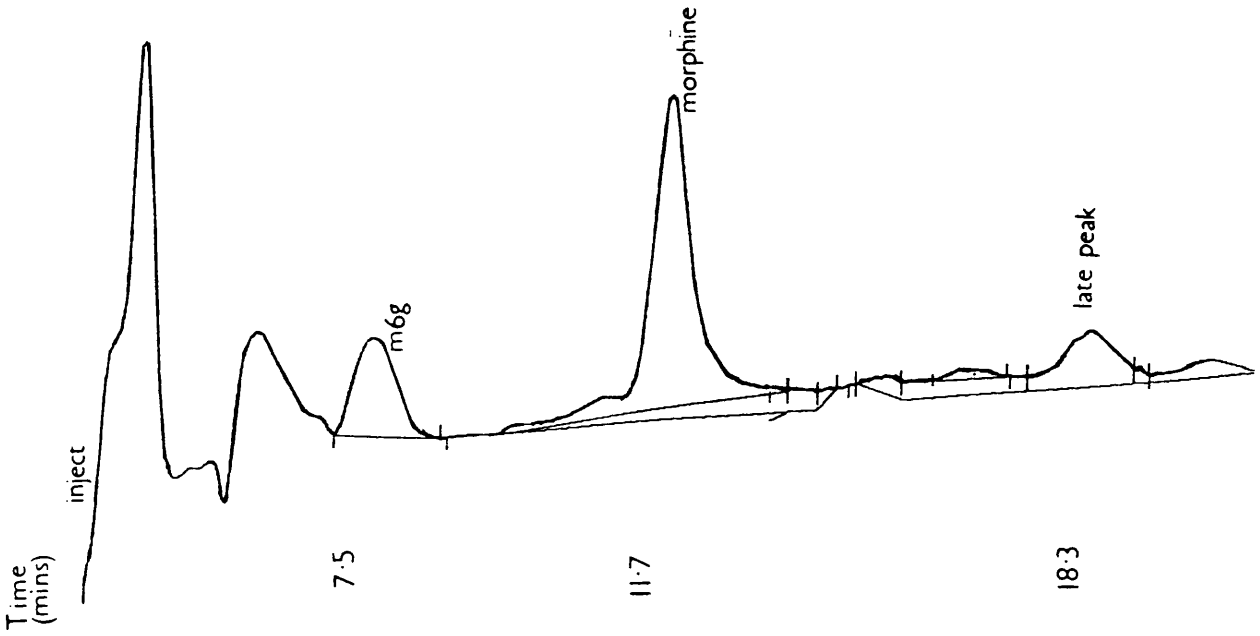
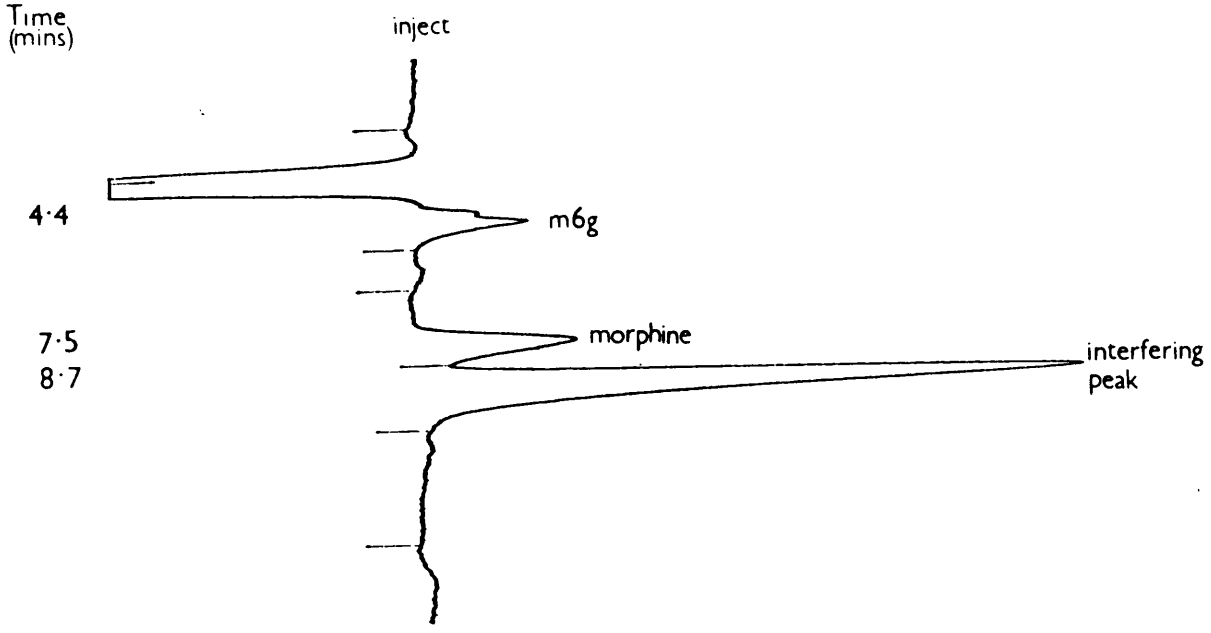


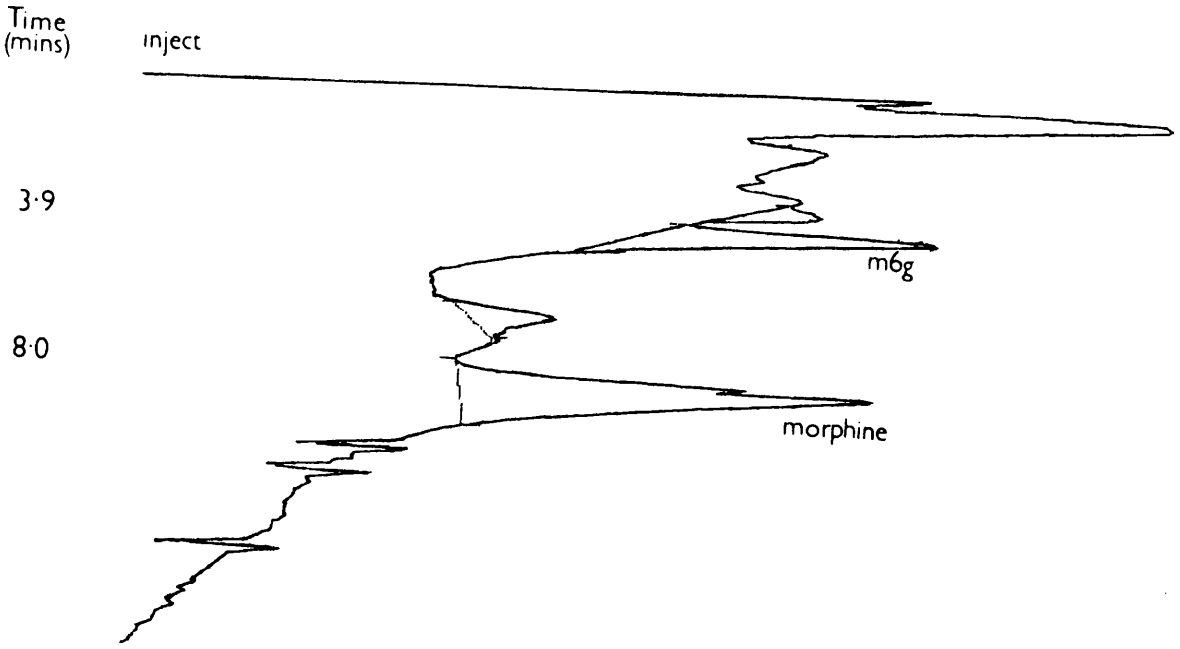
Figure 2.b.4
Interfering peak with morphine



b) Baseline fluctuations are a common problem resulting in chromatograms similar to those shown in figure 2.b.5.

Whilst minor fluctuations can be accounted for when determining the peak height, major variations such as that demonstrated are unacceptable and as a result samples may need to be re-run through the column on several occasions. No consistent cause for these fluctuations has been elucidated so far and other groups using this assay have had similar experiences. (Joel, personal communication). It is likely to be related to the use of the electrochemical detector cells on maximum gain in order to achieve the sensitivity required to measure nanogram quantities of morphine and M6G.

Figure 2.b.5
Baseline fluctuation



2c. RIA FOR MORPHINE

2.c.1. Antiserum

As discussed earlier in this chapter, in the past RIA for morphine has been unsatisfactory for pharmacokinetic studies because of the poor specificity of antisera which readily cross-react with morphine metabolites, in particular the two major glucuronide conjugates.

The antiserum used in the following studies is a specc antiserum raised in a sheep against an N-succinyl normorphine-bovine serum albumin conjugate (Guildhay Antisera Ltd, University of Surrey, Guildford). The binding characteristics of this antiserum are shown below in table 2.c.1.

It can be seen that there is significant cross reactivity with normorphine but not with other metabolites or derivatives of morphine. For clinical studies this is thought therefore to represent evidence of specificity for morphine since significant amounts of normorphine have not been detected in patients receiving regular oral morphine across a wide range of doses when measured by an HPLC with which normorphine can be readily detected in prepared standards (Sawe et al 1985, Joel personal communication, AlSayed O, personal communication).

Table 2.c.1

Cross reactivity of specific morphine antiserum (G/S/844-IIB)

Substance	Relative reactivity
Morphine	100
Diamorphine	<0.1
Codeine	<0.1
Normorphine	94
Morphine-3-glucuronide	0.015
Morphine-6-glucuronide	0.015

2.c.2. Assay Procedure

Reagents

1. (1,7,8(n)-^{3}H) dihydromorphine (DHM), specific activity 2.2-3.3TBq/mmol (70-90Ci/mmol) supplied by Amersham International plc (TRK 450). This is diluted 1:100 with ethanol (BDH-Analar) and stored at -20^{o}C. The working solution is prepared from this stock solution by further dilution using assay buffer to give a concentration which will yield around 2000 counts per minute per 100µl. This is equivalent to approximately 0.05pmol DHM.

2. 0.05M Phosphate buffer pH 7.4

Stock solution A:	Na_2HPO_4 anhydrous (0.1M)	14.2g
	Merthiolate	0.172g

Make up to 1 litre with distilled water.
Store at 4^{o}C.

Stock solution B:	KH_2PO_4 anhydrous (0.1M)	13.6g
	Merthiolate	0.172g

Make up to 1 litre with distilled water
Store at 4^{o}C.

The solutions are mixed in suitable volumes (approx. 4:1) to yield a pH of 7.4, diluted 1:1 with distilled water and stored at 4^{o}C.

3. Dextran-coated charcoal prepared by mixing overnight at 4^{o}C a 2.5g% suspension of Norit A (Sigma) containing a 0.25g% suspension of Dextran T-70 (Pharmacia). The fines are then removed by centrifugation and the charcoal resuspended in phosphate buffer and stored at 4^{o}C.

4. Assay buffer containing 1g gelatin (BDH) and 6g sodium chloride in 1 litre of phosphate buffer stored at 4^{o}C.

5. Antiserum diluted with assay buffer so that 50% of the maximum bound label is bound, as determined by an antiserum dilution curve.

6. Standard solutions of morphine alkaloid (McFarlane Smith Ltd, Edinburgh) prepared in ethanol and diluted in assay buffer.

7. Scintillation cocktail (Optiphane Safe LKB Instruments Ltd)

Preparation of samples

No extraction procedure of the samples is required for this RIA. At least 3 dilutions are prepared of the sample using assay buffer, each dilution being assayed in duplicate.

Procedure

(i) The assay is carried out in plastic tubes (LP3, Luckhams Ltd).

(ii) Diluted sample or standard made up to 400µl with assay buffer, 100 µl of diluted antiserum and 100 µl of diluted ^{3}H-dihydromorphine is incubated for 1 hour at 4^{o}C.

(iii) Phase separation is then carried out by incubation with 100ul dextran-coated charcoal for 10 minutes followed by centrifugation at 2500 rpm for 10 minutes.

(iv) 0.5mls of supernatant is removed and mixed with 4mls of scintillation cocktail.

(v) Each sample is then counted for at least 3 minutes.

(vi) A standard curve is constructed from which the value of each unknown sample is determined.

2.c.3 Sensitivity

The limit of detection of this assay for morphine in serum or plasma samples is approximately 0.1ng/ml.The recovery of morphine added to normal drug-free serum and the coefficient of variation for the assay is shown in table 2.c.2.

Table 2.c.2

Recovery of morphine added to drug-free serum and coefficients of variation for the specific RIA

Morphine concentration (ng/ml)	% Recovery (S.D.)		Coefficient of Variation
1	100.0	(0.04)	4.0%
10	105.0	(0.4)	3.8%
100	101.2	(6.4)	6.3%

2.d. RIA for Morphine metabolites

This technique for the measurement of concentrations of M3G and M6G is based on the differential radioimmunoassay described by Hand et al (1986). It takes advantage of the cross reactivity of certain antisera so that total concentrations of morphine and M3G and morphine and M6G can be measured. From these results, with a knowledge of the morphine concentration alone, determined by the specific RIA described in the previous section , the concentration of M3G or M6G glucuronide can be deduced by simple subtraction.

2.d.1. Antisera

a) Morphine-3-glucuronide

The antiserum used for measurement of total morphine and M3G was raised in a rabbit against a 6-succinyl morphine-bovine serum albumin conjugate (Guildhay Antisera Ltd, University of Surrey, Guildford). The binding characteristics of this antiserum are shown in table 2.d.1.

Table 2.d.1.

Cross reactivity of rabbit antiserum G/R/6.

Substance	Relative Reactivity
Morphine	100
Diamorphine	100
Codeine	100
Monoacetylmorphine	100
M3G	40
M6G	1.0

Normorphine, methadone and naloxone do not cross react.

As can be seen there is significant cross reactivity with M3G but not with other metabolites of morphine. In clinical practice patients will be taking either morphine or diamorphine and therefore this cross-reactivity is unlikely to be relevant in patient samples. Similarly, it is unlikely that both morphine and codeine will be administered together and the production of codeine by O-methylation, whilst a recognised minor pathway, results in negligible amounts of codeine being produced by metabolism in patients receiving morphine (Boerner et al 1975). Cross reactivity with M3G is not total and therefore a relative underestimate of M3G might be anticipated using this antiserum.

b) Morphine-6-glucuronide

The antiserum used for measurement of total morphine and M6G was raised in a goat against a 6-succinyl morphine-bovine serum albumin conjugate (Guildhay Antisera Ltd, University of Surrey, Guildford). The binding characteristics of this antiserum are shown in Table 2.d.2.

As can be seen there is complete cross reactivity with M6G and only slight cross-reactivity with M3G. Concentrations of "morphine equivalent" measured by this antiserum would therefore be expected to reflect the total morphine and M6G concentration present in a sample. However whilst there is only 3% cross-reactivity with M3G, the high concentrations present in patient samples may result in some overestimation of M6G using this antiserum.

Table 2.d.2.

Cross reactivity of goat antiserum G/G/I - VIIA

Substance	Relative reactivity
Morphine	100
Diamorphine	100
Codeine	100
Normorphine	<1
M3G	3
M6G	>100
Methadone	<0.1
Naloxone	<0.1

2.d.2. Assay Procedure

The assay procedure for these two non-specific assays is identical to that for the specific RIA described in section 2.c.2, except that an ^{125}I-labelled morphine tracer was utilised.

Standards prepared from morphine alkaloid solutions are used to construct the standard curve from which concentrations in samples are calculated. Since, however, it is recognised that the final concentration in patient samples represents morphine and morphine glucuronide, this is expressed in terms of "morphine equivalents".

The morphine glucuronide concentration is determined by subtraction of the morphine concentration obtained by measuring the sample using the specific RIA described in section 2c from the concentration of "morphine equivalents" obtained using the appropriate non-specific RIA as described in this section.

2.d.3. Sensitivity

For both M3G and M6G the lower levels of sensitivity are 0.1 ng/ml.

2.e Comparison of assay methods used; RIA versus HPLC

2.e.1 Introduction

The sensitive and specific measurement of morphine in body fluids has been a recurring problem in pharmacokinetic studies with this drug. In the following studies two assay methods have been used: RIA and HPLC, the details of which are given in the preceding sections.

In practice, RIA has considerable advantages over HPLC. It is far quicker in terms of sample analysis and the specific RIA described above does not require an extensive extraction procedure prior to analysis. This is an important factor in the day to day application of an assay in this series of studies which has generated several thousand individual samples. It has also enabled its application in not only plasma and serum but also CSF, bile and pleural fluid for which extraction procedures using HPLC have not been developed. In addition, the method has proven robust in regular use, in stark comparison to the HPLC method where numerous problems in reliability of the equipment and reproducibility of the results has been encountered.

The principal concern over the use of RIA lies in the possibility of cross-reaction by the antiserum with other metabolites of morphine which may be present in very high concentrations in plasma. HPLC has an important advantage over RIA in this respect providing specific results for not only morphine but also its individual metabolites. In the light of this we have attempted to correlate the specific RIA assay used in these studies with HPLC by measuring paired samples using both assay methods, and also by comparing the HPLC assay used with another similar HPLC assay.

2.e.2 HPLC vs HPLC

The HPLC assay used in these studies was developed in the Department of Clinical Pharmacology at St Bartholomew's Hospital, London. An identical assay is also used in the Department of Oncology, Hackney Hospital, London. A series of samples have therefore been exchanged between ourselves and the group at Hackney, and the results of these analyses on spiked samples, analysed blind, are shown in Table 2.e.1.

Table 2.e.1

Comparison of two HPLC assays for morphine and M6G with known standard solutions

Standard solution (ng/ml)	Morphine (ng/ml)		M6G (ng/ml)	
	Barts	Hackney	Barts	Hackney
5	4.6	4.0	6.5	4.2
12.5	12.5	8.1	9.4	8.4
25	24.4	20.6	27.6	21.1
50	54.1	40.8	50.5	42.1
62.5	62.0	61.3	62.2	63.2
100	83.8	81.0	97.5	84.2
Correlation coefficient				
a)HPLC vs Standard	0.99	0.99	0.97	0.99
b)HPLC vs HPLC	0.99		0.99	

2.e.3 HPLC vs RIA

The largest set of comparative data between these two assays is presented in Chapter 4.b., in which 300 samples representing two 12-hour profiles from a series of patients receiving regular morphine were analysed by both RIA and HPLC.

Figure 2.e.1 shows the correlation between the values for the area under the serum concentration versus time curve (AUC) derived from these samples.

In chapter 4.b it will be seen that there was a discrepancy in the relative bioavailability for controlled release morphine tablets obtained using the AUCs derived from this data. In an attempt to investigate this further these results have been analysed further using the method described by Bland and Altman (Bland and Altman 1986). This analysis is a more sensitive means of comparing two different assay methods than simple linear regression giving information on the relative levels obtained by one assay compared to the other by plotting the difference between the two assays against the mean concentration measured using the two assays. The mean difference indicates whether one assay is consistently higher or lower than the other and the limits of agreement represent the range within which 95% of measured concentrations will lie.

This has been carried out on two sets of 150 samples comprising those taken whilst the patient received morphine elixir and MST respectively, the samples containing concentrations of morphine ranging from 2.7ng/ml to 225ng/ml. The results of this analysis are shown in Table 2.e.2. This suggests that the RIA is tending to overestimate values particularly in Group 2 (MST) and the implications of this are discussed further in Chapter 4.b.

Figure 2.e.1

Correlation between the AUC obtained in 20 serum profiles analysed for morphine using both RIA and HPLC

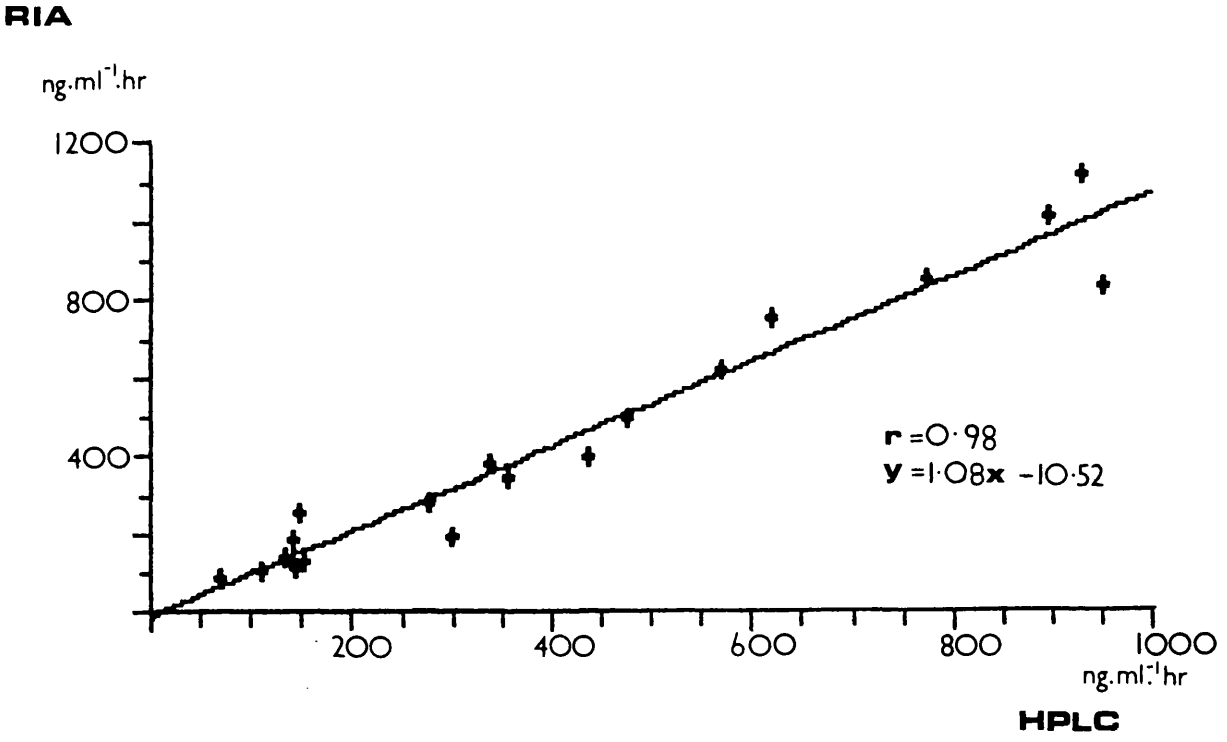


Table 2.e.2

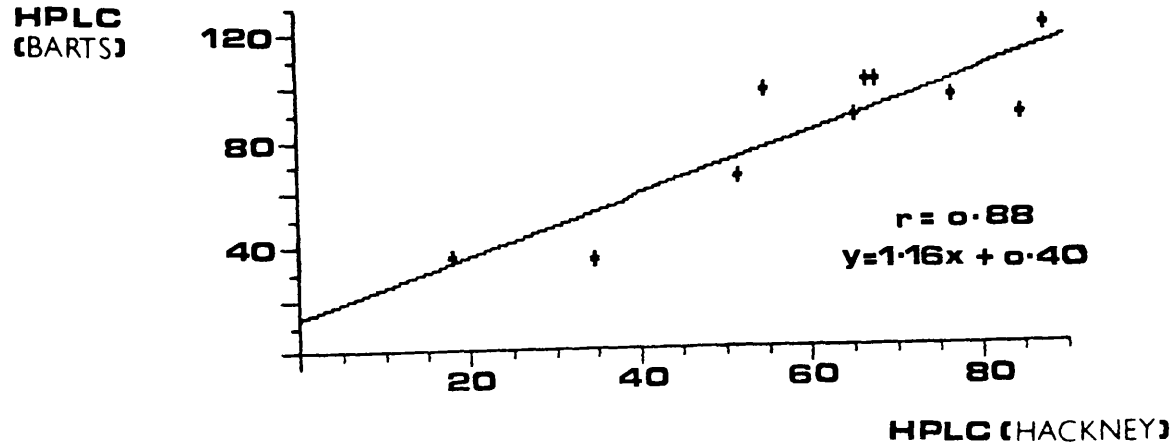
Comparison of HPLC and RIA using the mean difference over two series of 150 samples

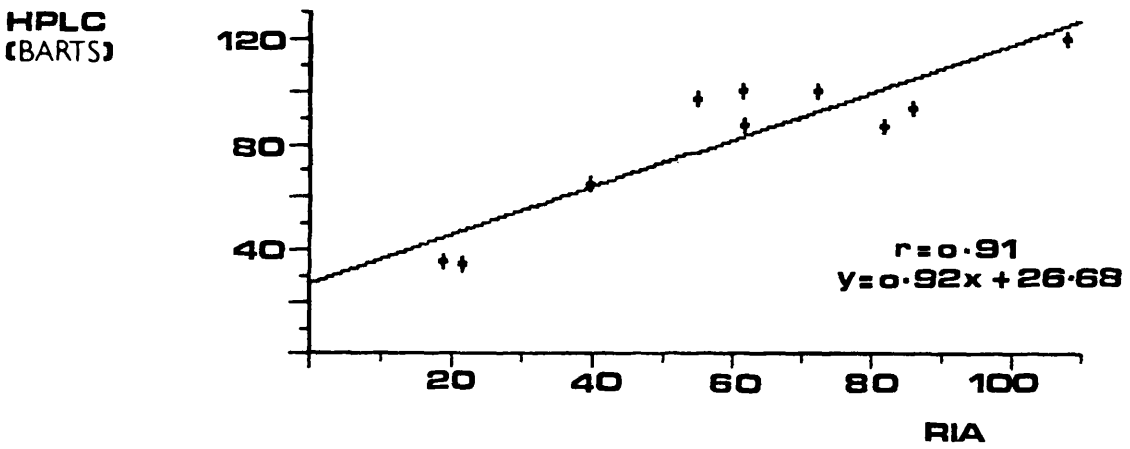
	Group 1 (elixir) n=150	Group 2 (MST) n=150
Mean difference RIA - HPLC	1.6	4.2
Standard deviation	14.4	8.1
Limits of agreement	-27.2 to 30.4	-12 to 20.5

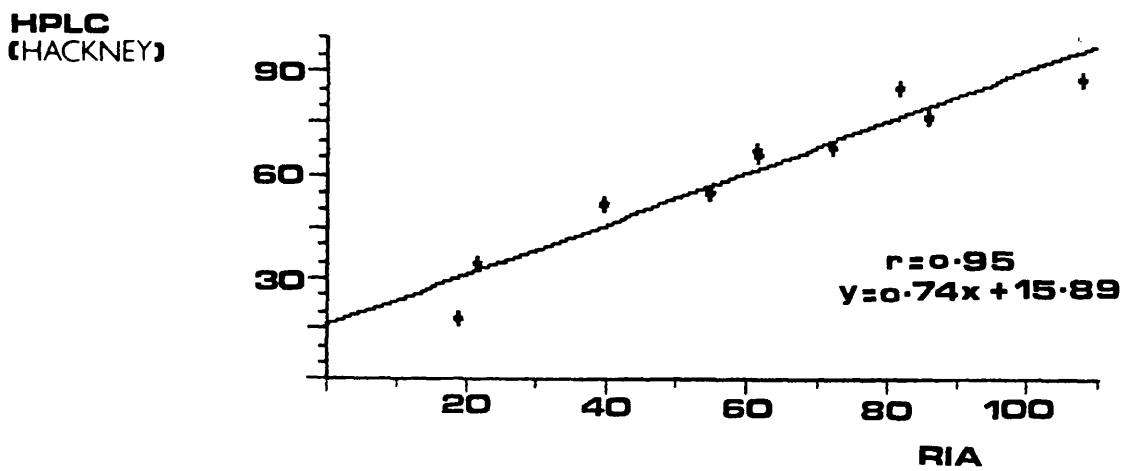
2.e.4 HPLC vs HPLC vs RIA

The results of a 3-way comparison between the St Bartholomew's HPLC, the Hackney HPLC and the RIA are shown in figure 2.e.2. Good correlation between the two assays is seen, with no statistically significant difference between them. It can be seen that the Barts HPLC tends to give relatively high results compared to both the Hackney HPLC and the RIA. The RIA tends to give relatively low results compared to both the HPLC assays which supports there being no significant degree of cross-reaction with this specific RIA.

Figure 2.e.2
Correlations between samples analysed by two different HPLC assays and RIA







2.e.5 Differential RIA

Only a limited number of samples have been analysed by both HPLC and differential RIA.

M6G has been measured in a series of 45 samples containing M6G concentrations between 5 and 100ng/ml using both HPLC and differential RIA. Linear regression of the RIA results against HPLC gives a regression line where y = 0.147 + 1.6x and the coefficient of correlation is 0.9601. These results have also been analysed by the method of Bland and Altman (Bland and Altman 1986) as shown in table 2.e.3, which shows that the RIA does tend to overestimate M6G concentrations compared to HPLC.

The validity of the differential RIA for measurement of M3G and M6G has also been investigated using recovery data from spiked samples. This is shown in Table 2.e.4. in which with the specific antiserum for morphine no interference from either M3G or M6G is seen.

With the G/G/1 antiserum (measuring total morphine + M6G),in samples spiked with morphine and M6G complete recovery of both morphine and metabolite is seen, (mean 98.5% ; CV 8.1%), but some recovery of M3G is also seen with ratios of morphine : M3G of > 1 : 10, despite only 3% cross-reactivity with M3G using this antiserum.

With the G/R/6 antiserum (measuring total morphine + M3G) in samples spiked with morphine and M3G less than 100% recoveries (mean 74.7%) are seen and some recovery of M6G occurs with ratios of morphine : M6G of 1 : 50 or more, despite only 1% cross-reactivity with M6G using this antiserum.

Table 2.e.3

Comparison of values for M6G measured by Differential RIA and HPLC.

Mean Difference (RIA - HPLC)	9.4 ng/ml
Standard deviation	9.4
Limits of agreement	-9.7 to 27.9

Table 2.e.4 Recovery data for differential RIA

a) Relative concentrations (molar ratios) of morphine : metabolite in each sample

Sample	Set 1 Morphine : M6G	Set 2 Morphine : M3G
1	1 : 0	1 : 0
2	1 : 1	1 : 1
3	1 : 5	1 : 5
4	1 : 10	1 : 10
5	1 : 50	1 : 50
6	1 : 100	1 : 100

b) Recovery (%) of *expected concentrations of morphine or morphine and metabolite

Sample	Antiserum 844 (morphine)		Antiserum G/G/1 (morphine + M6G)		Antiserum G/R/6 (morphine + M3G)	
	Set 1	Set2	Set 1	Set 2	Set 1	Set 2
1	100.0%	100.0%	86.0%	-	85.4%	105.4%
2	90.0%	96.0%	103.2%	92.3%	90.0%	46.5%
3	94.0%	91.0%	110.6%	112.8%	93.3%	88.4%
4	110.0%	78.0%	94.3%	129.6%	82.5%	83.3%
5	100.0%	90.0%	103.7%	143.7%	124.4%	72.2%
6	114.0%	89.0%	92.9%	197.2%	122.6%	52.4%

*The expected concentration is based on 844 antiserum measuring only morphine, G/G/1 measuring (morphine + M6G) and G/R/6 measuring (morphine + M3G). Percentage recoveries of >100% therefore indicate possible cross-reactivity.

2.e.6 Discussion

Comparison of the specific RIA for morphine and HPLC shows good agreement across a wide range of serum morphine concentrations in a large number of samples, and we are therefore confident that this particular RIA is producing accurate measurement of morphine in plasma.

The technique of differential RIA for measurement of morphine-3-glucuronide and morphine-6-glucuronide is less satisfactory and is unlikely to match HPLC for absolute accuracy by virtue of the wide spectrum of cross reactivity of the nonspecific antisera. This is demonstrated by the recovery data shown above where ratios of morphine : metabolite of $\geq$ 1 : 50 result in over-estimation of the total concentration of morphine and metabolite. For M6G relative concentrations of around 1 : 10 are expected in blood samples and this cross-reactivity may therefore not be significant in clinical samples. However ratios of morphine : M3G of 1 : 50 or more may be anticipated and some over estimation of M6G due to the cross-reactivity with M3G is possible. Conversely under-estimation of M3G may in fact occur due to the incomplete cross-reactivity of the G/R/6 antiserum with M3G.

It is also important to take into account the influence of different standard solutions being used for calibration, HPLC using M3G and M6G in aqueous solution whilst RIA uses morphine standards and relates the M6G concentration to "morphine equivalents".

Despite this, the limited comparisons performed together with the good recovery figures from known spiked samples suggest that a good estimation of M3G and M6G levels can be obtained by this technique.

2.f METHOD OF BLOOD SAMPLING

2.f.1 Introduction

In addition to the specific problems related to assay methodology which has been discussed,a further source of variation in results between different studies is the preparation of samples prior to measurement. This variable has received little attention in the past. A review of 57 publications between 1975 and 1987 in which morphine levels in blood were measured reveals considerable disparity between the use of plasma or serum, glass or plastic tubes and the anticoagulant used in the preparation of plasma samples, as shown in table 2.f.1.(overleaf). It has been suggested that glass may adsorb morphine onto its surface, thereby lowering the values obtained when samples are collected in glass tubes (Whelpton 1983, Gordon 1986) although one study has reported negligible binding of N-methyl-^{14}C-morphine to glass (Olsen et al,1975). Interaction between heparin and aqueous morphine has also been reported (Baker et al 1985). There are however no data available on the influence of sample preparation on specific assay results for morphine, M3G or M6G. This study was therefore performed to investigate the influence of sample preparation on results for morphine, M3G and M6G, using the HPLC assay.

Table 2.f.1

Details of sample preparation in published reports 1975-1987

PLASMA			
Anticoagulant	:	Heparin	19*
		Oxalate	1
		Citrate	1
		EDTA	2
		Not stated	19
Total			42
SERUM			11+
NOT STATED			4
TOTAL			57

* 6 used plastic tubes, 2 glass tubes, remainder not stated

\+ 1 used plastic tubes, 5 glass tubes, remainder not stated

2.f.2 Materials and Method

(i) Sample collection

Six different methods of sample preparation were chosen for investigation. These are detailed in table 2.f.2. Venous blood samples were obtained from 12 patients with advanced cancer receiving regular oral morphine either as 4-hourly morphine sulphate elixir or 12 hourly controlled release morphine sulphate tablets (MST Continus). Sampling was performed at the time of obtaining routine blood samples for specific clinical indications and the study was approved by the Ethics Committee of the Royal Marsden Hospital. 30ml of venous blood from each patient was used and divided into six aliquots of 5mls prepared as shown in table 2.f.2. The resultant plasma or serum was then transferred to plastic storage tubes and stored at -20^{o}C until analysis.

(ii) Assay Technique

Samples were analysed for morphine, M3G and M6G using the HPLC assay.

(iii) Statistical Analysis

The results for morphine, M3G and M6G from individual patients have been compared by two way analysis of variance.

Table 2.f.2

Details of sample preparation

Sample	Tube	Anticoagulant	Preparation	Superatant
1	Glass	None	Rolled 30 minutes then centrifuged	Serum
2	Plastic	None	Rolled 30 minutes then centrifuged	Serum
3	Glass	Lithium Heparin	Centrifuged immediately	Plasma
4	Plastic	Lithium Heparin	Centrifuged immediately	Plasma
5	Glass	*Sodium Citrate	Centrifuged immediately	Plasma
6	Glass	Potassium Oxalate	Centrifuged immediately	Plasma

*Present as 0.5ml of solution in the tube

All samples centrifuged at 3500 rpm for 10 minutes.

The tubes for samples 1,3,5 and 6 were made of borosilicate glass, and were not silanized.

The tubes for samples 2 and 4 were made of polystyrene/polypropylene plastic (Sterilin Ltd).

2.f.3 Results

Details of the 12 patients from whom blood was used for this study, together with their morphine dose, formulation and duration of medication are shown in table 2.f.3.

The results for each of the six sampling methods have been pooled to investigate the influence of sampling method on the concentrations of morphine, M3G and M6G measured. These results are shown in figures 2.f.1 - 2.f.3.

Comparing sampling methods 1 to 4 to show the influence of using a glass or plastic tube showed no significant difference in morphine, M3G or M6G levels. This was repeated to compare serum with plasma and again no significant difference in morphine or M6G levels was seen but for M3G significantly lower levels were obtained in plasma samples ($p=0.0001$).

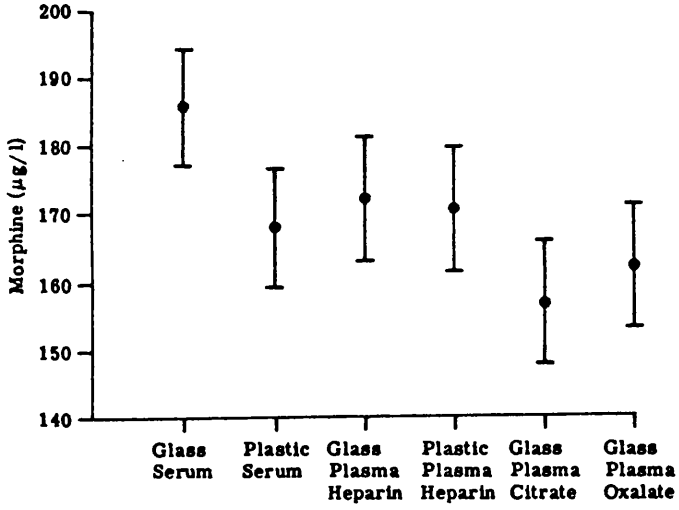
Table 2.f.3

Subject	Total 24 hour Dose (mg)	*Morphine Preparation	Duration on present dose
1	60	E	8 days
2	180	E	7 days
3	360	M	9 days
4	900	E	2 days
5	960	E	4 days
6	300	E	5 days
7	600	E	22 days
8	480	E	8 days
9	600	E	4 days
10	60	M	1 day
11	360	E	13 days
12	360	E	21 days

* E = 4 hourly morphine elixir

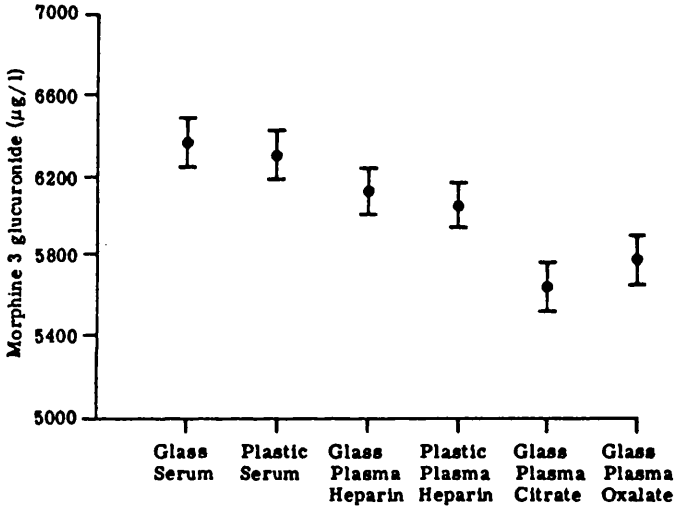
M = 12 hourly controlled release tablets (MST-Continus)

Figure 2.f.1
Morphine



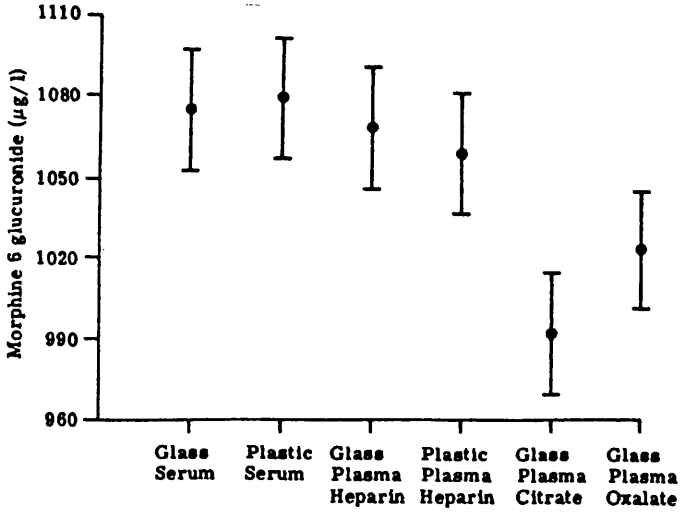
Bars represent 95 % least significant difference intervals
Analysis of variance; p = 0.049

Figure 2.f.2
M3G



Bars represent 95 % least significant difference intervals
Analysis of variance; p<0.0001

Figure 2.f.3
M6G



Bars represent 95 % least significant difference intervals
Analysis of variance; p = 0.0009

2.f.4 Discussion

These data indicate that the method of blood sample preparation may influence the measurement of morphine, M3G and M6G. The hypothesis that the use of glass tubes may reduce morphine levels is not supported, nor has any significant interaction with heparin been demonstrated. The use of sodium citrate as an anticoagulant for the preparation of plasma samples has produced lower levels of morphine, M3G and M6G compared to the other methods of sample preparation. This may be attributed to a dilution effect rather than a specific interaction since, in contrast to heparin and oxalate anticoagulants, sodium citrate is present in sample tubes in solution.

A lower concentration of M3G was found in plasma than in serum. It is possible that this difference reflects not only the use of anticoagulant in the plasma samples but also the difference in the time taken for sample preparation. Plasma samples were centrifuged immediately whilst the serum samples were rolled for 30 minutes at room temperature prior to centrifugation. During this time passage of morphine and metabolites across cell membranes could occur and be a further factor in determining the final concentration measured in serum. It is not clear why M3G was reduced in plasma but no effect was seen on concentrations of morphine and M6G.

These results emphasize the importance of attention to the method of blood sampling used when comparing data on the pharmacokinetics of morphine and its metabolites. This should be carefully considered in the design of future studies. The majority of studies to date which give details of sample preparation have used plastic lithium heparin tubes and no disadvantage for this emerges from the results of this study. On the basis of this plastic lithium heparin tubes have been

used for all except two studies described in the following chapters. The two exceptions used serum samples, having been initiated prior to these results being available.

CHAPTER 3

PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES WITH MORPHINE IN HEALTHY VOLUNTEERS

3.a Pharmocokinetics of morphine after :

(i) IV injection
(ii) Oral elixir
(iii) Controlled release tablet (MST)
(iv) Buccal tablet

3.b Pharmacokinetics of M6G after :

(i) IV injection
(ii) Oral elixir
(iii) Controlled release tablet (MST)
(iv) Buccal tablet

3.c Concentration - effect relationships for :

(i) Morphine
(ii) M6G

CHAPTER 3

PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES WITH MORPHINE IN HEALTHY VOLUNTEERS

3.a Pharmacokinetics of Morphine after

(i) IV Injection
(ii) Oral Elixir
(iii) Controlled Release Tablet (MST-Continus)
(iv) Buccal Tablet

3.a.1 Introduction

The first choice route of administration in chronic pain is the oral route and two formulations of morphine are available for use in this way, aqueous morphine solution (MSS) and a controlled release tablet based on the Continus system (MST Continus). As discussed in Chapter 1.a there is little data available for the absolute bioavailability of oral morphine.

Recently there has been interest in buccal administration of morphine which may be of particular value in patients who are unable to swallow. A controlled release formulation, again based on the Continus system, has been produced but no data on its bioavailability or efficacy is available.

Few of the previous studies in morphine pharmacokinetics have attempted to document the pharmacodynamics of morphine or to relate this to the observed pharmacokinetics and no correlation between blood levels and morphine analgesia have been demonstrated (Dahlstrom et al 1978).

The object of this study was therefore to determine the bioavailability of morphine and morphine-6-glucuronide following a

single dose of intravenous morphine sulphate, oral aqueous morphine sulphate solution, controlled release oral morphine sulphate tablet and a controlled release buccal morphine sulphate tablet in normal volunteers, to determine the pharmacokinetics of both morphine and morphine-6-glucuronide and to correlate this data with pharmacodynamic measurements made during the study.

3.a.2 Subjects and Method

Six healthy volunteers (four female, two male) were used with a mean age of 31 years (range 26-40). One regular smoker was included in these six subjects. All were screened for normal hepatic and renal function by routine blood biochemistry. The study had approval of the Ethics Committee of the Royal Marsden Hospital and written informed consent was obtained from each subject.

Subjects were fasted from midnight on the study day and at 8am a forearm intravenous cannula was placed in situ. The four formulations studied were :

(i) Intravenous morphine sulphate, 5mg

(ii) Oral aqueous morphine sulphate solution, 10mg

(iii) Controlled release oral morphine sulphate tablet (MST-Continus), 10mg

(iv) Controlled release buccal morphine sulphate tablet (Napp Laboratories Ltd), 10mg

The oral solution was freshly prepared no more than 24 hours prior to administration in the form of aqueous solution with no added preservative. The buccal tablet was obtained at an early stage in its development by Napp laboratories and is not available commercially. It is based on the Continus controlled release system used in the oral

tablet MST-Continus.

The subjects received each oral formulation with 100mls of tap water, at intervals of at least one week. The intravenous injection was administered over 2 minutes. The following order of administration was used; oral solution, buccal tablet, MST tablet, IV injection. After administration the subjects remained supine, fasting, for two hours. Venous blood sampling was performed at 15, 30, 45, 60 minutes, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hours, for the oral and buccal forms, and at 2, 5, 10, 15, 30, 45, and 60 minutes, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours after the intravenous injection. Venous blood was collected into a plastic heparinised tube and spun immediately at 3,500 rpm for 10 minutes. Plasma was separated and stored at -20^{o}C prior to analysis.

During the study, pharmacodynamic measurements were performed at 30 minutes, 1 hour, 2, 3, 4, 5, 6, 8, 10, and 12 hours. These included pupil size, pulse and blood pressure, peak expiratory flow rate, assessment of dry mouth, completion of visual analogue scales for nausea, relaxation, drowsiness and mood, and completion of a short digit symbol substitution test for psychomotor function. A questionnaire into the acceptability of the buccal tablet was also completed by each subject after receiving this formulation.

Caffeine containing drinks and alcohol were forbidden during the course of the study, but normal activities, eating and drinking were resumed after the initial 2 hours.

3.a.3 Assay Method

Measurement of morphine was performed using the specific radioimmunoassay described previously.

3.a.4 Statistical Analysis

The area under the curve from time zero to infinity $AUC_{(o-\infty)}$ and elimination half life was calculated using the trapezoidal method with the STRIPE program (Johnston and Woollard 1983). Clearance was determined by the ratio of dose over AUC. Elimination half-life ($t_{\frac{1}{2}}$)and volume of distribution (V_d) has been calculated using SIMP (Johnston 1985) based on a two compartment model for morphine using a weighting of $1/y^2$ to obtain the best fit between measured concentrations of morphine and the model. Data has been compared using Student's paired t-test.

3.a.5 Results

The individual profiles of plasma morphine for each subject are shown in figure 3.a.1.

Table 3.a.1 gives details of elimination half-life, clearance and volume of distribution after intravenous morphine. The $AUC_{0-\infty}$ for morphine after each of the four routes together with absolute bioavailability for each of the oral and buccal routes is shown in Table 3.a.2.

Table 3.a.3 shows the values for peak plasma concentration of morphine (C_{max}) and time to peak plasma concentration of morphine (t_{max}).

Table 3.a.4 shows the time to dissolution of the buccal tablet together with other subjective assessments of its use. All subjects were able to eat and drink normally whilst the tablet was in situ with varying degrees of acceptability as recorded. The characteristic bitter taste of morphine was noticeable on each occasion.

Figure 3.a.1

Individual plasma morphine concentration vs time profiles for individual subjects

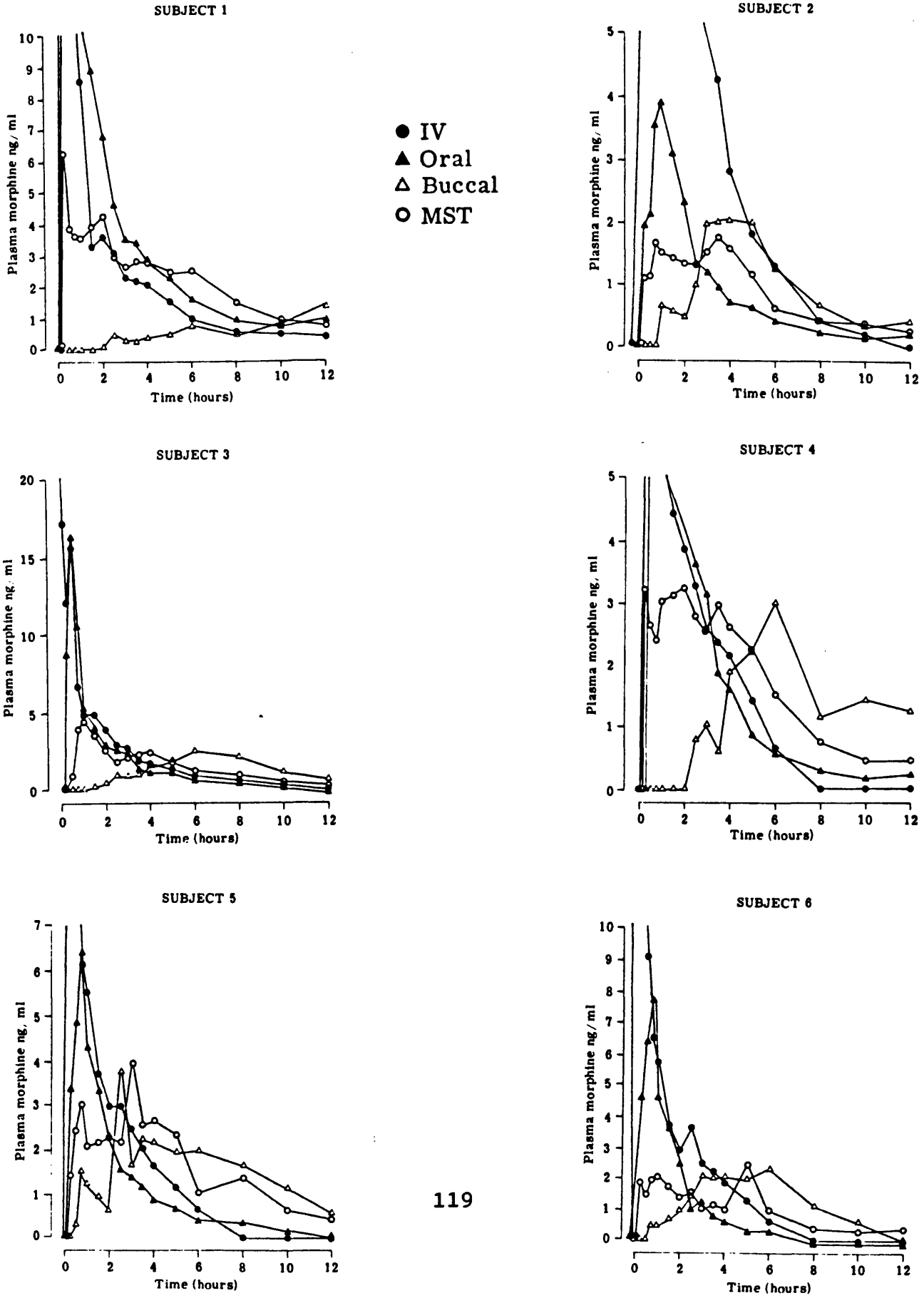


TABLE 3.a.1

Pharmacokinetic parameters for morphine after IV administration

Subject	$t_{½}$ (hours)	Clearance (ml min^{-1} kg^{-1})	Volume of Distribution (l Kg^{-1})
1	3.0	13.9	7.8
2	1.4	16.1	2.7
3	2.0	21.0	7.0
4	1.6	40.4	4.1
5	1.5	29.3	4.7
6	1.5	22.2	5.7
MEAN	1.8	23.8	5.3
SEM	0.2	4.0	0.7

Table 3.a.2

AUC and absolute bioavailability for morphine

(IV dose corrected to 10mg dose)

AUC ($ng.ml^{-1}.hr$)

SUBJECT	IV	ORAL SOLUTION	BUCCAL	MST
1	102.6	46.5	18.1	31.9
2	106.7	11.9	12.6	11.5
3	85.1	24.9	18.8	19.8
4	107.0	23.0	26.1	23.6
5	74.7	14.3	20.0	21.0
6	75.2	12.6	15.1	14.6
MEAN	91.9	22.2	18.5	20.4
SEM	6.3	5.4	1.9	2.9

ABSOLUTE BIOAVAILABILITY (%)

1	45.3	10.6	31.1
2	11.2	11.8	10.7
3	29.2	22.1	23.2
4	21.5	20.5	22.0
5	19.2	26.7	28.1
6	16.7	20.1	19.4
MEAN	23.8	18.6	22.4
SEM	4.9	4.9	2.9

Table 3.a.3

C_{max} and t_{max} for morphine

	C_{max} (ng/ml)			
	IV	ORAL SOLUTION	BUCCAL	MST
SUBJECT				
1	315.0	16.2	1.4	6.2
2	276.0	3.9	2.0	1.8
3	314.0	16.4	2.5	4.5
4	574.0	12.7	3.0	3.2
5	274.0	6.5	3.7	3.9
6	288.0	7.8	2.3	2.4
MEAN	340.2	10.6	2.5	3.7
SEM	47.3	2.1	0.3	0.6
	t_{max} (hours)			
1	0.03	0.25	>12.0	0.25
2	0.03	1.00	4.0	3.5
3	0.03	0.50	6.0	1.0
4	0.03	0.75	6.0	2.0
5	0.03	0.75	2.5	3.0
6	0.03	0.75	6.0	5.0
MEDIAN	0.03	0.75	6.0	2.5

Table 3.a.4

Subject acceptability of the buccal morphine tablet

Subject	Time to dissolution of tablet (hours)	Taste		Discomfort (time in hours)
		Nature	Duration	
1	10	Bitter	3	Yes (4-12)
2	4	Bitter	3	No
3	8	Bitter	5	No
4	12	Bitter	2	No
5	6	Bitter	6	No
6	6	Bitter	6	Yes (2)

3.a.6 Discussion

The pharmacokinetic parameters after intravenous administration of morphine in these healthy volunteers are in keeping with those reported from other studies. There are no reliable data for the bioavailability of oral elixir in normal volunteers but studies in cancer patients have reported values between 38 and 47% (Sawe et al 1981, 1985). The findings in this study show a lower absolute bioavailability in healthy volunteers perhaps reflecting the inclusion of patients with impaired bowel or hepatic function in the patient studies. One study has reported a bioavailability of 100% for oral solution in patients but the assay method employed in this study is now recognised to have cross-reacted with metabolites giving a falsely elevated result (McQuay et al,1983).

At the time of completion of this study, preliminary results from a similar volunteer study were reported in which bioavailability in 8 subjects under the age of 30yrs was compared with 9 subjects aged 68-90 yrs (Baillie et al 1987). The mean absolute bioavailability for MSS was 20.1% in the young patients and 29.3% in the elderly; for MST it was 22.9% for the young subjects and 28.7% for the elderly. These differences were not significantly different. The morphine assay used in this study was a specific RIA and the results are very similar to those presented here.

The bioavailability of controlled release morphine sulphate (MST Continus) was not significantly different from that after oral aqueous solution, in keeping with a number of studies (Hanks et al 1981, Poulain et al 1986, Savarese et al 1986, Sloan et al 1987,) which have shown the relative bioavailability of MST and aqueous solution to be between 85 and 94%. The absolute bioavailability of 22.4% is similar

to that reported by Vater (Vater et al 1984).

The buccal tablet resulted in a slightly lower AUC for morphine compared to aqueous solution and MST but with greater inter-subject variation, and no statistical difference in absolute bioavailability compared to the two oral formulations. In two subjects the AUC is derived because they did not reach an elimination phase at 12 hours and these results should therefore be interpreted with caution. The t_{max} was considerably later than with the oral controlled release preparation and in subject 1 was not reached at 12 hours. Subject acceptability of this preparation was poor due principally to the release of a bitter taste for considerable periods and to local discomfort.

3.(b) Pharmacokinetics of M6G after :

(i) IV Morphine injection

(ii) Oral Morphine elixir

(iii) Controlled Release Morphine tablet (MST-Continus)

(iv) Buccal Morphine tablet

3.b.1 Introduction

M6G is a highly active metabolite of morphine (Yoshimura et al 1973), but little is known about its pharmacokinetics. We have proposed that a significant component of the pharmacodynamic effects of morphine is the action of M6G (Hanks et al 1987), and hence an important part of this volunteer study was to determine the pharmacokinetics of M6G.

3.b.2 Patients and Methods

These have been described in 3(a) above, the same blood samples being used for both morphine and M6G levels.

3.b.3 Assay

M6G levels were measured using the differential radioimmunoassay technique described in chapter 2.

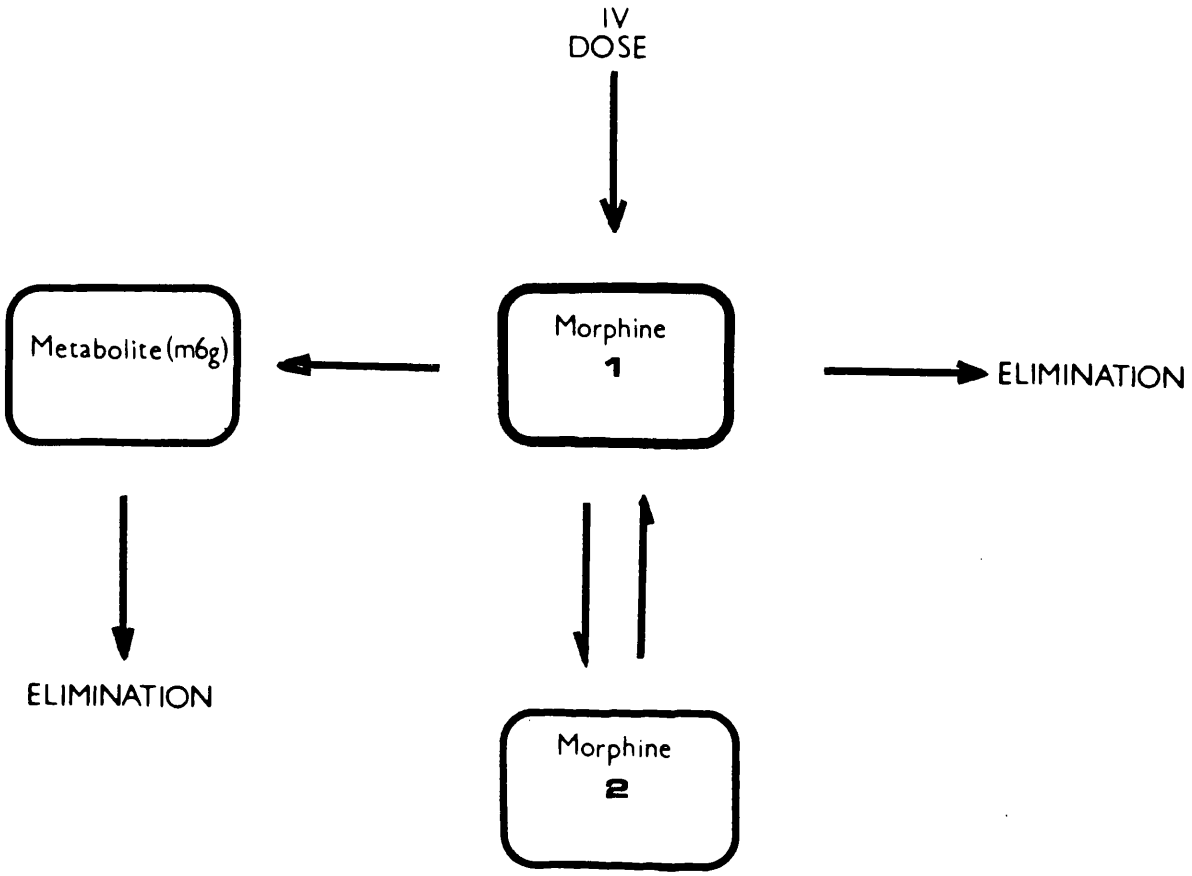
3.b.4 Statistical Analysis

The $AUC(_{0-\infty})$ was calculated using the STRIPE program. Other pharmacokinetic parameters for M6G were calculated using the SIMP program (Johnston 1985) based on a two-compartment model for morphine and a single compartment for the metabolite M6G as shown in

figure 3.b.1, using a weighting of 1/y to obtain the best fit between measured concentrations and the pharmacokinetic model. This model was used because the curve stripping program (STRIPE) does not take account of the continued production of M6G from morphine during the study period, and is therefore inaccurate in estimating the parameters dependant upon the rate of change in M6G concentration, although still accurate for measuring the overall AUC. Concentrations of morphine and M6G measured in ng/ml were converted to nanomolar concentrations using a conversion factor of 2.636 for morphine and 2.0099 for M6G which is based on the molecular weights of morphine sulphate in the form of $(morphine)_2SO_4.5H_2O$ and M6G in the form of $M6G.2H_2O$ as used for standards in the HPLC assay.

Figure 3.6.1

Two compartment model for morphine with single metabolite compartment



3.b.5 Results

The $AUC_{0-\infty}$ for morphine-6-glucuronide and the relative amount of this metabolite compared to morphine in plasma after each of the four routes of administration is shown in Table 3.b.1. Significantly more metabolite is found in plasma after oral administration or buccal administration than after intravenous administration ($p<0.001$).

Table 3.b.2 shows the values for peak plasma concentration of M6G (C_{max}) and time to peak plasma concentration of M6G (t_{max})

Table 3.b.3 shows the values for elimination half-life ($t_{½}$) and volume of distribution (V_d) for M6G derived using the kinetic model shown in figure 3.b.1.

Table 3.b.1

AUC and morphine:M6G ratios

(IV data corected to 10mg dose)

	AUC ($ng.ml^{-1}.hr$)			
SUBJECT	IV	ORAL SOLUTION	BUCCAL	MST
1	210.4	310.7	227.9	206.5
2	189.8	185.2	138.0	199.5
3	170.9	149.6	144.3	151.7
4	247.1	257.8	300.1	191.7
5	140.6	218.9	268.1	254.0
6	143.7	131.6	145.0	221.5
MEAN	183.7	209.0	204.0	204.2
SEM	20.2	27.6	26.6	13.8

	M6G : MORPHINE RATIO			
1	2.0:1	6.7:1	12.6:1	6.5:1
2	1.8:1	15.5:1	10.9:1	17.3:1
3	2.0:1	6.0:1	7.7:1	7.7:1
4	2.3:1	11.2:1	11.5:1	8.1:1
5	1.9:1	15.3:1	13.4:1	12.1:1
6	1.9:1	10.5:1	9.9:1	15.1:1
MEAN	*1.98:1	10.9:1	11.0:1	11.1:1
SEM	0.1	1.6	0.8	1.8

*Difference is significant compared to oral MST and buccal routes, $p<0.001$

Table 3.b.2

C_{max} and t_{max} for M6G

	IV	ORAL SOLUTION	BUCCAL	MST
		C_{max} (ng/ml)		
SUBJECT				
1	20.1	61.6	20.5	29.8
2	17.4	59.9	24.7	30.6
3	16.8	50.4	24.0	20.9
4	85.7	53.1	16.3	41.6
5	19.5	66.2	31.4	47.4
6	12.9	33.7	18.0	42.3
MEAN	28.7	54.1	22.5	35.4
SEM	11.4	4.7	2.2	9.9
		t_{max} (hours)		
1	1.0	0.75	>12.0	2.0
2	1.5	2.0	4.0	2.0
3	0.5	1.0	6.0	2.0
4	0.03	1.0	10.0	2.0
5	0.75	1.0	6.0	1.0
6	0.75	1.0	6.0	2.5
MEDIAN	0.75	1.0	6.0	2.0

Table 3.b.3
Elimination half-life and volume of distribution for M6G

Subject	Elimination half-life ($t_{½}$) (hours)	Volume of Distribution (V_d) (l/kg)
1	3.8	3.1
2	1.9	3.0
3	2.4	2.8
4	1.3	3.1
5	1.8	4.4
6	1.8	5.2
MEAN	2.2	3.6
S.E.	0.4	0.4

3.b.6 Discussion

The amount of M6G present in plasma after each of the oral and buccal preparations was remarkably similar. Relatively more metabolite is produced after oral administration than intravenous administration and it is perhaps a little surprising that a similar amount is also produced after buccal administration when a reduced first pass effect would be expected. This may reflect swallowing of morphine released from the buccal preparation since no measures were taken to prevent this. Good absorption by the buccal route in normal volunteers has however been previously demonstrated (AlSayed et al 1987).As with morphine (chapter 3.a) the values of AUC are likely to be less reliable than by the intravenous or oral routes because of the plasma profile obtained and the need to model the elimination phase on the IV data.

The ratio of M6G to morphine of 2:1 after intravenous administration and around 11:1 after oral administration is greater than that reported by Sawe et al (1985) in cancer patients although it is in keeping with our own data in cancer patients receiving regular oral morphine (see Chapter 4). The possibility of some over-estimation of M6G using the differential RIA may also account in part for this discrepancy.

A consistently longer time to peak plasma concentration is seen for M6G compared with morphine. This is in keeping with the prolonged and late clinical effects sometimes seen after a single dose of morphine, and which were observed in these subjects, and may be further evidence of a role for M6G in the pharmacodynamic effects of morphine.

The volume of distribution is low compared with morphine, mean values being 5.0 for morphine and 3.6 for M6G, as would be expected with a polar metabolite of a more lipid soluble drug, and this still

represents significant distribution of M6G outside the vascular compartment. A recent preliminary report (Osborne et al 1988) of the pharmacokinetics of M6G after intravenous injection in a single patient with normal renal function describes an elimination half life of 1.9 hours and a volume of distribution of 14.7 l/70kg. The elimination half life is in good agreement with the data presented here but the volume of distribution is considerably lower. One explanation for this discrepancy may be the inherent inaccuracies in using indirect methods to derive the value of a metabolite after administration of the parent drug compared to direct measurement after intravenous injection of the metabolite. Other considerations are that there may be an interaction between morphine and M6G affecting distribution which would not be seen after injection of M6G alone, and also that it has been shown that there is a significant effect of age on morphine distribution (and possibly therefore also M6G) with a mean value for the volume of distribution for morphine of 2.1 l/kg being found in healthy subjects under 50 compared to 1.1 l/kg in subjects over 50 (Owen et al 1983). The mean age of the subjects in this study was 31 years so that a relatively high value for the volume of distribution may be expected if the distribution of M6G is similar to morphine with respect to age.

A larger series of patients in which the pharmacokinetic parameters of M6G are measured directly after intravenous injection of M6G is required against which the modelled data presented here can be compared.

3.c Concentration-Effect Relationships

(i) Morphine

(ii) M6G

3.c.1 Introduction

An important component of the volunteer study described in this chapter was the measurement of certain pharmacodynamic effects of morphine during the period of blood sampling following the administration of morphine.

There is no evidence in the current literature of a relationship between the pharmacodynamic effects of morphine, in particular analgesia, and blood levels of morphine. A direct relationship between administered dose and plasma morphine concentration as measured by radioimmunoassay has been shown (Neuman et al 1982) but no relationship between plasma concentrations and pain scores could be demonstrated in a study of 7 cancer patients receiving long term morphine (Sawe et al 1983). A more complex pharmacokinetic analysis of morphine kinetics in rats using multi-compartment models failed to show a direct relationship between analgesic effect and morphine levels in either the plasma compartment or the brain compartment (Dahlstrom et al 1978).

3.c.2 Method

During the 12 hour study period the following pharmacodynamic measures were performed on the volunteers:

1. Resting pulse and blood pressure.

2. Pupil size using a simple "pupil gauge" composed of rows of dots of varying distances apart. This method has previously been validated against photographic pupil measurement (Maserti, M personal communication).

3. Peak expiratory flow rate (PEFR) using a mini peak flow meter.

4. A categorical four point scale assessment of dry mouth (none, mild, moderate or severe).

5. Visual Analogue Scales using a 100mm line were completed for

   a) Nausea

   b) Drowsiness

   c) Depression

   d) Relaxation

5. A short digit symbol substitution test (DSST) was performed (Hindmarch 1980), the subject being timed whilst completing three rows of the test shown in Figure 3.c.1.

Figure 3.c.1

Example of Digit Symbol Substitution Test used

DSST

Subject ..... Work Period No / Session No } ..... Date ..... Time .....

Drug .....

1	2	3	4	5	6	7	8	9	0
Δ	⁓	⊣	⋈	⋌	⋔	⊥	⊓	⋈	⌙

1	4	0	9	5	3	7	2	6	8	7	3	4	2	9	1	8	5	0	6

9	2	8	3	6	1	5	7	0	4	6	1	5	9	7	8	4	2	3	0

3	7	6	0	8	2	9	4	5	1	0	2	8	6	5	9	3	1	7	4

3.c.3 Results

a) No significant changes were seen during the twelve hour study period after any drug preparation in any subject for

1. Pulse and blood pressure
2. Pupil size
3. Peak expiratory flow rate
4. Digit symbol substitution test timings
5. Visual analogue scale scores for depression

b) Only one subject recorded a positive nausea score on a single occasion at five hours after receiving MST.

c) Changes were seen in the visual analogue scale scores for drowsiness and relaxation and the categorical scale score for dry mouth for each of the formulations. These were most marked after intravenous and oral aqueous solution where pronounced peak effects were seen. These scores are shown in appendix 1.
In figure 3.c.2 the changes in the mean scores for drowsiness, relaxation and dry mouth, have been plotted against plasma levels of morphine and M6G.

Figure 3.c.2
Changes in mean scores for drowsiness, relaxation and dry mouth with plasma profiles of morphine and M6G

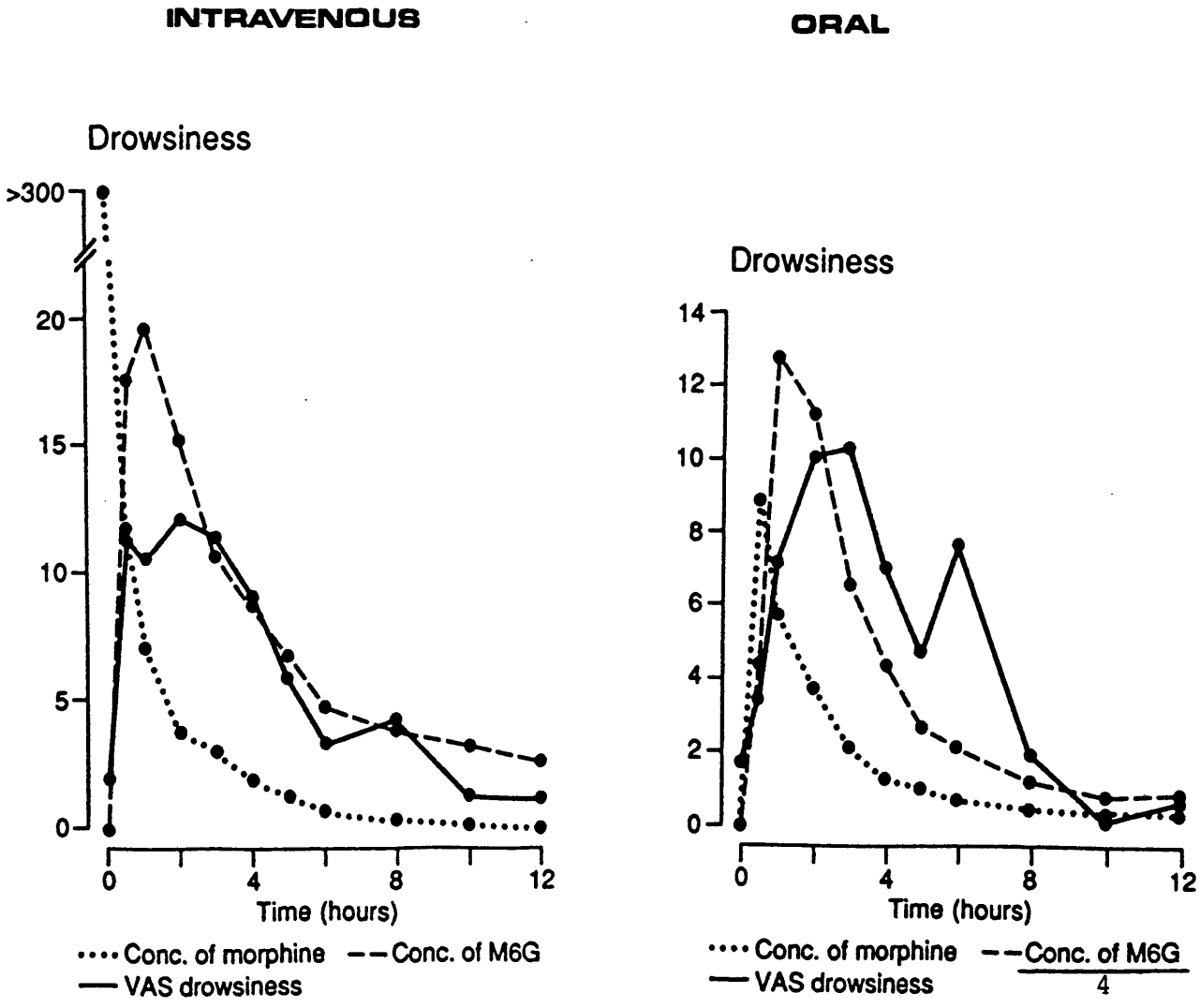
The y axis in the following figures is morphine or M6G concentration in ng/ml.

The plasma concentrations after intravenous morphine are plotted unchanged.

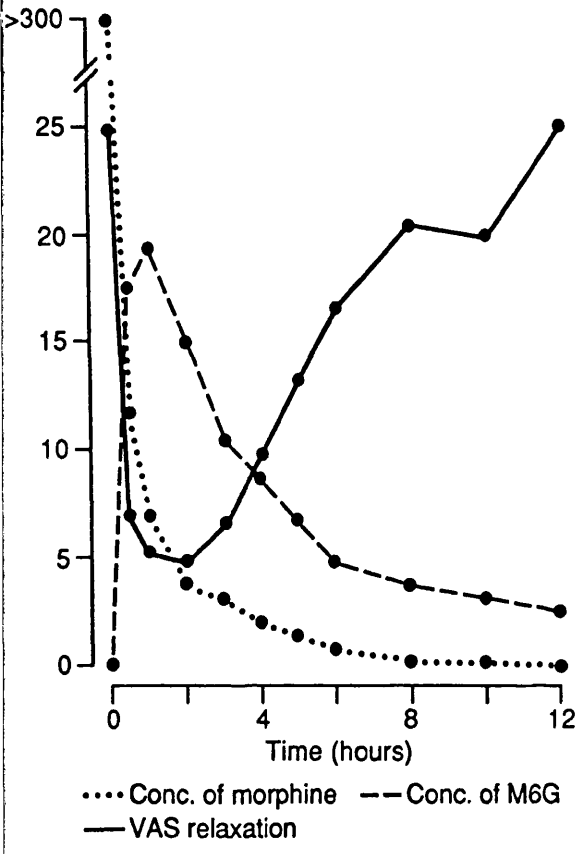
The plasma concentrations after oral morphine solution have been multiplied by a suitable factor to enable them to be plotted on the same axes together with the pharmacodynamic data.

The profile of the pharmacodynamic parameters has been imposed on the plasma profiles again using an appropriate factor to adjust the scores to fit the y axis.

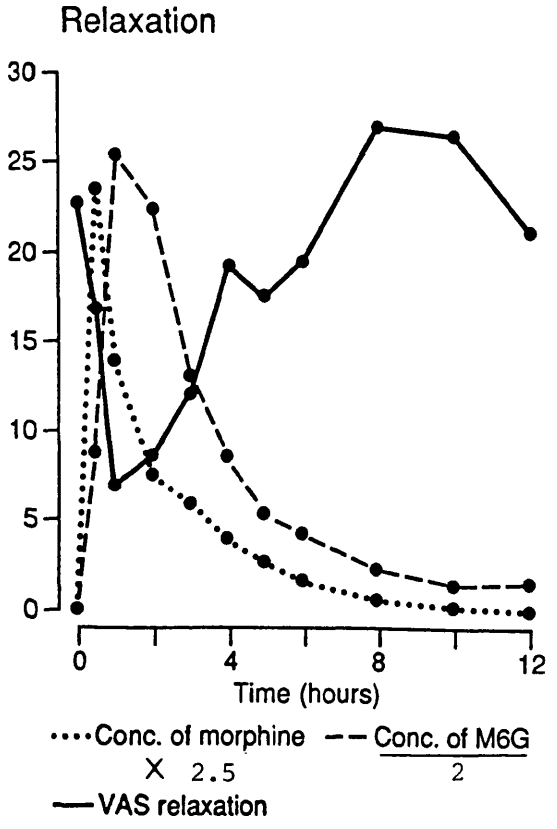
For drowsiness and dry mouth increasing score reflects increasing drowsiness or dry mouth. For relaxation a reduction in score reflects an increase in relaxation.



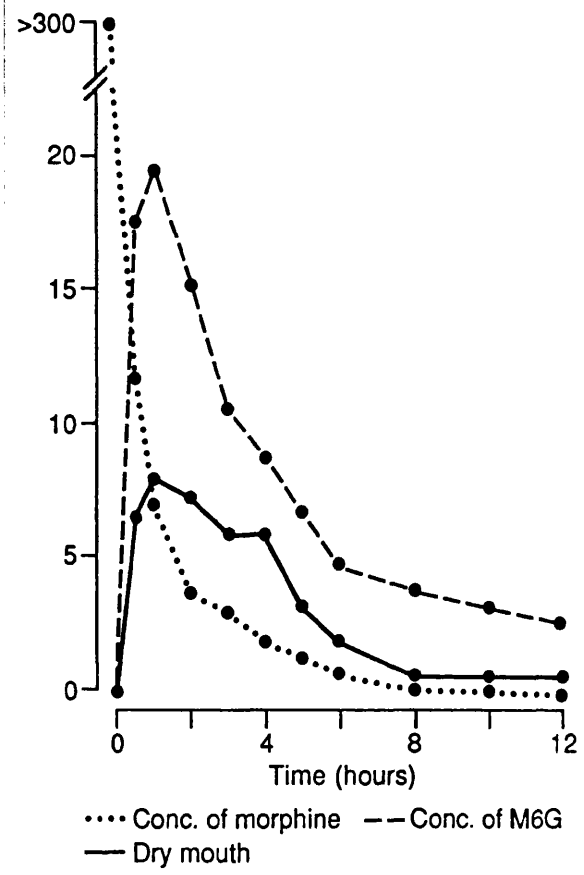
Relaxation



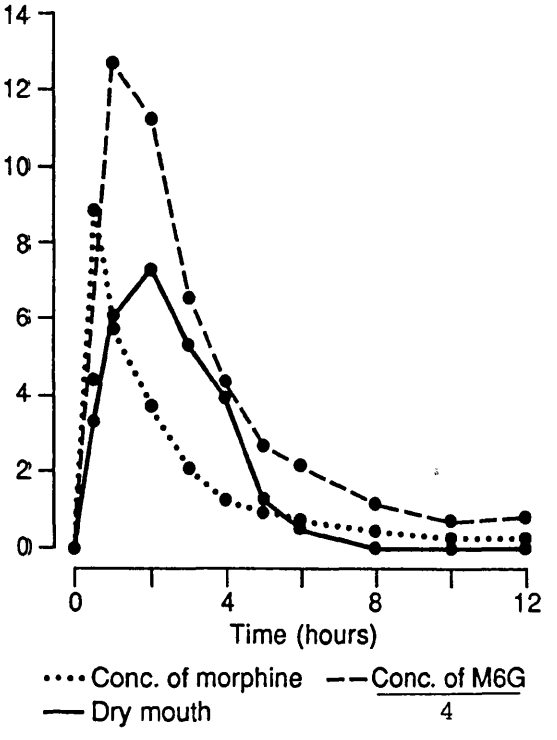
Relaxation



Dry mouth



Dry mouth



3.c.4 Discussion

The design of this study did not allow for blind assessment of the pharmacodynamic effects nor were the different preparations administered in random order so that anticipation and an order effect may have influenced these results.

There appears in figure 3.c.2 to be a relationship between drowsiness, relaxation and dry mouth and plasma levels of morphine and of M6G, with the metabolite M6G appearing to have a closer relationship to the changes in pharmacodynamic score than morphine itself. This does not, however, necessarily infer that the pharmacodynamic effect can be attributed to M6G rather than morphine. For example, the delay between peak morphine plasma level and peak pharmacodynamic effect could equally well be explained by a delayed distribution of morphine, particularly within the central nervous system (Kaiko et al 1978).

Separation of the individual contributions of the parent drug and its metabolite is not possible using the simple concentration-effect plots shown here. More complex models for the parent drug effects have been described (Jackson et al 1987) and for the future it may be possible to fit both the parent drug and metabolite concentrations to the observed effects. At present however it is possible only to conclude that the observations in this section are consistent with a pharmacological effect of M6G but may equally well be interpreted as an effect of the parent drug morphine alone.

CHAPTER 4

STUDIES ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF MORPHINE IN PATIENTS WITH ADVANCED CANCER

4.a Bioavailability of morphine in patients with advanced cancer

4.b The relative bioavailability of oral morphine elixir and controlled release tablets (MST)

4.c Evaluation of the use of a loading dose of morphine elixir when starting controlled release tablets (MST)

CHAPTER 4

STUDIES ON THE BIOAVAILABILITY AND PHARMACOKINETICS OF MORPHINE IN PATIENTS WITH ADVANCED CANCER

4.(a) Bioavailability of Morphine in patients with advanced cancer:

(i) Normal hepatic function
(ii) Impaired hepatic function

4.a.1 Introduction

The use of morphine for pain due to advanced cancer is based upon the principle of dose titration, with careful escalation of dose until satisfactory pain relief is achieved. This results in a very wide range of dose requirements within a group of patients, as illustrated in Chapter 6.b. A number of factors may influence a patient's individual dose requirement such as the site and cause of their pain, the associated emotional component and the use of co-analgesic drugs, non-drug pain relieving treatment or specific tumoricidal therapy.

Pharmacokinetic variations may also be important in determining an individual's response to morphine. In the current literature only two studies have evaluated the pharmacokinetics of morphine in cancer patients. Both demonstrate a wide individual variation in the parameters measured and used only small single doses (Sawe et al 1981, 1985). There are no data available on the absolute bioavailability of morphine in chronic dosage, nor of the influence of hepatic function upon this, and no information on the metabolite profiles present in these situations.

The purpose of this study therefore was firstly to determine absolute bioavailability for morphine in patients stabilised on a regular 4-hourly dose of morphine elixir and to investigate the

influence of hepatic metastases and impaired hepatic function, and secondly, in the light of its potential role in the analgesic action of morphine, to establish the pattern of M6G production in these situations.

4.a.2 Method

Patients under the care of the continuing care unit at the Royal Marsden Hospital, Sutton, receiving regular 4-hourly morphine elixir, in whom dose requirements had been stabilised after careful dose titration, were entered into this study. Exclusion criteria included progressive disease and general debility, haemoglobin < 10g/dl, a need for regular top-up doses of morphine for breakthrough pain, impaired renal function and inability to give informed consent. Hepatic function was measured by routine biochemical testing (serum bilirubin, alanine transaminase, alkaline phosphatase), and liver ultrasound or CT scan had been used to determine the presence or absence of liver metastases.

A forearm venous cannula was inserted and two four-hour blood profiles were performed; in all but two patients this was done after consecutive doses given at 11am and 3pm. In one patient two profiles were performed on consecutive days after the 11am dose, and one patient deteriorated after the first 4 hour profile and a second profile was not performed.

The first 4-hour profile was taken after the usual oral dose of aqueous morphine elixir, samples being taken at zero, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180 and 240 minutes. The second 4-hour profile was taken after an intravenous dose of morphine sulphate. This was given in a dose of one-third the usual oral dose and injected directly

over two minutes into a vein in the opposite arm to that cannulated. Sampling was carried out at zero, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180 and 240 minutes.

Blood samples were taken into a lithium heparin tube, centrifuged immediately and the plasma separated and stored at -20°C prior to analysis.

During the eight hour study period measurement of pain was performed at 1 - 2 hourly intervals depending upon the compliance of the patient using both a 4-point categorical scale and a 100mm visual analogue scale for pain and for pain relief. A side-effect questionnaire using a 4-point categorical scale for nausea, vomiting, drowsiness, sweating, dry mouth, tremor, dizziness and jerking was also completed at these intervals.

4.a.3 Sample analysis

Analysis for plasma morphine was performed using the RIA described in Chapter 2.

4.a.4 Statistical Analysis

The AUC_{0-4} has been calculated using the trapezoidal method. The elimination half-life has been derived using a non-linear least-squares method based on a two compartment model with a weighting for y values of $1/(y+yhat)^2$ (Jennrich and Sampson 1968). Clearance has been calculated from the ratio of dose/AUC. Comparison of data between groups has been performed using Student's t-test.

4.a.5 Results

Ten patients were entered into this study of whom five had impaired hepatic function. Individual details of these patients are shown in Tables 4.a.1 and 4.a.2.

The pharmacokinetic parameters for morphine are shown in Tables 4.a.3 and 4.a.4. A highly significant correlation between administered dose and AUC is seen both after intravenous administration ($r=0.97$, $p<0.001$) and after oral administration ($r=0.88$, $p<0.001$).

The results of the AUC's for M6G are shown in Table 4.a.5 and the relative amounts of morphine and M6G are shown in Table 4.a.6. The values for t_{max} and C_{max} for M6G are shown in table 4.a.7. The influence of hepatic function on the results for both morphine and M6G are shown in table 4.a.8.

Analysis of the pharmacodynamic data collected in this study is shown in Table 4.a.9.

Table 4.a.1

Patient characteristics

Patient	Age	Sex	Primary Tumour	Regular 4-hrly morphine dose	IV dose given in study
1	63	M	Ca Bronchus	60mg	20mg
2	59	M	Ca Oesophagus	80mg	27mg
3	59	M	Mesothelioma	50mg	18mg
4	63	F	Ca Breast	20mg	7.5mg
5	62	F	Ca Breast	70mg	24mg
6	19	M	Melanoma	400mg	120mg
7	32	M	Melanoma	60mg	20mg
8	60	M	Mesothelioma	60mg	21mg
9	66	F	Ca Pancreas	20mg	7.5mg
10	43	F	Ca Breast	120mg	-

Table 4.a.2

Details of liver metastases and hepatic function as determined by blood biochemistry

Patient	ALP (IU/l)	ALT (IU/l)	GGT (IU/l)	TBil (μmol/l)	Liver Metastases
1	100	9	40	<17	None
2	113	25	22	<17	None
3	131	10	35	<17	None
4	156	20	25	<17	None
5	107	8	23	<12	None
6	138	48	273	<12	Yes (CT)
7	275	90	114	263	Yes (CT)
8	426	9	91	<12	Yes (US)
9	1462	48	804	35	Yes (US)
10	1095	10	620	<17	Yes (US)

ALP: Serum alkaline phosphatase (normal range 25-92 IU/l)

ALT: Serum alanine transaminase (normal range <22 IU/l)

GGT: Serum gamma glutamyl transferase (normal range <30 IU/l)

TBil: Serum total bilirubin (normal range <17 μmol/l)

CT : Liver metastases confirmed on computerised tomography

US : Liver metastases confirmed on ultrasound

Table 4.a.3

AUC for morphine after intravenous and oral administration and absolute bioavailability.

Patient	AUC (iv) $ng.ml^{-1}.hr$	AUC (oral) $ng.ml^{-1}.hr$	Bioavailability (%)
1	659.6	203.1	30.8%
2	954.1	242.4	24.4%
3	1109.9	351.1	31.6%
4	288.4	74.0	25.6%
5	2562.4	1251.1	48.8%
6	7556.5	2174.2	28.8%
7	1194.3	436.6	36.5%
8	1508.0	778.5	51.6%
9	562.1	149.0	26.5%
10	-	576.2	-

Table 4.a.4

Pharmacokinetic parameters for morphine after intravenous or oral administration in steady state

Patient	t_{max} (mins)			clearance ($ml.min^{-1}.kg$)	$t_{½}$ (hours)
	iv	oral			
1	5	30		20.8	3.0
2	5	15		17.8	2.7
3	10	45		10.7	3.0
4	5	30		18.5	1.7
5	5	30		8.4	2.8
6	5	90		14.0	2.9
7	5	30		9.7	3.9
8	5	60		11.2	2.8
9	5	75		9.6	1.7
Median	5	30			
			Mean	13.4	2.7
			SEM	1.5	0.2

Table 4.a.5
$AUC_{(0-4)}$ ($ng.ml^{-1}.hr$) for M6G after intravenous and oral administration

Patient	AUC (IV)	AUC (ORAL)	AUC(ORAL)/AUC(IV)
1	6921.0	2036.0	0.29
2	7930.5	4475.1	0.56
3	3712.9	1819.4	0.49
4	1601.2	1071.1	0.67
5	10961.1	5488.9	0.50
6	24061.8	6691.6	0.28
7	3789.1	1274.7	0.34
8	2304.2	588.4	0.25
9	3601.6	1314.0	0.36
10	-	7483.5	-

Table 4.a.6
Ratio of AUC's for morphine and M6G after intravenous and oral administration

Patient	AUC (M6G) / AUC (Morphine)	
	IV	ORAL
1	10.49	10.02
2	8.31	18.46
3	3.34	5.18
4	5.55	14.48
5	4.28	4.39
6	3.18	3.08
7	3.17	2.92
8	1.53	0.75
9	6.41	8.82
10	-	12.99
Mean	5.14	7.57

Table 4.a.7
Values of t_{max} and C_{max} for M6G

	Intravenous		Oral	
Patient	t_{max} (hrs)	C_{max} (ng/ml)	t_{max} (hrs)	C_{max} (ng/ml)
1	0.17	890.00	0.75	626.50
2	0.50	1056.50	1.00	1469.00
3	0.17	724.00	2.50	622.00
4	0.50	301.50	2.50	304.90
5	0.30	1323.00	1.75	1743.00
6	0.08	8713.00	1.75	1997.00
7	0.25	527.00	3.00	443.00
8	0.17	347.00	1.75	212.00
9	0.25	394.70	3.00	368.80
10	-	-	0.75	2296.00
Median	0.25		1.75	

Table 4.a.8

Comparison of pharmacokinetic data in patients with normal hepatic function and those with impaired hepatic function

	Normal (Patients 1 - 5)	Impaired (patients 6 - 9)
Mean (SEM) Ratio AUC(oral)/AUC(iv)		
a) Morphine	0.32 (0.43)	0.35 (0.57)
b) M6G	0.50 (0.06)	*0.30 (0.02)
Mean(SEM) Ratio AUC(M6G)/AUC(morphine		
a) IV	6.4 (1.3)	3.6 (1.0)
b) Oral	10.5 (2.7)	5.7 (2.3)
Median t_{max} (IV)		
a) Morphine	5mins	5mins
b) M6G	12.6mins	18mins
(oral)		
a) Morphine	30mins	*67.5mins
b) M6G	105mins	105mins
Mean clearance (iv)	15.2 $ml.min^{-1}.kg$	11.1 $ml.min^{-1}.kg$
Mean t (iv)	2.6 hrs	2.8 hrs

* difference is significant, $P<0.02$

Table 4.a.9

Changes in pharmacodynamic data during study period

Time (hours)	ORAL 0	ORAL 2	ORAL 4	IV 0	IV 2	IV 4
Mean pain VAS (SEM)	29.1 (10.7)	25.0 (10.4)	[1]19.2 (7.2)	26.6 (10.5)	[2]20.7 (6.5)	
Mean pain relief VAS (SEM)	78.3 (6.8)	77.0 (8.6)	81.9 (5.5)	67.1 (12.2)	80.6 (5.8)	
Drowsiness Median score (range)	2 (0-3)	2 (0-3)	2 (0-3)	2 (0-3)	2 (0-3)	
Sweating Median score (range)	1 (0-2)	1 (0-2)	1 (0-1)	1 (0-2)	1 (0-2)	
Tremor Median score (range)	0.5 (0-2)	0.5 (0-2)	0.5 (0-2)	0.5 (0-2)	0.5 (0-2)	
Dry mouth Median score (range)	1.5 (0-3)	1.5 (0-2)	1.5 (0-2)	1.0 (0-2)	0 (0-2)	

[1] Difference from score at time zero is significant P<0.02
[2] Difference from score at time zero is significant P<0.05

4.a.6 Discussion

The patients entered into this study are representative across a wide age range, although relatively young with various sites of primary malignancy, of patients with advanced cancer requiring regular oral morphine for pain control. A wide dose range has been studied from 20 to 400mg 4-hrly. Previous suggestions that patients with impaired hepatic function may require lower doses of morphine than those with normal hepatic function are not reflected in this population, the mean dose for those with hepatic impairment being 110mg 4-hourly (range 20-400) compared to 56 mg 4-hourly (range 20-80 mg 4-hourly) in those with normal function.

The bioavailability for morphine of 34% is similar to that obtained in single dose studies both in healthy volunteers (Chapter 3.a) and in cancer patients (Sawe et al 1981) but no significant effect of hepatic function on bioavailability has been seen.

The other pharmacokinetic parameters obtained for morphine are also in keeping with previously published studies after single doses (Table 1.a.2). There are however some differences between these values and those obtained in healthy volunteers (Chapter 3.a) with in particular a longer half life and reduced clearance. This may in part reflect the wide individual variation seen in morphine pharmacokinetics and the small number of selected patients in this study. Plasma morphine clearance and half-life are determined mainly by hepatic function and other important considerations in accounting for this observed difference are the effect of other drugs in this group of patients and the effect of greater activity and regular meals in the healthy volunteers.

The only significant effect of hepatic impairment is seen in a prolonged t_{max} after oral administration and a reduced amount of M6G in plasma. This is in keeping with current views on morphine metabolism

with the liver being the principal source of morphine conjugation (Hanks and Hoskin 1987).

After a single dose of morphine in healthy volunteers we have found relatively more M6G after oral administration than after intravenous administration, the mean ratio of morphine to M6G after IV administration being 1:2, and 1:11 after oral administration (Chapter 3.a) In cancer patients in chronic steady state a ratio of 1:9 has been found (Chapter 4.b) but it is important to take into consideration that this was obtained using the HPLC assay which has been shown to give relatively lower values for M6G than the RIA used here and in the volunteer study.

The principal difference in metabolite pattern observed here is of a relative increase in amount of M6G after intravenous administration and a relative decrease after oral administration, the ratios of M:M6G in fact showing no statistical difference between intravenous and oral administration.

The pharmacodynamic measurements show remarkably consistent values across the two four-hour study periods. The only significant changes were seen in the scores for pain where a significant reduction in pain was seen at the end of each four-hour period. This does not correlate with the t_{max} in plasma of either morphine or M6G but may reflect the rate of distribution into the central nervous system.

There remains considerable confusion and controversy over the correct oral : parenteral potency ratio for morphine. In chronic use a ratio of 1:2 or 1:3 is commonly used although the only prospective randomised study to investigate this issue found a ratio of 1:6 after a single dose (Houde et al 1965). No change in either pain control or side effect profile was seen during the intravenous four-hour period

compared to the routine oral inter-dose period in this study. A dose reduction of one-third was used to determine the intravenous dose used which, together with the bioavailability figures of around 33% for morphine, supports the continued use of an oral parenteral potency ratio of 1:3 during the chronic administration of morphine.

In conclusion, the data from this study have shown no significant difference in the bioavailability of morphine in chronic oral dosing compared to single dose studies. Relatively more M6G has been found in plasma after the introduction of a single intravenous dose during chronic oral dosing than after a single intravenous dose alone. In impaired hepatic function relatively less M6G is produced which may be of importance in view of its potential role as an active analgesic (Hanks et al 1987). Using an oral to parenteral potency ratio of 1:3 equivalent analgesia and side effect profile has been observed.

4.b The relative bioavailability of oral Morphine Elixir and Controlled Release Morphine tablets (MST-Continus)

4.b.1 Introduction

Controlled release morphine tablets (MST Continus, MS Contin, MOS Contin) are widely used in the treatment of cancer pain. Controlled clinical trial data are limited, but suggest that for the majority of patients twice daily administration of MST is equivalent to a four-hourly regimen of aqueous morphine. This is supported by empirical clinical experience.

Investigations of the absolute bioavailability of MST in single dose studies have produced conflicting results. In one study in healthy volunteers, the mean systemic availability of MST in the first seven hours after administration was 18.3%(Vater et al 1984.) In contrast, in a study in patients, the bioavailability of MST was calculated to be 122% (McQuay et al 1984).

An important difference in the methodology used in the two studies is that the first employed a specific high performance liquid chromatography (HPLC) assay to measure plasma concentrations of unconjugated morphine (Svensson et al 1982, Svensson 1986) whereas the second used a radioimmunoassay (RIA) utilising antibodies raised to 6-succinylmorphine BSA (Aherne et al 1975) which has been shown to cross-react with morphine-6-glucuronide (Aherne and Littleton 1985).

An investigation of the steady state kinetics of MST in healthy volunteers (using an HPLC assay) indicated a bioavailability of 86% relative to morphine sulphate in aqueous solution(Savarese et al 1986) and this figure is consistent with data from an earlier study in postoperative patients (Hanks et al 1981).

The volunteer study described in Chapter 3 found an absolute bioavailability for morphine of 22.4% after MST in keeping with the above data and not significantly different from the value of 23.8% for MSS.

This study investigates the relative bioavailability of MST in patients with advanced cancer stabilised on oral morphine sulphate in aqueous solution (MSS). Both the specific RIA and the HPLC have been used, the latter enabling measurement of both M3G and M6G in addition to morphine .

4.b.2 Patients and Methods

Patients with advanced cancer who were in-patients in the Continuing Care Unit at the Royal Marsden Hospital and who had pain requiring oral morphine were eligible for entry to the study. Patients were admitted if their pain was controlled on a four-hourly regimen of morphine sulphate elixir (MSS) in the same dose for at least five consecutive days. The MSS was morphine sulphate in chloroform water with ethylene diamine tetracetic acid and benzoic acid as preservative. The concentration of MSS varied according to the dose being administered between the limits of 10mg in 10mls and 60mg in 10mls.

Patients whose clinical condition was poor or whose pain was not stable were excluded. Also excluded were patients receiving high daily doses of morphine (>1g) who would require a large number of MST tablets.

Patients who fulfilled the entry criteria had a cannula inserted into a convenient forearm vein. The study extended over a period of three days. On the first study day patients continued their usual 4-hourly doses of MSS and blood samples were taken over a twelve hour

period from the 8am dose. Sampling was performed at time zero and then at 30 minute intervals for five hours, and at 7, 8, 11 and 12 hours. This study was initiated before the results of the sampling study were available (see Chapter 2f) and serum samples were used. Venous blood was collected into plain glass bottles which were rolled for at least 20 minutes, before being centrifuged at 3500 rpm and the serum separated and immediately frozen at -20°C.

On the second day patients were converted to MST maintaining the same total daily dose in two equal parts. The final dose of MSS was given at 4am and the first dose of MST at 8am. No blood samples were taken.

On the third day blood samples were taken for a 12 hour period following the 8am dose of MST, at the same times as on day one. A final sample was taken three weeks later at midday (approximately four hours after dosing) from patients who were maintained on MST.

On days 1 and 3 patients completed 10cm-line visual analogue scales for pain intensity and pain relief at 8am and 8pm, and a four point verbal rating scale for morphine-related side effects was completed each day.

4.b.3 Analytical Method

The serum samples were divided into two. One group was analysed using the specific radioimmunoassay for morphine, and the other was analysed using sample extraction and HPLC to measure morphine M3G and M6G levels. Both assays are described in Chapter two, together with a detailed comparison between the two assay methods based on these results.

4.b.4 Statistical Analysis

The area under the serum concentration versus time curve (AUC) was calculated using STRIPE (Johnston and Woollard 1983). Student's paired t-test was used to compare assay techniques and AUCs from the different preparations. For MST the AUC for the 12-hour monitoring period was calculated, but for morphine elixir the AUC for only the first 4 hours was calculated and multiplied by three for the purpose of comparison. The timing of the blood samples was designed to give an accurate estimate of a 4-hour dosing period for morphine elixir and of the full 12-hour dosing period for MST.

4.b.5 Results

(i) Patient Population

Ten patients entered the study. Six were females aged 60 to 79 years weighing 35 to 90 kg, with cancer of the breast (3), lung (2) and colon. The four males were aged 44 to 72 years and weighed 65 to 102 kg, with cancer of the lung (2), kidney, and a soft-tissue sarcoma.

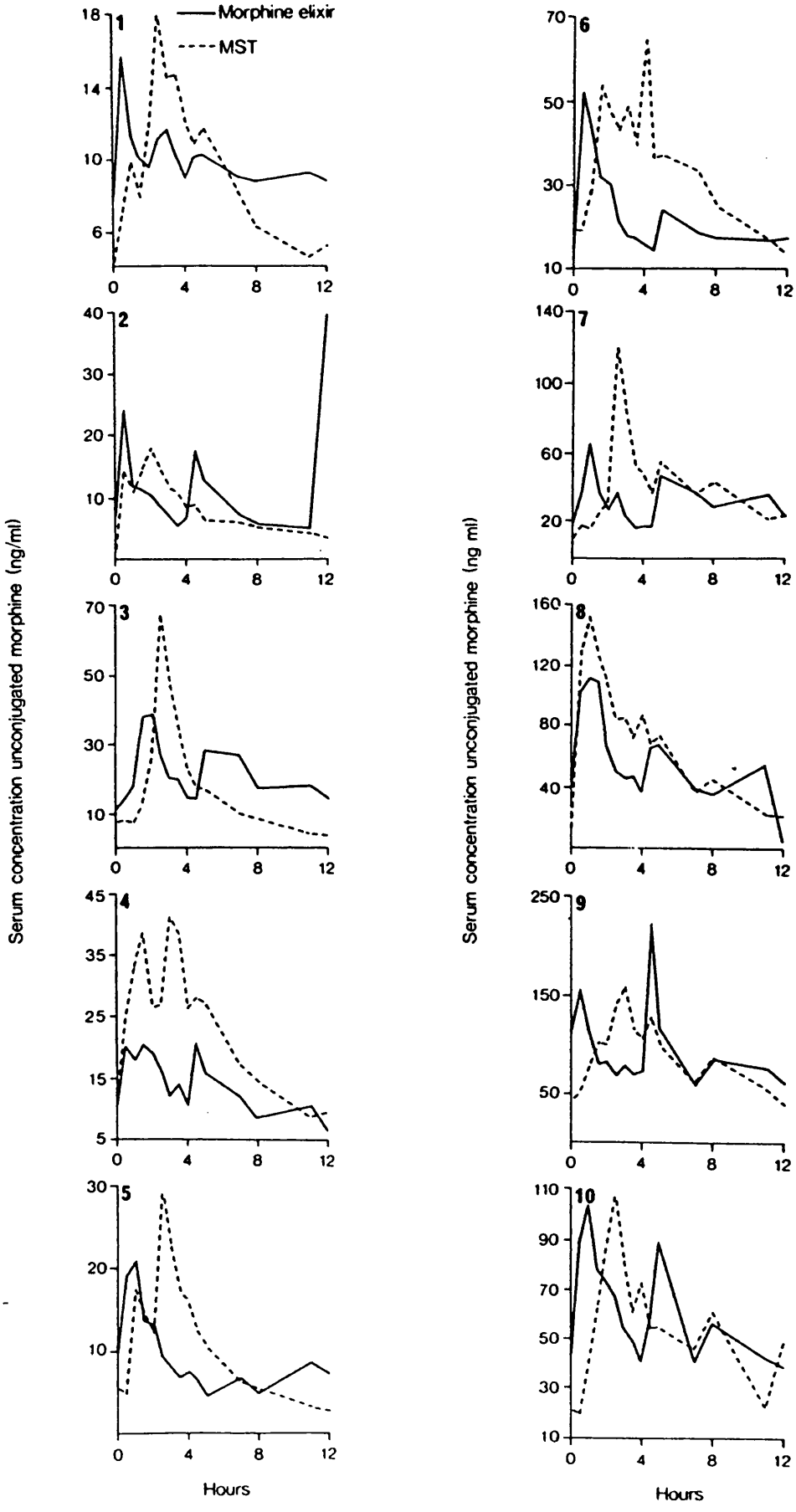
The dose range of morphine was 40 to 360mg/day (0.7 - 5.5mg kg^{-1}). All patients had normal renal and hepatic function as assessed by blood biochemistry.

(ii) Individual Profiles

The individual serum morphine concentration-time curves for the ten patients measured by HPLC are shown in Figure 4.b.1. A secondary peak in the concentration of unconjugated morphine is seen 2 to 4 hours after dosing with morphine elixir in patients 1 and 7, but there is also a consistent 'shoulder' in the curves of patients 2,3,5,6,9 and 10. Similarly, in the MST curves in patients 7,9 and 10 there appears to be a secondary peak 4 to 6 hours after dosing.

Figure 4.b.1

Individual serum concentration versus time curves



(iii) Relative Bioavailability of Morphine

The individual AUC's for each patient measured by both RIA and HPLC are shown in Table 4.b.1 and the relationship of AUC to dose together with relative bioavailability is shown in Table 4.b.2.

Statistical analysis demonstrates a highly significant linear relationship between the dose administered and the AUC for both formulations (RIA: $r=0.92$, $p<0.0001$ in each case, HPLC: $r=0.95$,MSS;$r=0.91$,MST. $p<0.001$ in each case).

However,whilst comparison of the AUCs determined by RIA reveals no difference between the two formulations (using a paired t-test, $t = 1.28$, $p > 0.2$) with a mean relative bioavailability of MST of 94% (range 72% - 131%) the results using HPLC do show a significantly lower AUC for MST compared with MSS ($t=2.4$, $p<0.02$) with a mean relative bioavailability of MST of 80% (range 50-109%).

Table 4.b.1: Comparison of the 12-hour cumulative area under the serum concentration time curve (AUC_{0-12}) for morphine as measured by RIA and HPLC

($ng.h.ml^{-1}$)

Patient	12-hour dose (mg)	MSS		MST	
		RIA	HPLC	RIA	HPLC
1	20	131.9	153.5	106.1	149.4
2	30	128.0	143.2	91.7	71.5
3	30	282.8	288.0	227.3	145.2
4	30	196.5	176.4	257.2	180.1
5	30	140.1	181.1	116.1	145.4
6	90	344.7	357.4	384.7	339.4
7	120	402.9	439.5	496.2	478.2
8	120	852.6	758.3	750.1	623.2
9	180	1115.7	929.8	1016.5	898.3
10	180	833.7	950.9	624.4	572.0

Table 4.b.2: Mean AUC_{0-12} for different dose levels and relative bioavailability

12-hour dose (mg)		AUC_{0-12} (ng.h.ml^{-1})					
		RIA			HPLC		
	n	MSS	MST	MST/MSS	MSS	MST	MST/MSS
20	1	131.9	106.1	0.80	153.5	149.4	0.97
30	4	186.9	173.1	0.93	197.3	135.2	0.68
90	1	344.7	384.7	1.12	357.2	337.8	0.95
120	2	627.8	623.2	0.99	598.5	550.5	0.92
180	2	974.7	820.5	0.84	940.5	734.8	0.78
Mean (All doses)	10			0.94			0.80
SEM				0.07			0.06

(iv) C_{max} and t_{max} for Morphine

Table 4.b.3 shows peak serum concentration (C_{max}) and time to peak serum concentration (t_{max}) for morphine obtained by RIA.

There was no significant difference between trough serum concentrations at 12 hours ($t = 1.12$, $p > 0.2$), and attenuation of the C_{max} for morphine is seen after MST. The ratio of C_{max} after MST to C_{max} after MSS is 1.32 $\pm$0.13 (mean +SEM) while the dose ratio of MST to MSS is 3. The values of C_{max} and t_{max} measured by HPLC are shown alongside the metabolite data in Tables 4.b.6 and 4.b.7.

Table 4.b.3 C_{max} and t_{max} after MSS and MST measured by RIA

Patient No	12-hour dose (mg)	C_{max} ($ng.ml^{-1}$)		t_{max} (h)	
		MSS	MST	MSS	MST
1	20	15.5	18.0	0.5	2.5
2	30	24.0	18.0	0.5	1.5
3	30	38.6	68.2	2.0	2.5
4	30	20.2	41.3	1.5	3.0
5	30	20.7	29.4	1.0	2.5
6	90	52.6	65.4	0.5	3.5
7	120	63.7	121.0	1.0	2.5
8	120	111.0	152.0	1.0	1.0
9	180	155.0	159.0	0.5	3.0
10	180	103.0	108.0	1.0	2.5
			Median	1.0	2.5

(v) Metabolite Data

Table 4.b.4 shows the AUCs for the two metabolites M3G and M6G together with their relative bioavailability.

For MSS there is a significant correlation between the AUC for both metabolites and dose of morphine (M3G: $r= 0.86$, $p<0.001$; M6G: $r=0.83$, $p<0.001$), but this is not the case with MST (M3G: $r=0.24$; M6G: $r=0.47$). No significant difference between the formulations is seen in the relative bioavailability of either metabolite, though there is wide inter-individual variation.

The values for the AUCs corrected to a standard dose of 100mg morphine are shown in Table 4.b.5. The mean ratios of morphine : M6G : M3G are 1 : 9.3 : 56.2.

Tables 4.b.6 and 4.b.7 show the C_{max} and t_{max} respectively for morphine, M3G and M6G as measured by HPLC.

The metabolites follow a similar pattern to the parent drug and attenuation of C_{max} is again seen after MST; the mean ratio of C_{max} MST : MSS being 1.47 ±0.26 for M3G and 1.25 ±0.10 for M6G.

Table 4.b.4: 12-hour cumulative area under the serum concentration time curve (AUC_{0-12}) and relative bioavailability for morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)

Patient	12-hour dose (mg)	AUC_{0-12} ($ng.h.ml^{-1}$)				Relative Bioavailability	
		MSS		MST		MST/MSS	
		M3G	M6G	M3G	M6G	M3G	M6G
1	20	4694.5	700.9	5786.3	870.5	1.23	1.24
2	30	4013.9	455.5	9438.1	432.7	2.35	0.94
3	30	6890.0	545.6	8271.0	430.1	1.20	0.79
4	30	20784.3	4756.5	32069.2	4983.0	1.54	1.05
5	30	7503.3	1474.5	5185.1	1330.0	0.69	0.90
6	90	13588.7	3670.0	40827.8	6848.0	3.00	1.86
7	120	31962.8	4975.3	30700.0	4443.4	0.96	0.89
8	120	36770.8	5921.7	35313.7	6208.3	0.96	1.05
9	180	33180.7	5664.0	18972.7	5675.9	0.57	1.00
10	180	32790.8	6005.8	6887.7	1530.0	0.21	0.25
					Mean	1.27	1.00
					SEM	0.25	0.13

Table 4.b.5

12-hour cumulative area under the serum concentration time curve (AUC_{0-12}) for morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) after dose correction to 100mg administered morphine.

AUC
($ng.h.ml^{-1}$)

	MSS			MST		
Patient	Morphine	M3G	M6G	Morphine	M3G	M6G
1	767.5	23472.3	3504.4	747.5	28931.5	4352.7
2	477.3	13379.9	1518.3	238.4	31460.3	1444.9
3	960.7	22966.6	1818.7	290.1	27570.0	1433.7
4	589.0	69280.7	15856.7	600.0	106896.7	16612.0
5	603.3	25011.0	4915.0	484.3	17285.3	4433.3
6	397.1	15098.8	4077.8	377.1	45364.2	7608.8
7	366.2	26635.7	4146.0	398.5	25583.3	3702.9
8	631.9	30642.4	4935.0	519.3	29428.1	5173.5
9	516.5	18433.7	3146.7	499.0	10540.4	3153.4
10	528.3	18217.1	3336.6	317.8	3826.5	850.0
MEAN	583.8	26313.8	4725.5	447.2	32688.6	4876.5
SEM	55.7	5062.6	1288.4	48.9	9025.4	1452.7

Table 4.b.6

Peak serum concentrations (C_{max}) for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) ($ng.\ ml^{-1}$)

Patient	12-hour dose (mg)	MSS			MST		
		Morphine	M3G	M6G	Morphine	M3G	M6G
1	20	19.3	476.6	71.8	25.9	855.2	113.8
2	30	19.4	426.1	59.0	15.3	1413.9	74.3
3	30	36.9	728.8	55.7	50.8	1138.9	77.4
4	30	20.4	1871.0	440.3	39.4	3395.1	506.9
5	30	25.8	826.9	145.4	27.7	782.3	189.2
6	90	50.3	2476.5	491.2	66.7	4480.5	717.6
7	120	50.7	2886.1	473.2	104.3	3300.4	539.2
8	120	96.8	3548.8	574.2	128.3	4497.6	907.4
9	180	122.3	3072.6	557.7	135.5	2082.3	649.2
10	180	114.8	3251.9	616.9	87.6	1408.9	336.1

Table 4.b.7

Time to peak serum concentration (t_{max}) for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) (h)

	MSS			MST		
Patient	Morphine	M3G	M6G	Morphine	M3G	M6G
1	0.5	1.5	2.5	2.5	3.0	4.0
2	0.5	1.0	1.0	2.0	3.0	3.0
3	2.0	2.0	2.0	2.5	3.0	3.0
4	0.5	1.0	2.0	3.0	4.5	4.5
5	1.0	2.5	1.0	2.5	3.5	3.0
6	0.5	1.5	1.5	4.0	4.0	4.0
7	0.5	1.0	1.5	2.5	3.0	3.5
8	1.0	1.5	1.5	0.5	2.0	2.5
9	0.5	1.5	1.0	3.0	4.0	3.5
10	0.5	1.5	1.5	2.5	3.0	3.0
MEDIAN	0.5	1.5	1.5	2.5	3.0	3.25
RANGE	0.5-2.0	1.0-3.5	1.0-3.5	0.5-4.0	2.0-4.0	2.5-4.0

(vii) Pain Scores

Analysis of the VAS ratings for pain and pain relief (Table 4.b.8) shows no difference between the two study days, nor is there any difference in the incidence or severity of adverse effects.

Table 4.b.8: Visual analogue scales for pain & pain relief
Mean±SEM (mm)

	PAIN[1]		PAIN RELIEF[2]	
	8am	8pm	8am	8pm
Aqueous morphine	12.3±3.02	14.8±3.74	87.3±4.15	79.5±6.51
MST	10.3±2.69	14.1±4.12	86.8±7.23	81.4±6.89
t	1.220	0.498	0.064	1.032
p	>0.2	>0.5	>0.5	>0.2

[1] 0 = no pain; 100 = worst possible pain

[2] 0 = no relief; 100 = complete pain relief

(viii) **Steady State Samples**

The midday serum concentrations at three weeks (Table 4.b.9) measured by RIA only are not significantly different from the midday (4-hour) serum concentrations on day 3 ($t = 2.36$, $p > 0.05$).

Table 4.b.9: Midday plasma concentration at three weeks in patients maintained on MST

Patient	12 hour dose (Day 3)	4 hour serum concentration (Day 3) (ng.ml)	Midday serum concentration (Week 3) (ng.ml)
1	20	12.2	16.8
3	30	23.5	26.4
4	30	26.8	32.3
7	120	49.5	56.6
10	180	72.3	95.3

4.b.6 Discussion

Patients entered into this study were stable clinically and were at steady state on 4-hourly oral aqueous morphine. This study was primarily a pharmacokinetic investigation and was not blinded, so that the ratings of pain intensity and pain relief must be interpreted in this light. However, MST appeared to provide equally good pain relief, as has been shown previously in both open and controlled studies (Knudsen et al 1985, Hanks et al 1987, Homesly et al 1987, Meed et al 1987) in cancer patients. Similarly there was no difference in side-effects.

The relative bioavailability of MST was measured 24 hours after changing to this formulation, and patients will have achieved steady state by this time if they have already been stabilised on morphine elixir, since the elimination of morphine is not changed by the controlled release formulation. This is supported by the serum concentrations at three weeks which are very similar to those on the second day of dosing.

This pharmacokinetic data indicates that MST has a similar or perhaps slightly lower systemic availability compared with aqueous morphine. Analysis of serum samples using RIA showed no statistically significant difference in the bioavailability of MST and MSS with respect to concentrations of morphine, though in seven out of ten patients the AUC after MST was lower. Using HPLC, however, MST appears to have a significantly lower bioavailability than MSS. No significant difference between the two assay methods has been shown when all of the data are compared. Examination of the data suggests that a possible explanation for this apparent contradiction is that the RIA overestimates morphine concentrations after MST and underestimates

morphine concentrations after MSS, the ratio comparing AUC's obtained by RIA to those by HPLC being 0.95±0.05 after MSS and 1.16±0.07 (mean± SEM) after MST. As a result no overall difference between the two methods is seen when both MST and MSS results are taken together.

The most likely explanation for a difference between the two methods is that the RIA is cross-reacting with a morphine metabolite. No cross reaction with the major metabolites M3G or M6G has been demonstrated but a cross-reaction with normorphine is possible since the antiserum used is raised to an N-succinyl normorphine-BSA conjugate. If this cross reaction is the explanation for the difference in bioavailability estimations with the two assay methods, the implication is that more of the cross-reacting metabolite is produced by MST, than by MSS. It is possible that the prolonged absorption phase of MST may result in greater amounts of normorphine being produced by the gut mucosa. We have not detected normorphine in the serum samples but this may be due to technical inadequacies in the HPLC method: interfering peaks occur in the region of the normorphine peak. However, others have also been unable to detect normorphine in plasma samples even in patients taking large doses of oral morphine over prolonged periods (Sawe et al 1983).

The median values for t_{max} for both MSS and MST are similar to those reported elsewhere in normal volunteers (Vater et al 1984) and a little shorter than those reported in post-operative patients (Hanks et al 1981). The attenuation of C_{max} after MST is also in keeping with findings in normal volunteers (Savarese et al 1986). This may be accounted for by reduced absorption in the postoperative state. There was no evidence of accumulation with regular administration of MST in

the blood samples taken at three weeks in five of these patients.

The secondary peak in the serum concentrations of unconjugated morphine seen in several patients is of considerable interest. It may represent enterohepatic circulation of morphine. This has been clearly demonstrated in rodents (Walsh and Levine 1975, Dahlstrom and Paalzow 1978) but there is no unequivocal evidence for its occurrence in man. A previous study (in healthy volunteers) showed a secondary peak in plasma concentrations 4 to 5 hours after dosing with MST (Leslie et al 1980). In our data the secondary peak is most clearly seen in MSS curves between 2 and 4 hours after dosing. Enterohepatic circulation may be part of the explanation for the greater efficacy of repeated doses of oral morphine compared with single doses and that morphine-6-glucuronide may play an important role in the analgesic activity of repeated doses of oral morphine.

The results for M3G and M6G are also of particular interest since there is little comparable data in the literature. Sawe and her colleagues have demonstrated ratios of 1:24.4 for morphine to M3G and 1:2.5 for morphine to M6G after small single doses in cancer patients (Sawe et al 1981) and ratios of 1:34 and 1:3.9 respectively in 4 patients after chronic use (Sawe et al 1985). The corresponding ratios in this larger study are 1:56.2 and 1:9.3, which are considerably higher. A possible explanation for this could be the accumulation of metabolites in chronic use. However the ratio for M6G is very similar to that obtained in volunteers after single doses as described in Chapter 3, which argues against this possibility. An important difference between this study and that in Chapter 3 is in the use of the differential RIA for metabolite estimation in Chapter 3 and HPLC in this study. Overestimation of the metabolite levels by RIA

due to cross-reaction with other unrecognised metabolite could account for the discrepancy seen between these results and those of Sawe et al (1981) after a single dose.

The use of a loading dose of morphine solution when introducing controlled release morphine tablets (MST-Continus)

4.c.1 Introduction

Controlled release morphine tablets (MST Continus) provide a convenient means of delivering regular morphine in patients with pain due to advanced cancer, and in a recent survey (see chapter 6.a) they emerged as the formulation of choice in this indication amongst both hospital doctors and general practitioners. For unstable pain however, and in patients who are first starting treatment with morphine, the controlled release nature of this formulation makes it less appropriate and oral aqueous morphine solution is preferred. This will result in a peak serum concentration of morphine at around 45 minutes compared to a delay of around two and a half hours following administration of MST. It is therefore a relatively common event in clinical practice for a patient receiving regular oral morphine in the form of aqueous solution, having had the dose titrated to their pain and a stable effective dose established, to be converted to controlled release tablets replacing the 4-hourly administration of aqueous solution by 12-hourly tablets. It has been demonstrated in a number of studies that oral solution and MST tablets are dose equivalent (Savarese et al 1986, Sloan et al 1987, Poulain et al 1986) so that the same 24 hour dose is given regardless of formulation. A potential problem, however, exists during the changeover period when following the final dose of MST there will be a lag period of 2-3 hours before peak blood concentrations from the controlled release tablet are achieved, and during which the effects of the previous dose of aqueous solution four

hours before will be waning. One solution to this problem would be to give an additional loading dose for oral morphine solution with the first dose of MST to cover the lag period before morphine levels from the MST build up. This study evaluates the need for a loading dose in this situation, both in terms of pain control and morphine pharmacokinetics.

4.c.2 Method

The patients entered into this study were under the care of the Continuing Care Unit at the Royal Marsden Hospital and receiving regular oral morphine in the form of four-hourly aqueous solution. They were required to be receiving a stable dose for at least the previous five days and to have achieved pain control on this dose. The study was approved by the Ethics Committee of the Royal Marsden Hospital and informed consent was obtained from each patient. Exclusion criteria included a prognosis of <4 weeks, a total morphine dose >800mg daily, a serum haemoglobin of <9g/dl, and inability to give informed consent.

Patients were prospectively randomised to receive either an additional loading dose of morphine solution or placebo. To avoid patients distinguishing the active solution from placebo by taste both preparations were prepared to have an identical taste and physical appearance and the total volume was made up to 10ml. The loading dose where given was the same as the regular 4-hourly dose given before changing to MST tablets. Randomisation was performed the day before changing to MST. The additional solution was prepared freshly by the hospital pharmacy the day before administration and the randomisation code was kept in the hospital pharmacy so that the study remained

double blind.

On the day of the study a forearm vein was cannulated and a baseline blood sample taken, followed by administration of the first dose of MST together with the additional dose of morphine solution or placebo. Venous blood was then collected at half-hourly intervals for the first 7 hours, and then hourly intervals for the next 5 hours until the next dose of MST was due. Blood samples were collected into a glass tube and rolled for 30 minutes before being centrifuged at 3,000 rpm for ten minutes. Serum was separated and stored at -20^{o}C until analysis.

During the 12-hour study period measurements were made of pain using a 100mm visual analogue scale and a 4-point categorical scale and of pain relief using a 100mm visual analogue scale. Details of side effects were also collected using a 4-point categorical scale for nausea, vomiting, drowsiness, tremor, sweating and jerking. These scales were administered at time 0, 4 hrs, 8 hrs, and 12 hrs. At completion of the study day the nurse who had looked after the patient for that day was asked to complete a short questionnaire to indicate their own assessment of the patient's pain, side-effects and whether they had received placebo or active drug.

4.c.3 Analysis

Analysis of the serum samples for morphine was performed using a specific radioimmunnoassay.

4.c.4 Statistical Analysis

The area under the plasma concentration vs time curve (AUC) for the 12 hour study period has been calculated using the trapezoidal method. Correlation between dose and AUC has been calculated using the least squares method and comparison of pharmacokinetic and pharmacodynamic data between the two study groups has been performed using Student's unpaired t-test.

4.c.5 Results

Twenty patients were randomised into the study. One patient was withdrawn on the day of the study, his condition having deteriorated during the previous 12 hours. Of the remaining 19 patients, ten received an active loading dose of morphine solution with their first dose of MST and 9 received placebo. Details of the patients are shown in Table 4.c.1, including their regular dose of morphine and the duration of treatment.

The results for time to peak plasma concentration (t_{max}), peak plasma concentration (C_{max}), minimum plasma concentration (C_{min}) and plasma concentration at 1 hour (C_1) are shown in Table 4.c.2.

In view of the wide range of doses used, the effect of the loading dose on the plasma concentration has been explored by determining the ratios of C_{max}/C_{min}, Cl/C_{max} and Cl/C_{min} which are shown in Table 4.c.3.

Table 4.c.4 shows the actual values for $AUC_{(0-12)}$ in the two groups and values corrected to a standard dose of 100mg. A good correlation between AUC and dose was obtained ($r = 0.97$, $p<0.001$ for placebo group and $r = 0.85$, $p<0.001$ for the active group).

Mean data for pain and pain relief scores are shown in Table 4.c.5. No statistically significant change in these scores over the 12 hour study period is seen and no significant change in side effect profile was seen.

Table 4.c.1

Details of patients, duration of medication and morphine dose

Patient	Age	Primary Tumour	Morphine Dose mg/24hrs	Duration on morphine a)Overall dose	b)Current
Placebo					
1	65	Breast	60mg	169days	169days
2	62	Stomach	600mg	38days	5days
3	68	Anal Canal	360mg	123days	13days
4	81	Breast	120mg	420days	15days
5	65	Breast	720mg	480days	5days
6	67	Prostate	120mg	72days	14days
7	73	Breast	250mg	150days	10days
8	72	Lung	60mg	11days	11days
9	75	Breast	42mg	9days	6days
Active loading dose					
10	65	Colon	480mg	127days	8days
11	74	Bronchus	600mg	60days	6days
12	84	Penis	80mg	21days	7days
13	64	Unknown	100mg	9days	9days
14	74	Prostate	100mg	21days	6days
15	51	Lung	240mg	71days	15days
16	63	Lung	60mg	7days	7days
17	66	Ovary	120mg	42days	5days
18	72	Bronchus	180mg	150mg	9days
19	65	Ovary	360mg	105days	28days

Table 4.c.2

Results for time to peak plasma concentration (t_{max}), peak serum concentration (C_{max}), minimum serum concentration (C_{min}) and serum concentration at 1 hour (C_1).

Patient	t_{max} (hrs)	C_{max} ng/ml	C_{min} ng/ml	C_1 ng/ml
Placebo				
1	2.0	26.0	4.2	12.8
2	2.5	456.2	91.6	293.7
3	2.0	275.2	40.1	115.2
4	1.5	429.1	20.2	74.3
5	3.5	593.4	100.0	172.2
6	1.0	41.5	7.6	41.5
7	0.5	50.6	10.9	34.4
8	4.5	69.8	16.7	25.3
9	1.5	17.0	6.0	15.1
Median	2.0			
Active loading dose				
10	2.0	203.4	32.8	95.2
11	0.5	511.6	174.5	489.4
12	1.5	48.8	9.6	42.5
13	0.5	50.6	10.2	34.4
14	1.0	60.1	10.6	60.1
15	3.5	198.0	49.4	161.8
16	5.5	34.0	3.6	8.9
17	1.0	134.5	19.3	134.5
18	3.5	56.4	27.0	33.7
19	0.5	348.5	54.3	251.1
Median	1.25			

Table 4.c.3

Ratios of C_{max}/C_{min}, C_1/C_{max} and C_1/C_{min}

Patient	C_{max}/C_{min}	C_1/C_{max}	C_1/C_{min}
Placebo			
1	6.2	0.5	2.9
2	5.0	0.6	3.2
3	6.9	0.4	2.9
4	21.2	0.2	3.7
5	5.9	0.3	1.7
6	5.5	1.0	5.5
7	4.6	0.7	3.1
8	4.2	0.4	1.5
9	2.8	0.9	2.5
Mean	6.9	0.55	3.0
SE	1.8	0.09	0.39
Active loading dose			
10	6.2	0.5	2.9
11	2.9	1.0	2.8
12	5.1	0.9	4.4
13	5.0	0.7	3.4
14	5.7	1.0	5.7
15	4.0	0.8	3.3
16	9.4	0.3	2.5
17	7.0	1.0	7.0
18	2.1	0.6	1.2
19	6.4	0.7	4.6
Mean	5.4	0.75	3.8
SE	0.7	0.07	0.5

Differences between placebo and active loading dose are not significant ($p>0.05$)

Table 4.c.4

Absolute values for $AUC_{(0-12)}$ and values corrected to 100mg administered dose

Patient	$AUC(0-12)$ $ng.ml^{-1}.hr$	Corrected AUC $ng.ml^{-1}.hr$
Placebo		
1	130.2	433.9
2	2837.6	945.9
3	1306.6	725.9
4	790.7	1317.8
5	2846.8	790.8
6	314.2	523.7
7	350.8	350.8
8	399.4	1331.5
9	125.8	629.0
	Mean	783.2
	SE	118.8
Active loading dose		
10	933.0	291.6
11	4129.6	1032.4
12	286.2	540.1
13	349.6	521.7
14	354.3	528.9
15	1591.4	994.6
16	148.3	370.7
17	542.0	677.5
18	459.4	382.9
19	1554.7	647.8
	Mean	598.8
	SE	78.9

Difference between corrected AUC's not significant ($p>0.05$)

Table 4.c.5
Mean pain and pain relief scores for placebo and active loading dose groups during 12 hour study period

	Time (hours)			
	0	4	8	12
Pain VAS score mean (SE)				
a) Placebo	14.3 (4.8)	18.7 (7.1)	18.8 (4.9)	19.1 (6.2)
b) Active	14.1 (5.7)	6.7 (2.4)	13.3 (4.3)	11.2 (3.8)
Pain relief VAS score mean (SE)				
a) Placebo	75.9 (7.5)	76.4 (7.2)	70.7 (8.7)	67.8 (8.7)
b) Active	86.8 (5.8)	83.6 (6.4)	79.4 (7.3)	86.4 (4.4)
*Pain category score median (range)				
a) Placebo	1 (0-2)	1 (0-3)	2 (0-3)	1 (0-3)
b) Active	0.5(0-2)	0(0-2)	0.5(0-2)	0.5(0-3)

*4-point scale: No pain (0)
Mild (1)
Moderate (2)
Severe (3)

Observed differences are not significant $p>0.05$

Table 4.c.6 shows the median scores for each of the side effects scored using a 4-point scale, and table 7 shows the results of the nursing assessment on completion of the study day.

Table 4.c.6
Median scores (range) for side effects based on 4-point scale

		Time (hours)			
		0	4	8	12
Nausea	a) Placebo	0 (0-2)	0 (0-3)	0 (0-1)	0 (0-2)
	b) Active	0 (0-3)	0 (0-2)	0 (0-2)	0 (0-2)
Vomiting	a) Placebo	0 (0-1)	0 (0-3)	0 (0-1)	0
	b) Active	0 (0-3)	0 (0-1)	0 (0-2)	0 (0-2)
Drowsy	a) Placebo	0 (0-2)	1 (0-3)	1 (0-3)	0 (0-3)
	b) Active	1 (0-1)	1 (0-3)	1 (0-3)	1 (0-3)
Sweating	a) Placebo	0 (0-1)	0 (0-2)	0 (0-1)	0 (0-1)
	b) Active	0 (0-2)	0 (0-1)	0 (0-2)	0 (0-2)
DryMouth	a) Placebo	1 (0-3)	0 (0-2)	1 (0-2)	0 (0-2)
	b) Active	1.5(1-2)	1.5(0-3)	1.5(0-3)	1.5(0-2)
Tremor	a) Placebo	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
	b) Active	1 (0-3)	1 (0-3)	0 (0-2)	1 (0-3)
Dizzy	a) Placebo	0 (0-1)	0 (0-1)	0 (0-2)	0 (0-2)
	b) Active	1 (1-2)	0 (0-1)	1 (0-1)	0 (0-1)

Differences within each group are not significant $p>0.05$

Table 4.c.7

Nursing assessment of pain, side effects and whether placebo or active drug given

Placebo				Active			
	Pain	Side effects	Preparation		Pain	Side effects	Preparation
Patient				Patient			
1	-	-	-	10	U	U	P
2	U	U	M	11	U	U	P
3	B	W	M	12	U	W	M
4	U	U	M	13	U	W	M
5	U	U	M	14	U	U	M
6	U	U	P	15	U	U	M
7	U	W	P	16	U	U	P
8	U	W	M	17	U	U	M
9	B	U	M	18	U	U	P
				19	U	U	P

B = Better than previous 24 hours

U = Unchanged

W = Worse than previous 24 hours

P = placebo

M = Active loading dose

4.c.6 Discussion

The population of patients entered into this study is representative of those with advanced cancer requiring regular oral morphine for pain across a wide dose range. No effect from the addition of a loading dose with the first dose of controlled release tablets (MST) has been observed either in terms of pharmacokinetic or pharmacodynamic parameters.

Furthermore, nursing staff were unable to predict whether or not a loading dose had been given and for most patients both pain control and side effects were rated as being unchanged from the previous treatment with the same dose of oral aqueous morphine solution.

The absence of any demonstrable effect is perhaps a little surprising in view of the considerations discussed in the introduction. This may in part reflect the relatively small number of patients entered into this study so that the power of detecting a real difference is low. This is particularly the case in the light of the wide individual variation seen between subjects so that whilst the median t_{max} with placebo was 2.0 hours and the loading dose was 1.25 hours, and the ratio of C_1/C_{max} was 0.55 hours with placebo and 0.75 hours with loading dose, this difference was not statistically significant due to the large standard deviations within the population. This may also explain an apparently large effect on pain scores seen with loading dose between 0 and 4 hours when the mean value falls from 14.1 to 6.7, again not reaching statistical significance. However, the finding that 6 out of 8 patients receiving placebo were thought by nursing staff to have received active morphine solution and 6 out of 10 patients receiving active solution were thought to have received placebo mitigates against there being any clinically relevant effect

effect from using a loading dose.

In conclusion, this study has found no evidence that when changing from regular 4-hourly aqueous morphine solution to regular 12-hourly controlled release tablets an additional dose of morphine solution is required to cover the theoretical lag period before significant amounts of morphine are absorbed from the controlled release tablet.

CHAPTER 5

STUDIES INTO THE DISTRIBUTION OF MORPHINE AND MORPHINE-6-GLUCURONIDE IN PATIENTS WITH ADVANCED CANCER

5.a Evidence for enterohepatic circulation of morphine in man

5.b The passage of morphine and M6G across the blood-brain barrier into CSF

5.c The passage of morphine and M6G into malignant effusions

5.a. EVIDENCE FOR ENTEROHEPATIC CIRCULATION OF MORPHINE IN MAN

5.a.1. Introduction

In rats, biliary excretion has been shown to account for approximately half of a subcutaneously administered dose of morphine, with predominantly morphine glucuronide being excreted into the duodenum (Walsh and Levine 1975), and extensive enterohepatic circulation with deglucuronidation and reabsorption of free morphine in the large bowel has also been demonstrated.

We have suggested that a similar enterohepatic circulation of morphine in man may account for secondary peaks seen in plasma profiles of morphine after oral administration, and may be important in maintaining plasma levels during chronic oral administration of morphine (Hanks et al 1987). Evidence of biliary excretion of morphine in man has to date been limited as detailed in Chapter 1.

Since the presence of an enterohepatic circulation for morphine may be important in considering its action, particularly after chronic oral use, this study was set up to obtain bile samples from patients with advanced cancer receiving regular treatment with morphine wherever this was practically possible with minimum disruption to the patient.

5.a.2 Patients and Method

Bile samples have been obtained from three patients in whom access to the biliary system was readily available, and a random steady state plasma sample also taken at the time of bile sampling. In two of the patients it was possible to measure the total 24 hour volume of bile produced.

5.a.3 Analysis

Bile and plasma samples have been analysed using the differential radioimmunoassay technique described in Chapter 2.

5.a.4 Results

Details of the three patients studied are shown in Table 5.a.1, and the concentrations of morphine, M3G and M6G are shown in Table 5.a.2.

The total 24 hour biliary excretion of morphine, M3G and M6G is shown in table 5.a.3 and the bile/plasma ratios in table 5.a.4 for the two patients in whom this can be calculated.

Table 5.a.1

Details of patients

Patient	Age	Primary Diagnosis	Source of Bile	Morphine Dose mg/24hrs	Route
1	48	Ca Pancreas	T-tube	140	Oral/SC
2	32	Ca Ovary	Gastrostomy	570	IV/SC
3	68	Ca Pancreas	Post Mortem	192 (Diamorphine)	SC

Table 5.a.2

Bile and Plasma concentrations of Morphine(M), M3G and M6G

Patient		Concentration (ng/ml)			Metabolite concentrations relative to morphine		
		M	M3G	M6G	M	M3G	M6G
1	Bile	106	846	173	1	7.98	1.63
	Plasma	51	1510	149	1	29.6	2.9
2	Bile	1730	13800	1470	1	7.98	0.85
	Plasma	352	10200	2700	1	28.98	7.67
3	Bile	2930	660	1920	1	0.22	0.65
	Plasma	-	-	-	-	-	-

Table 5.a.3

24 Hour Biliary excretion of morphine, M3G and M6G

Patient	24 hour bile volume (ml)	24 Hour biliary excretion* (µg)		
		Morphine	M3G	M6G
1	200	21.2	169.2	34.6
2	1700	2941.0	23460.0	2499.0
3	24 hour volume not obtained			

*assuming stable concentrations in bile

Table 5.a.4

Bile/plasma ratio for morphine. M3G and M6G

Patient	Bile/plasma ratio		
	Morphine	M3G	M6G
1	2.08	0.56	1.16
2	4.91	1.35	0.54
3	Plasma sample not obtained		

Discussion

Significant quantities of both morphine and its two major metabolites have been detected in bile from patients receiving chronic dosing with morphine, highly suggestive of an active enterohepatic circulation for morphine and its two major metabolites. In the two patients where plasma samples were also available, the ratios of morphine to its metabolites are remarkably consistent, although the plasma ratios are a little lower than those found in the two earlier studies described. Relatively more morphine compared to metabolites is present in bile and the absolute values for morphine concentration in bile are also considerably higher than in plasma.

The glucuronide levels in the bile from subject 3 are considerably lower than would be predicted from the two preceding patients, and the morphine concentration is considerably higher if some relation between dose and bile concentration is assumed. This could be explained by the fact that this was a post mortem sample taken approximately 18 hours after death during which time deglucuronidation of M3G and M6G may have occurred. There is no data available on the stability of M3G and M6G at mortuary temperature, although at -20^{o}C they do appear stable (S Joel, personal communication).

In the two patients in whom 24 hour biliary volumes are available, the actual amounts of morphine and metabolites excreted have been calculated assuming a stable concentration in bile. The kinetics of morphine and morphine glucuronide in bile are unknown however and the actual concentrations measured were obtained from single samples rather than aliquots from a pooled collection due to the difficulties in obtaining samples from patients with advanced cancer. The derived 24 hour excretions may therefore be misleading and this is reflected in

the presence of 0.225mg total morphine equivalents in patient 1 over 24 hours and 28.9mg in patient 2 over 24 hours, representing 0.16% and 5.4% respectively of the administered dose.

In conclusion, this study has demonstrated that bile is a definite route of excretion for morphine, M3G and M6G. Once excreted into the duodenum, deglucuronidation by bacterial β-glucuronidases and reabsorption of morphine is to be expected thereby setting up an enterohepatic circulation. This has implications both in considering the distribution of morphine in chronic use and also suggests a potential adverse effect of antibiotics on the analgesic action of morphine. There is no clinical evidence available to confirm or refute this hypothesis.

5.b The passage of morphine and morphine-6-glucuronide (M6G) across the blood-brain barrier into cerebrospinal fluid (CSF).

5.b.1 Introduction

The analgesic action of opioid drugs is considered to be a result of their binding to specific opioid receptors in the central nervous sytem. Recently it has been postulated that much of the activity of morphine may be due to the analgesic action of one of its metabolites, morphine-6-glucuronide (M6G). For this to be the case, passage into the central nervous system is an essential prerequisite. The glucuronide metabolites of morphine are polar, water soluble compounds which would not be expected to pass readily across the blood-brain barrier. Whilst direct examination of CNS tissue is not possible in man, cerebrospinal fluid (CSF), which is in intimate contact with the spinal cord and brain stem where the main sites for opioid receptors are found, can be obtained.

Significant quantities of morphine-3-glucuronide (M3G) have been detected in patients receiving chronic oral morphine (Sawe 1986). A recent report gives details of 15 patients who received a single intramuscular dose and 11 patients who received a single oral dose of morphine following which a CSF sample was taken (Hand et al 1987). Significant levels of morphine, M3G and M6G were detected in the CSF.

This study was designed to investigate the presence of morphine, M3G and M6G in the CSF of patients receiving chronic oral morphine. It is in this situation that the role of M6G in the activity of morphine has been emphasised and no data on its levels in CSF under these conditions are available.

5.b.2 Patients and Method

Patients were entered into this study who were receiving chronic oral therapy with morphine or diamorphine. CSF was obtained at the time of diagnostic myelography in patients presenting with suspected spinal cord compression, in whom lumbar puncture and removal of CSF is a routine part of the procedure. At the time of lumbar puncture, a peripheral venous blood sample was also obtained, collected into a plastic heparin tube and after centrifuging at 3500 rpm for 10 minutes the plasma was separated and stored at -20°C prior to analysis. CSF was collected into a plain plastic container and also stored at -20°C prior to analysis.

5.b.3 Analysis

Morphine, M3G and M6G were measured using the differential radioimmunoassay technique described in Chapter 2.

5.b.4 Results

The characteristics of the six patients included in this study are shown in table 5.b.1.

The absolute concentrations of morphine, M3G and M6G measured in the plasma and CSF samples, and the ratios of the metabolites relative to morphine are shown in table 5.b.2. The ratio of morphine, M3G and M6G in CSF compared to plasma is shown in table 5.b.3. Using a least squares correlation, for all except plasma morphine levels, a significant correlation is seen with dose (table 5.b.4).

Table 5.b.1

Patient	Age	Sex	Primary Diagnosis	Dose Morphine mg/24 hrs	Duration present dose of morphine
1	63	F	Ca breast	100mg	8 days
2	58	M	Myeloma	260mg	6 months
3	26	F	Lymphoma	20mg	3 months
4	52	F	Ca breast	300mg	8 days
5	67	F	Myeloma	[1] 60mg	6 months
6	71	M	Ca prostate	40mg	4 weeks

[1] Given as 60mg diamorphine

Table 5.b.2

Patient	Sample	Concentration ng/ml Morphine	M3G	M6G	Ratio of concentration Morphine	M3G	M6G
1	CSF	* -	68.3	12.1			
	Plasma	6.5	527.6	76.4	1	: 82	: 12
2	CSF	25.1	157.5	36.0	1	: 5	: 0.4
	Plasma	10.3	369.2	107.4	1	: 36	: 10
3	CSF	1.0	3.6	1.0	1	: 4	: 1.1
	Plasma	0.3	27.7	3.2	1	: 79	: 9
4	CSF	69.9	1089.1	151.3	1	: 16	: 2
	Plasma	118.5	1216.5	184.2	1	: 10	: 1.5
5	CSF	3.6	89.8	4.1	1	: 25	: 3
	Plasma	28.5	446.5	76.1	1	: 16	: 3
6	CSF	7.6	198.1	27.4	1	: 26	: 4
	Plasma	4.4	239.1	57.8	1	: 55	: 13
MEAN	CSF				1	: 15	: 2
	Plasma				1	: 46	: 8

* Insufficient sample for morphine assay therefore stated concentrations of M3G and M6G are actually total concentration of morphine and metabolite.

Table 5.b.3

CSF/Plasma ratios for morphine, M3G and M6G

Patient	Morphine	M3G	M6G
1	-	0.16	0.13
2	2.44	0.10	0.36
3	2.71	0.31	0.13
4	0.59	0.82	0.95
5	0.13	0.15	0.20
6	1.74	0.48	0.83
Mean	1.52	0.34	0.43

Table 5.b.4

Correlation between administered dose and plasma and CSF levels of morphine, M3G and M6G

Parameter	Correlation Coefficient (R)	Level of significance (p)
Plasma morphine	0.693	> 0.05
CSF morphine	0.882	< 0.02
Plasma M3G	0.754	< 0.05
CSF M3G	0.732	< 0.05
Plasma M6G	0.776	< 0.05
CSF M6G	0.798	< 0.05

5.b.5 Discussion

All the patients in this study had been on oral morphine, or in one case diamorphine, receiving a stable dose for between 8 days and 6 months prior to sampling. The results will therefore represent steady state concentrations in chronic use. Since oral diamorphine will be completely deacetylated to morphine on its first pass through the liver there is no reason to expect the one patient receiving diamorphine not to be comparable to those receiving morphine. The results of this study confirm that after oral administration not only morphine, but also M3G and M6G cross the blood-brain barrier and are present in cerebrospinal fluid. It would seem reasonable to extrapolate from this that they also enter the brain and spinal cord itself where their pharmacological actions will be exerted.

Considerable individual variation is seen in the amounts of morphine, M3G and M6G entering the CSF. In two patients CSF concentrations are considerably lower than plasma, in three others they are considerably higher. For M3G and M6G, CSF concentrations are in all cases lower than plasma concentrations which is keeping in their more polar nature, although again wide individual variation between patients is seen. High CSF/plasma ratios for morphine do not necessarily seem to correlate with similarly high ratios for M3G and M6G, although greater concordance is seen in ratios for the two glucuronides. This may infer different transport mechanisms for morphine compared with its polar metabolites.

Although there is again inter-individual variation, the ratios between morphine, M3G and M6G in plasma and in CSF are more consistent. The mean ratio in plasma of 1:46:8 is in keeping with other data we have obtained in patients receiving chronic oral

morphine. Relatively lower concentrations of metabolites are found in CSF, the mean ratio being 1:15:2 for morphine:M3G:M6G. This may be explained by the relatively poor entry of the metabolites into the CNS.

In view of the marked individual variation it is of interest that the relationship between CSF and plasma concentrations and dose is relatively consistent. However, the finding of only a poor correlation between dose and plasma morphine where previously a very clear correlation between these two parameters has been demonstrated, suggests that these correlations should be regarded with caution and may be altered if larger numbers were studied.

After single doses of oral morphine in post-operative patients, the ratio of mean values for morphine:M3G:M6G was found to be 1:1.1:0.18 (Hand et al 1987) which is very different from the data presented here. However, these were single sample estimations from patients who were not in steady state, after a single dose and are therefore difficult to interpret and not comparable with the results of this study.

Using data from the activity of M6G in rats (Shimomura et al 1971), which found M6G to be 45 times more potent than morphine when injected intracerebrally, it has been suggested (Hand et al 1987) that M6G may account for 85% of the analgesic activity of morphine. When a similar calculation is performed using the data from this study, an even greater contribution by M6G to the analgesic action of morphine is derived with M6G accounting for over 98% of the total analgesic activity. This is, however, based on a number of assumptions which may be erroneous, in particular that the relative potency between morphine and M6G is the same in man as that derived by experimental pain methods

in a single study in rats, and that CSF levels are an accurate predictor of levels of morphine or M6G actually binding to opioid receptors in the CNS.

In conclusion, this study has demonstrated that in chronic oral use, not only morphine but also its two major metabolites, M3G and M6G enter the CSF. The passage of the metabolites into CSF is less efficient than for morphine and both relatively and absolutely lower values of M3G and M6G are found in CSF than in plasma. Despite this, the high relative potency of M6G suggests that in the concentrations observed in CSF it could account for a significant proportion of the analgesia produced by oral morphine.

5.c The passage of morphine and M6G into malignant effusions

5.c.1 Introduction

The common use for morphine and the basis of the work presented here is as the strong opioid analgesic of choice in advanced cancer. By its very nature, advanced cancer is accompanied by widespread metastases and frequently pleural, pericardial or peritoneal deposits result in large collections of fluid in the associated body cavity. The volume of distribution for a drug which enters these effusions which may contain several litres of fluid, may therefore become considerably increased and introduce a further variable to consider in the wide interindividual variation in morphine dose requirements within this population which is illustrated in chapter 6.b. There is no data in the literature on the distribution of morphine or its metabolites in malignant effusions and this study therefore was to investigate the possibility of their passage into malignant pleural effusions or ascites.

5.c.2 Patients and Method

Aspiration of pleural effusions is performed when the accumulation of fluid within the pleural cavity is such as to cause troublesome symptoms, usually dyspnoea. At the time of therapeutic pleural aspiration, samples of the pleural effusion were obtained from four patients who were receiving regular medication with morphine.

Therapeutic paracentesis is also performed when fluid accumulates within the peritoneal cavity and is causing symptoms, usually discomfort or pain and occasionally dyspnoea or vomiting. In one patient who was receiving regular oral morphine therapeutic

paracentesis was performed and ascitic fluid retained for estimation of morphine, M3G and M6G.

5.c.3 Analysis

Morphine, M3G and M6G have been measured in pleural fluid and ascitic fluid using the differential RIA technique described in Chapter 2.

5.c.4 Results

Details of the five patient entered in this study are shown in table 5.c.1. The concentrations of morphine, M3G and M6G and the ratios of the metabolites relative to morphine are shown in table 5.c.2..

Table 5.c.1

Details of patients and type of effusion

Patient	Age	Primary Diagnosis	*Sample	Morphine Dose mg/24hrs	Duration present dose
1	29	Ca. Lung	Pl	600mg	10days
2	51	Ca. Lung	Pl	240mg	9 days
3	27	Fibrosarcoma	Pl	300mg	4 days
4	59	Ca. Lung	Pl	120mg	8 days
5	51	Ca. Breast	Asc	40mg	4 weeks

* Pl = Pleural fluid
Asc = Ascitic fluid

Table 5.c.2

Concentrations of morphine, M6G and M3G in effusions

Patient	Concentration (ng/ml)			Ratio		
	Morphine	M3G	M6G	Morphine	M3G	M6G
1	46.9	1353.1	289.8	1	29	6
2	240.7	3729.3	879.3	1	16	4
3	73.7	1756.3	333.8	1	24	5
4	40.5	534.5	169.5	1	13	4
5	8.9	297.4	71.8	1	33	8
			Mean	1	19.2	4.5

5.c.5 Discussion

The results presented above show high concentrations of not only morphine but also M3G and M6G in both pleural fluid and ascites. All patients were receiving oral morphine and may be assumed to be in steady state. Whilst unfortunately no paired blood samples were taken in this study, the concentrations present in these malignant effusions are of the same order as would be expected in blood after the doses given, suggesting that a simple diffusion equilibrium may be reached with morphine, M3G and M6G between the effusion and the blood compartment. None of the effusions in this study were blood-stained on visual examination so that contamination from the blood compartment is thought unlikely to account for the presence of morphine and its metabolites in the effusion.

It is not possible to draw hard conclusions from such a small sample of patients with regard to the effect of the distribution of morphine, M3G and M6G into the effusions upon dose requirements. All four patients in whom pleural fluid was measured were receiving high doses of morphine but they were all under 60 years of age, and high dose requirements may therefore have been anticipated on this basis alone as demonstrated in chapter 6.b. These patients were part of the cohort studied in the retrospective analysis reported in chapter 6.b which confirmed this association.

In conclusion, pleural effusions and ascites appear to represent a considerable pool for the distribution of morphine, M3G and M6G and when present in a patient with advanced cancer may contribute to the altered distribution of the drug and influence dose requirements.

CHAPTER 6

CLINICAL STUDIES ON THE USE OF OPIOID DRUGS IN PATIENTS WITH ADVANCED CANCER

6.a Questionnaire study into the use and attitudes of medical staff to opioid drugs in advanced cancer

6.b Retrospective review of treatment patterns in a continuing care unit

CHAPTER 6

CLINICAL STUDIES ON THE USE OF OPIOID DRUGS IN PATIENTS WITH ADVANCED CANCER

a. Questionnaire study into the use and attitudes of medical staff to opioid drugs in advanced cancer

6.a.1 Introduction

The management of pain in patients with advanced cancer has changed considerably in the past 10-20 years with the advent of the hospice movement and its emphasis on regular analgesia of appropriate strength to prevent pain recurrence (Saunders 1963). This contrasts with early statements in the literature emphasising the dangers of drug addiction and authoritative reviews from one of which comes the following quotation:

"A review of the literature indicates that 15mg doses of morphine are probably unnecessary to relieve pain ..... in view of these findings the routine use of 15mg seems unwarranted." (Lasagna and Beecher 1954).

A review of medical inpatients published in 1973 (Marks and Sachar 1973) found that 73% of patients had poor control of their pain, 32% of these reporting continued severe distress from their pain, and that inappropriate and inadequate medication with low doses of pethidine had been prescribed for 63% of the patients studied. This study included a questionnaire survey of staff physicians in two large New York Hospitals which revealed considerable misinformation about the use of narcotic drugs, with underestimates of their potency and duration of action and exaggerated fears of the dangers of addiction.

In current practice this is supported by figures from hospices

and continuing care units reporting around 75% of patients being admitted in pain, contrasting with the figures of unrelieved pain reported from these centres which apply the preceding principles of analgesic use where an incidence of between 1 and 10% is reported. (Twycross and Lack 1983).

In view of the continuing disparity between individual medical practices in the use of opioid drugs, in particular morphine, for pain due to advanced cancer, this questionnaire study was set up to assess both the prescribing practices of individual doctors and their understanding of various principles upon which this practice could be based.

6.a.2 Subjects and Method

An initial pilot study was carried out at the Royal Marsden Hospital, Sutton, in which a copy of the questionnaire with a covering letter, together with an addressed envelope for return, was sent to each member of the medical staff. Following this the study was extended to cover various representative groups of doctors who it was felt, in view of their training and type of practice, may exhibit differing views on the use of opioid drugs in advanced cancer. The groups studied were:

1. A specialist oncology hospital (The Royal Marsden Hospital, London SW3).
2. An undergraduate teaching hospital (Manchester Royal Infirmary).
3. A District General Hospital (Basingstoke General Hospital).
4. General Practice:
   A. Inner City (Islington , Bloomsbury and Hampstead)
   B. Suburban (Hounslow, Middlesex and Elstree, Herts)

Formal permission to perform the study was obtained from both the administration and medical executive committees of the outside hospitals involved. Current medical staff lists were supplied from each hospital and postal questionnaires with prepaid reply envelopes were to each member of medical staff at the chosen hospitals. The general practitioners were approached on an individual basis, their names having been obtained from the lists of the appropriate family practitioner committees.

A copy of the questionnaires received by the doctors taking part in this study is shown in appendix 2.

6.a.3 Statistical Analysis

Completed questionnaires were analysed in the Department of Epidemiology, Institute of Cancer Research, Sutton, Surrey.

6.a.4 Results

An overall response rate of 42.4% (265/625) was obtained from the six groups who received questionnaires. The response according to institution is shown in table 6.a.1 below:

The composition of the study population in terms of status, years since qualification, speciality and duration of specialist oncology experience is shown in Tables 6.a.2 to 6.a.5 inclusive.

Table 6.a.1

Details of response to questionnaire

Study Group	Number of Replies	Number of Questionnaires Sent	% Response
RMH Sutton	42	58	72.4%
RMH London	36	58	62.0%
Manchester	95	284	33.4%
Basingstoke	34	100	34.0%
G.P.	58	125	46.4%

Table 6.a.2
Study Population : I Status

	Consultant	Senior Registrar	Registrar	SHO	HO	*Total
RMH Sutton	42.9% (18)	26.2% (11)	14.3% (6)	16.7% (7)	-	100% (42)
RMH London	36.1% (13)	30.6% (11)	8.3% (3)	25% (9)	-	100% (36)
Manchester	31.6% (30)	20% (19)	13.7% (13)	17.9% (17)	4.2% (4)	87% (83)
Basingstoke	23.5% (8)	2.9% (1)	29.4% (10)	26.5% (9)	14.7% (5)	97% (33)

Table 6.a.3
Study Population ; II Years since qualification

	<5yrs	<5-10yrs	11-20yrs	>20yrs	*TOTAL
RMH Sutton	19% (8)	28.6% (12)	40.5% (17)	11.9% (5)	100% (42)
RMH London	22.2% (8)	22.2% (8)	38.9% (14)	16.7% (6)	100% (36)
Manchester	24.5% (23)	26.6% (25)	30.9% (29)	18.1% (17)	99% (94)
Basingstoke	39.4% (13)	36.4% (12)	15.2% (5)	9.1% (3)	97% (33)
G.P.	3.6% (2)	17.9% (10)	35.7% (20)	42.9% (24)	98% (58)

*Where total less than 100% this is due to this question not being answered.

Table 6.a.4
Study Population ; III Speciality

	[1]General Medicine	[2]Surgery	Medical Oncology	RT	Anaes-thetics	Haem-atology
RMH Sutton	-	11.9% (5)	38.1% (16)	38.1% (16)	9.5% (4)	2.4% (1)
RMHLondon	-	33.3% (12)	16.7% (6)	19.4% (7)	16.7% (6)	5.6% (2)
Manchester	26.3% (25)	36.8% (35)	-	-	14.7% (14)	6.3% (6)
Basingstoke	12% (4)	58.8% (20)	-	-	14.7% (5)	-
Overall	14% (29)	35% (72)	11% (22)	11% (23)	14% (29)	4% (9)

[1]Includes geriatrics and medical subspecialities e.g. cardiology and neurology
[2]Includes orthopaedics, gynaecology, ENT and ophthalmology

Table 6.a.5
Study Population ; IV Oncology Experience

	None	<6mths	6mths-1yr	1-3yrs	>3yrs
RMH Sutton	7.1% (3)	16.6% (7)	-	16.6% (7)	59.5% (25)
RMH London	8.3% (3)	11.1% (4)	27.8% (10)	5.6% (2)	47.2% (17)
Manchester	66% (63)	15% (14)	5.5% (5)	-	10.5% (10)
Basingstoke	59% (20)	20% (7)	6% (2)	3% (1)	9% (3)
G.P.	76% (44)	9% (5)	7% (4)	2% (1)	-
Overall	50% (133)	14% (37)	8% (21)	4% (11)	21% (55)

The drug of first choice for analgesia in the patient with advanced cancer is shown in Table 6.a.6. In this table the category mild/moderate analgesics refers to codeine-based preparations and weak opioid drugs, in particular dihydrocodeine and coproxamol.

Table 6.a.6
First choice analgesic according to centre

RMH Sutton

Morphine elixir	19(46.3%)
Diamorphine	11 (26.8%)
MST	9 (22%)
NSAID	1
Mild/moderate analgesic	1

RMH London

MST	12 (36.4%)
Morphine elixir	11 (33.3%)
Mild/moderate analgesic	4 (12.1%)
Other opiate	3 (9.1%)
Buprenorphine	2 (6.1%)

Manchester

MST	44 (50.6%)
Morphine elixir	15 (17.2%)
Diamorphine	10 (11.5%)
NSAID	5 (5.7%)
Mild/moderate analgesic	5 (5.7%)
Buprenorphine	4 (4.6%)
Other opiate	4 (4.6%)

Basingstoke

MST	13 (39.4%)
Diamorphine	9 (27.3%)
Morphine elixir	5 (15.2%)
Buprenorphine	3 (9.1%)
NSAID	1
Mild/moderate analgesic	1
Other opiate	1

General Practice

MST	38 (67.9%)
Mild/moderate analgesic	7 (12.5%)
Buprenorphine	5 (8.9%)
Diamorphine	3 (5.4%)
Morphine elixir	1
NSAID	1
Other Opiate	1

Morphine emerges as the most commonly used drug with overall 80% of doctors choosing either morphine or diamorphine. Controlled release morphine (MST) is the most popular preparation, particularly for younger doctors being used by 61.1% of those qualified for less than 5 years compared to 32% of those qualified for over 20 years. A total of 49 doctors did not choose morphine or diamorphine including 16 GP`s and 14 in surgical specialities. Weaker analgesics, either codeine based drugs, coproxamol or nonsteroidal antiinflammatory drugs (NSAIDs) were chosen by 28% of those qualified for over 20 years compared with only 7.4% of those qualified for less than 5 years. Both extent of specialist oncology experience and status also influenced choice of analgesic. Those with greater oncology experience preferred morphine or diamorphine elixir to MST (52% of those with more than 3 years oncology experience, compared to 24.2% of those with no oncology experience) and the use of weak analgesics was almost exclusively seen in those with less than one year of oncology experience (4 doctors only with more than 3 years oncology experience chose mild/moderate analgesics).

The influence of status on choice of strong opioid drug is shown in Table 6.a.7. in which an inverse relationship between MST and morphine or diamorphine elixir is seen, with more senior hospital staff preferring elixir to MST whilst GPs and junior hospital staff preferred MST.

Table 6.a.7

Influences on choice of morphine or diamorphine formulation

First Choice Drug	Status		
	G.P.	Registrar/SHO/ HP/HS	Senior Registrar Consultant
MST	66%	58%	25%
Morphine or Diamorphine Elixir	10%	29%	53%

231/248 respondents (93%) indicated that they would administer their drug of first choice regularly, and 17 (6.5%) would use as required administration (17 respondents did not answer this question). Of those who would not give the drug regularly, only 6 had chosen morphine as their drug of first choice, all of these in the form of MST. The remainder chose buprenorphine (6), NSAID (2), codeine based drugs (2) and 'other opioids' (1), as their drug of first choice.

208/248 respondents (84%) chose the oral route as their first choice route of administration as shown in table 6.a.8. Some anomalies between drug of choice and route of choice was seen; 14 chose parenteral administration but gave an oral drug preparation as their drug of choice (10 chose MST, and 4 NSAID). 13/20 (65%) of those choosing intermittent parenteral injections were from the non-specialist hospitals. Of the 19 who chose a continuous infusion, 12 (63%) had previous oncology experience in contrast to the 20 who chose intermittent injections of whom only 5 (25%) had previous oncology experience.

The preferred frequency of administration was inevitably influenced by the drug of first choice. The results for the strong opioid drugs morphine or diamorphine is shown in Table 6.a.9.

Table 6.a.8

Route of administration of first choice

Route	Number (%)
Oral	208 (83.9%)
Intravenous injection	2
Subcutaneous or Intramuscular injection	18 (7.2%)
Continuous subcutaneous infusion	19 (7.7%)
Rectal	1
TOTAL	248

Table 6.a.9
Frequency of Administration for Morphine or Diamorphine

Frequency	Morphine or Diamorphine Elixir	MST
2 hourly	4 (4.5%)	1
4 hourly	58 (70%)	13 (11%)
6 hourly	3 (4.0%)	5 (4%)
8 hourly	1	15 (13%)
12 hourly	0	72 (62.5%)
Other*	17 (20.5%)	9 (8%)
TOTAL	83 (100%)	115 (100%)

*Includes statements such as "as often as required", "more often if necessary", "4hourly and top-ups" etc.

43 (37.3%) of those who chose to give MST, would do so at less than 12 hourly intervals. These comprised 15 (39.5%) of GP`s using this drug, 23 (40%) of those at MRI or BDGH and 5 (23.8%) of those at the Royal Marsden Hospital.

The dose range given in answer to this question also yielded a range of answers dependent upon the drug of choice to which it referred, but for each drug an appropriate starting dose was stated. Greater disparity was seen in defining the dose range across which doctors were prepared to titrate their first choice analgesic, many giving relatively narrow, fixed ranges as shown in Table 6.a.10; 35 out of 201 (17.4%) of doctors choosing morphine or diamorphine defined an upper dose limit.

Table 6.a.11 shows the relative importance of five factors influencing drug dosage as scored by the respondents. Pain severity emerges as by far the most important determinant of dose, the remaining four factors being approximately equal. No clear trends within sub-groups of the population in their choice of these factors was seen.

Table 6.a.10
Dose limits stated related to drug of first choice

First choice drug	Maximum limit stated	No maximum limit stated	Total
Diamorphine	6	28	34
Morphine elixir	5	46	51
MST	24	92	116
Buprenorphine	8	6	14
NSAID	2	6	8
Mild/moderate analgesic	16	2	18
Other opioid	6	3	9

Table 6.a.11

Factors influencing drug dose

	Factor				
	Pain	Impaired renal or hepatic function	Body Weight	Age	Chronic airways disease
Most important	210 (84%)	9 (3.6%)	11 (4.4%)	12 (4.8%)	7 (2.8%)
2nd important	8 (3.2%)	60 (24.3%)	68 (27.4%)	57 (23%)	37 (14.8%)
3rd important	14 (5.6%)	55 (22.3%)	54 (21.8%)	60 (24.2%)	60 (24.1%)
4th important	8 (3.2%)	65 (26.3%)	62 (25%)	69 (27.8%)	84 (33.7%)
5th important	10 (4%)	58 (23.5%)	53 (21.4%)	50 (20.2%)	61 (24.5%)
*TOTAL	250 (100%)	247 (100%)	248 (100%)	248 (100%)	249 (100%)

*Total indicates number of doctors answering each category i.e. not all respondents gave five rankings.

Table 6.a.12 shows the action which respondents would take if their initial treatment resulted in either an inadequate degree or insufficient duration of analgesia.

Table 6.a.13 shows the importance respondents placed upon four recognised side-effects or contra-indications to the use of strong analgesics and Table 6.a.14 shows the influence of expected prognosis for the patient upon the use of strong analgesics.

Table 6.a.12
Responses to either insufficient duration or degree of analgesia

Response	Degree of analgesia inadequate	Duration of analgesia inadequate
Increase dose	170 (68.3%)	55 (22.1%)
Increase frequency	9 (3.6%)	124 (49.8%)
Give breakthrough medication	24 (9.6%)	43 (17.3%)
Change to regular medication	6 (2.4%)	5 (2.0%)
Change drug to:		
a) One of equivalent strength	3 (1.2%)	2 (0.8%)
b) Stronger drug	30 (12%)	15 (6.0%)
Other	7 (2.8%)	5 (2.0%)
*TOTAL	249 (100%)	249 (100%)

*16 respondents failed to answer this question

Table 6.a.13
Relative contraindications to the use of first choice analgesic

Contraindication	Response			*Total
	Yes	No	Possibly	
Sedation	11 (4.5%)	145 (58.9%)	90 (36.6%)	246
Respiratory Depression	28 (11.2%)	108 (43.4%)	113 (45.4%)	249
Nausea or Vomiting	47 (19.0%)	118 (47.8%)	82 (33.2%)	247
Addiction	3 (1.2%)	237 (96.3%)	6 (2.4%)	246

Table 6.a.14
Influence of expected prognosis on drug use

Prognosis	Influence on use of strong analgesic			*Total
	Yes	No	Possibly	
<1month	2	246 (98.4%)	2	250
1-6 months	1	242 (97.2%)	6 (2.3%)	249
>6 months	7	187 (74.2%)	58 (21.9%)	252

*Disparity between this column and total number of replies (265) due to individuals failing to answer certain questions

6.a.5 Discussion

The results reported above are based upon an overall response rate of 42% and can therefore be regarded only as a guide to prescribing patterns and attitudes amongst medical staff.

The first choice analgesic was either morphine or diamorphine for 201/250 (80%) of respondents, and this reply would be in keeping with published recommendations (Saunders 1963, Twycross and Lack 1983, World Health Organisation 1986). It is possible that the question as put in the questionnaire was considered slightly ambiguous by some respondents despite the emphasis on an analgesic for chronic severe cancer pain and this may explain the choice of codeine containing analgesics or coproxamol by 18 of respondents, and 9 who stated "an opiate drug" but did not specify their drug of choice. This leaves a further 22 who chose buprenorphine, a NSAID or other drug. Only five of those who gave a moderate analgesic as their first choice subsequently chose as their drug of second choice a strong opioid drug, the others choosing either to give a NSAID or a drug of equal analgesic strength. The finding that older doctors in particular gave drugs other than the strong opioid drugs may be due to resistance in this group to the use of strong opioid drugs for cancer pain..

The pattern of use of different morphine preparations is also of interest. Morphine elixir was overall the drug of choice at the Royal Marsden Hospital, perhaps reflecting the influence of a specialist continuing care unit whose policy is to recommend the use of this preparation (Hanks and Hoskin 1986). In contrast, the controlled-release formulation (MST) was the preferred form of morphine at both other hospitals and in general practice. This may reflect a number of factors. MST was clearly preferred by those qualified for less than

five years, perhaps due to its relatively recent introduction and the exposure of this group to marketing influences. Its popularity in general practice may also reflect the influence of drug marketing but also the fact that this preparation is much more convenient in general practice compared to the hospital ward where regular 4-hourly administration of morphine or diamorphine is more viable.

Regular oral administration of analgesia in patients with advanced cancer pain is recommended and this was chosen by most respondents. Of those who did not choose regular administration, the majority also chose inappropriate first choice drugs. Of greater concern was the reply by 6 respondents that they would use MST "as required" which, due to the nature of its controlled release formulation, is both inappropriate and probably ineffective (Hanks et al 1981). Further misunderstanding over the use of MST was seen when considering frequency of administration. Despite it being clearly stated that MST is a 12-hourly preparation (Data Sheet, Napp Laboratories Ltd) 43/115 (37%) chose to give it more frequently than this and even more disturbing were the replies of 19 (16%) who chose to give MST 6-hourly or less, under which conditions drug accumulation and consequent toxicity may occur.

16% chose a parenteral route as their first choice mode of administration. Again some difficulty in interpretation and in linking the drug chosen initially with their response to this question is seen, evidenced by those choosing oral preparations and parenteral administration. Despite this, however, a rather high incidence of parenteral administration as the route of administration of choice is revealed.

There were two questions regarding the most appropriate manoeuvre

to be performed if pain control is inadequate with the initial choice of drug. Some of these manoeuvres were dependent upon previous answers, for example a change from "as required" administration to regular administration could only be considered by those choosing as required administration. As might be expected, the majority chose, if the degree of pain relief were inadequate, to increase the dose. Most others chose to either give breakthrough medication or change to a stronger analgesic, all of which depending upon their initial answers regarding drug of choice, would be entirely appropriate manoeuvres. In contrast, where the duration of analgesia was inadequate, half of respondents chose to increase the frequency of administration, a potentially hazardous manoeuvre which could result in significant drug accumulation, whilst only 22% chose the more appropriate manoeuvre of increasing drug dose. For both degree and duration of analgesia being adequate only 2% shows change from "as required" to regular analgesia, despite 7% choosing "as required" administration as their method of choice, inferring that at least 5% of respondents would continue with "as required" medication in the face of persisting or recurrent pain.

Replies regarding the relative contraindications to the use of strong opioid drugs in pain due to advanced cancer showed a significant change in attitude to that commonly cited in the literature where fear of respiratory depression and addiction are held to be important reasons for witholding adequate analgesia in this situation (Saunders 1963, Marks and Sacher 1973, Twycross and Lack 1983). In this study only 11.2% considered respiratory depression to be a definate contraindication and only 1.2% stated that addiction would be an absolute contraindication . Nausea and vomiting was found to be the greatest problem in using strong analgesics with 19% considering this

to be a definite contraindication to their use.

In general, the prognosis of the patient was not considered to be an important factor in the use of analgesia, although 22% had reservations about its use in patients with a prognosis of more than 6 months. It may be that these respondents were considering patients potentially cured in whom the use of strong opioids is controversial.

In conclusion, the majority of respondents in this study have chosen to use regular morphine or diamorphine given orally with escalation of dose where pain relief is inadequate without an arbitrary upper dose limit. A number of respondents may have found the initial question a little ambiguous and chose a moderate painkiller such as coproxamol or dihydrocodeine which will have influenced their subsequent answers. Areas where there appear to be problems in the correct use of strong analgesics for pain due to advanced cancer, are in the use of "as required" medication by a significant minority, the use of MST at dose intervals less than 12-hourly, in the significant incidence of parenteral administration, the response to an inadequate duration of pain control and in providing adequate control of nausea and vomiting in conjunction with the use of strong analgesics. Respiratory depression, addiction and a relatively long prognosis no longer appear to be significant factors in limiting the use of strong analgesics amongst the selected group of doctors who replied to this questionnaire.

6.b Retrospective review of treatment patterns in a continuing care unit

6.b.1 Introduction

Optimal symptom control for patients with advanced cancer depends upon a detailed analysis and diagnosis of the underlying causes and careful selection of appropriate therapeutic manoeuvres individualised for each patient. Hospices and other specialised units have been established in recent years and have produced clear recommendations for the management of pain and other symptoms (Saunders 1963, Twycross and Lack 1983, Hanks and Hoskin 1986). There is, however, little published data on the resultant patterns of drug use and the relative importance of other therapeutic options in the management of symptoms due to advanced cancer.

A retrospective review of the treatments received by patients admitted to the Continuing Care Unit of the Royal Marsden Hospital, Sutton, has been carried out. The review covers the first year of operation of the Unit and provides information on the patterns of drug use and the importance of more specific therapies in these patients.

6.b.2 Patients and Method

Between January 1986 and January 1987 there were 233 admissions to the 13-bedded Continuing Care Unit at this hospital. Admissions are both by transfer from other wards in the hospital and, following discharge or outpatient referral, from home. Of 168 patients admitted to the Unit for the first time in the year of study, 97 (58%) were subsequently discharged home and 128 (76%) ultimately died as inpatients in the unit.

The case records of 158 patients admitted in this period have been reviewed, the remaining 10 records being unavailable or lost at the time of analysis. Details of the patients and the treatment they received whilst inpatients have been analysed.

Non-parametric analysis using the Mann-Witney test has been used to compare morphine doses in different population groups since neither the raw data nor log-transformed data were in a normal distribution.

6.b.3 Results

(i) Analgesics

Clinical details of the 158 patients analysed are shown in Table 6.b.1 and the pattern of oral analgesic and coanalgesic use in Table 6.b.2.

Twenty-seven patients (17%) received no morphine during their admission, their symptoms being adequately controlled with simple (non-opioid) or moderate (mild opioid) analgesics together with appropriate co-analgesics. In five patients a combination of coproxamol with additional paracetamol was given, in six paracetamol was used in combination with morphine and in seven patients coproxamol was used as breakthrough analgesia in patients on morphine.

Table 6.b.1

Patient characteristics (N = 158)

Mean age (Range)	63.2 (19-85)	
Male : Female	1:1.32	
Primary Tumour:	Breast	37 (23%)
	Bronchus	36 (22%)
	Prostate	11 (7%)
	Colorectal	10 (6%)
	Ovary	9 (5.5%)
	Kidney	6 (4%)
	Lymphoma	6 (4%)
	Sarcoma	5 (3%)
	Unknown Primary	9 (5.5%)
	Other	29 (20%)

Table 6.b.2

Analgesic and Co-analgesic use

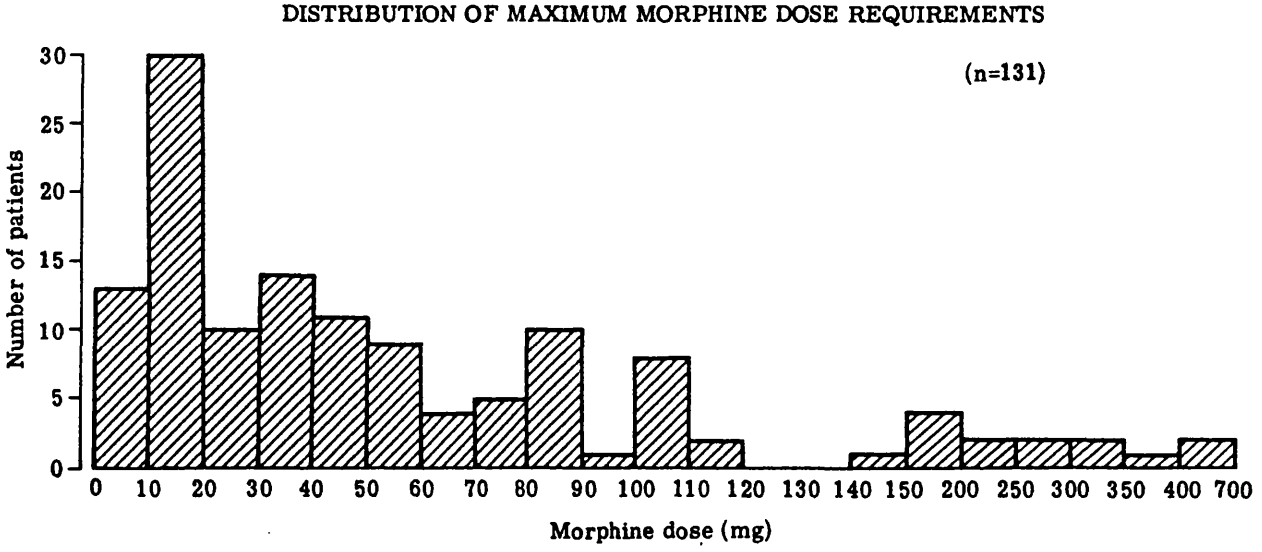
Analgesics	Simple analgesics (paracetamol)	19 (12%)
	Moderate analgesics (coproxamol or dihydrocodeine)	23 (14.5%)
	Strong analgesics (morphine and diamorphine)	131 (83%)
Coanalgesics	NSAID	40 (25%)
	Steroids	67 (42%)
	Antidepressant	30 (19%)
	Anxiolytic	61 (39%)

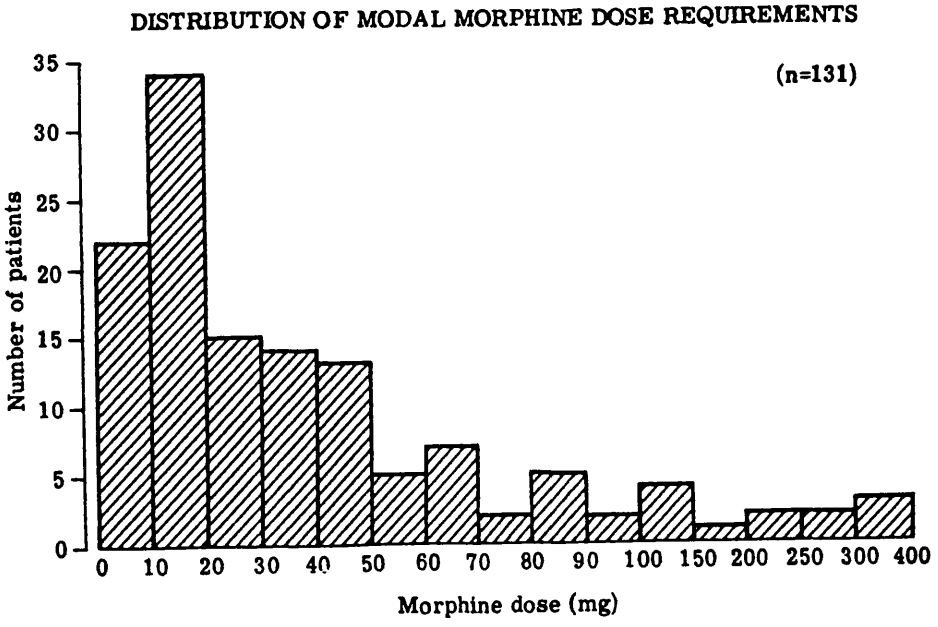
Of the 131 patients who received morphine, four used suppositories and one had oxycodone suppositories substituted for oral morphine. When given orally, morphine elixir was used for most patients (aqueous morphine sulphate solution containing EDTA and sodium metabisulphite as preservatives). Thirty patients (23% of those receiving morphine) had morphine in slow release formulation (MST Continus) at some time during their admission. In 10 patients MST was the only morphine preparation used. Four patients were taking oral diamorphine tablets at the time of referral. The only other strong opioid drug to be used regularly was dextromoramide, which three patients received as a short-acting top-up analgesic to cover painful dressing changes. One patient was taking pethidine and one methadone at the time of referral. The former was changed to morphine and the latter continued with methadone. All other patients who required a strong opioid analgesic and were able to take oral medication were managed with oral morphine.

Details of both the modal dose of morphine and the maximum dose received by the 131 patients requiring morphine are shown in Figure 6.b.1. In 65% of patients a modal 4-hourly dose of less than 40mg was required and in 51% a maximum 4-hourly dose of less than 40mg was given. Only 11% required doses greater than 120mg 4-hourly.

Figure 6.b.1

Distribution of modal and maximum 4 hourly morphine dose requirements





Sixty-one patients who received morphine had either renal impairment (serum creatinine > 120 mmol/l), hepatic impairment (alanine transaminase > 30 IU/L or GGT > 50 IU/L) or both. Table 6.b.3 shows that the median doses of morphine (both modal and maximum) were lower in patients with renal and hepatic impairment compared with those with normal function, though the differences did not achieve statistical significance.

In contrast, a highly significant inverse relationship between morphine dose requirement and age was seen (Table 6.b.4).

TABLE 6.b.3

Morphine dose in relation to renal and hepatic function

	Modal morphine dose(mg) Median (range)	Maximum morphine dose(mg) Median (range)
Renal* Impairment (N=19)	15 (3-160)	25 (3-220)
Hepatic+ Impairment (N=41)	20 (3-320)	30 (3-360)
Renal & Hepatic Impairment (N=11)	20 (5-40)	20 (5-100)
Normal (N=60)	30 (3-400)	45 (5-700)

* Serum creatinine > 120 mmol/l

\+ Alanine transaminase > 30 Iu/l or Gamma glutamyl transferase > 50 Iu/l

Differences are not statistically different using Mann Witney test.

TABLE 6.b.4

Morphine dose in relation to age

Age Group	A	B	C
Age Range (years)	19-59	60-69	70-86
Median age (years)	50.5	64.0	74.5
Number of patients	44	43	44
Modal Dose(mg)			
Median (Range)	55 (3-700)	30 (3-100)	25 (2-200)
Maximum Dose(mg)			
Median (Range)	40 (3-400)	15 (3-100)	17.5 (5-160)

The following differences are statistically significant using the Mann-Witney Test:

Maximum Dose	Modal Dose
Group A vs Group B, p=0.0001	Group A vs Group B, p=0.0023
Group A vs Group C, p=0.0007	Group A vs Group C, p=0.0012

Parenteral diamorphine was given to 85 patients (54%). The indication for parenteral administration in these patients was inability to take oral medication or suppositories. In 76 of the 85 patients (89%) this was due to deteriorating levels of consciousness in the final hours before death, in eight (9%) intestinal obstruction was present, and in one case parenteral medication was used because of intolerance to high doses of oral morphine. Where patients were judged to be close to death diamorphine was administered by intermittent subcutaneous injection. In the 59 patients who received diamorphine in this way a median of one dose and mean of 2.3 doses (range 1-12) was required, median survival from the initiation of diamorphine being 12 hours (range 2-48 hours). To avoid multiple injections in patients with longer life expectancy a subcutaneous infusion was used in 26 patients. In two patients with sub-acute intestinal obstruction the duration of infusion was four weeks and three months respectively. In the remaining 24 patients the median duration was 96 hours, and the mean 49.8 hours (range 12-192 hours).

(ii) Coanalgesic Use

Hyoscine by injection was given with diamorphine to ameliorate respiratory symptoms from retained secretions in 54 patients (34%) and one patient received an infusion over four days. When given by injection the median number of injections required was one, mean 3.6 (range 1-20).

Non-steroidal antiinflammatory drugs were selected for those patients with bone pain or other musculoskeletal pain. In the 40 patients receiving these drugs, 24 were given flurbiprofen, the drug of first choice in this unit, seven received ibuprofen, three benorylate,

two naproxen, one diclofenac and three patients received indomethacin by suppository.

The indications for steroids in the 67 patients receiving them are shown in table 6.b.5. Fifty-three patients received dexamethasone, our steroid of choice, the remaining 14 having been started on prednisolone prior to referral.

(iii) Antiemetic Use

A total of 78 patients (49%) received antiemetic drugs. Of the 131 patients receiving morphine, 74 (56%) required an antiemetic. Thirty-nine of these patients were female and 35 male. The pattern of individual antiemetic drug use is shown in Table 6.b.6. This reflects a policy of using haloperidol as first choice antiemetic for opioid related nausea or vomiting and metoclopramide as the drug of choice where there is thought to be an element of gastric stasis.

Table 6.b.5

Indications for the use of steroids

Soft Tissue Infiltration (including hepatic metastases)	20 (30%)
Nerve Root Compression	11 (16%)
Cerebral Metastases	10 (15%)
Antiemetic	8 (12%)
Spinal Cord Compression	4 (6%)
Non-specific effects	14 (21%)

Table 6.b.6

Patterns of antiemetic use

	HALOPERIDOL	CYCLIZINE	METOCLOPRAMIDE	CHLORPROMAZINE	PROCHLORPERAZINE	DOMPERIDONE
ALONE	28	15	15	6	1	0
IN COMBINATION*	7	7	6	3	0	2
TOTAL	35	22	21	9	1	2

* 12 patients required a combination of antiemetics; 11 received 2 drugs, 1 received 3 drugs

(iv) Antitumour Therapy

Many patients also received specific tumoricidal therapy for symptom control. Twenty-one patients (13%) were treated with radiotherapy and the indications for this are shown in table 6.b.7.

Twenty-three patients (14.6%) received hormone therapy, details of which are given in Table 6.b.8. Six patients (3.7%) received chemotherapy: three had 5FU for colo-rectal cancer, one had 5FU, adriamycin and mitomycin C for carcinoma of the stomach, one carboplatin for a paraganglioma, and one tumour necrosis factor for lung cancer. Five patients had surgical procedures performed: two had Nottingham tubes passed for obstructive dysphagia, two had internal fixation of a bone (in one case prophylactically and in the other after pathological fracture) and one patient had examination under anaesthetic and cystoscopy. In addition, two patients had dental procedures under general anaesthetic.

Table 6.b.7

Indications for Radiotherapy

Bone Pain	11
Cerebral Metastases	3
Spinal Cord Compression	2
Pelvic Mass	2
Painful Skin Nodule	1
Primary Cerebral Tumour	1
Base of Skull Infiltration	1

Table 6.b.8

Details of hormone therapy

a) Primary Tumour

Breast	Prostate	Kidney	*Other	Total
11	3	3	6	23

* Includes; Unknown primary tumour (3), Lung (2), Colon (1)

b) Drug

Tamoxifen	MPA	AG	*Other	Total
11	5	3	4	23

* Includes: stilboestrol (1), norethisterone (1), 4-hydroxyandrostenedione (2)

MPA = medroxyprogesterone acetate

AG = aminoglutethamide

(v) Other Therapies

Other pain relieving measures were also employed in selected patients. Twenty-one (13%) received treatment with a graduated compression sleeve (Lymphapress) for lymphoedema. Transcutaneous nerve stimulation, acupuncture and relaxation was given to some patients but accurate figures for their use are not available. Only one patient had a specific nerve blocking procedure; a coeliac plexus block for pain and nausea resulting from a primary carcinoma of the pancreas.

3.b.4 Discussion

The data presented demonstrate the wide range of therapeutic options available to control the symptoms of advanced cancer. The use of a simple analgesic ladder escalating from paracetamol to coproxamol or dihydrocodeine and then to morphine has meant in practice that only a limited number of analgesic drugs were used. Seventeen percent of patients achieved good symptom control without the use of morphine or any other strong opioid analgesic. This may reflect in part the fact that pain was a presenting symptom on admission in only 127 patients (80%), although this is more than balanced by the finding that the prime indication for morphine in 29 patients (22%) was relief of respiratory symptoms rather than pain.

The pattern of morphine dosage is similar to that reported in other published data (Twycross 1984, Hanks and Twycross 1984). In one series 67% of patients required a maximum 4-hourly dose of less than or equal to 30mg in contrast to 40% in this study, and 2% a maximum 4-hourly dose of greater than 200mg 4-hourly compared to 7% in this study. Other studies have reported only maximum doses whilst the modal doses seen here demonstrate that much lower doses are required for most of the period that the patient requires morphine. Approximately one-quarter of patients received slow-release morphine tablets. These are used once a patient's pain has been controlled on a stable dose of 4-hourly morphine elixir, and they provide a highly convenient means of delivering regular morphine. In patients who are starting morphine or who require frequent dose adjustments, however, this formulation is unsatisfactory and 4-hourly elixir is preferred. The relatively small percentage of patients receiving MST may be a reflection of the fact that this was an in-patient population, often with difficult pain

problems or an otherwise unstable clinical state.

A previous report has examined the influence of renal and hepatic impairment on morphine requirements and found much lower median dose requirements (in terms of maximum doses) in patients with renal but not hepatic impairment (Regnard and Twycross 1984). These data were not subjected to statistical analysis. Our data show that although lower median doses were required, in this case for both renal and hepatic impairment, there was wide individual dose variation and the differences were not statistically significant. In contrast, a highly significant effect of age can be seen with much higher morphine dose requirements in younger patients. The explanation for this is not clear. It may reflect a more marked affective component to chronic cancer pain in younger patients making pain control more difficult, although a similar effect has also been observed in acute post-operative pain (Kaiko 1980) where a significant affective component of pain would not be expected. Pharmacokinetic data suggest that the disposition of morphine in the elderly is altered with a much smaller volume of distribution which may account to some extent for their lower dose requirements (Owen et al 1983).

True intolerance to oral morphine is rare if side effects are anticipated and prevented. Three of our patients had particular difficulties: one was troubled by persistent nausea and vomiting, and two by excessive drowsiness. In these patients, conversion to a subcutaneous diamorphine infusion (one patient) or oral phenazocine (two patients) proved effective in reducing side effects but maintaining pain control. All other patients who required a strong opioid analgesic and were able to take oral medication were managed with oral morphine.

Previous reports have indicated that 69% (Twycross and Lack 1983) and 51% (Walsh et al 1981) of patients have required parenteral diamorphine before death. In this series the figure was 54%.

Spinal opioid administration is not used in this unit and the evidence to date does not support any particular advantage for this route of administration (Leading Article 1986), except in rare situations when patients are unable to tolerate any strong opioid given systemically.

Only 49% of all patients required an antiemetic and of those receiving morphine, 56%. This proportion is lower than previously reported (Hanks 1982, Walsh 1982) and supports the policy for inpatients of close surveillance with immediate introduction of antiemetics where symptoms arise, rather than routine administration in all patients. The proportion of patients receiving combination antiemetics is similar to that reported by Hanks (Hanks 1982) and significantly lower than the series from St Christopher's Hospice (Walsh 1982). This latter report also showed that a greater proportion of females required antiemetics though this was not apparent in the Oxford data (Hanks 1982) and in the present series the sex incidence was approximately equal.

Co-analgesics were used to enhance the pain control provided by conventional analgesia in 124 patients (78%). The significant affective component of chronic cancer pain is reflected in the relatively high proportion of patients receiving an antidepressant or anxiolytic drug. As far as NSAIDs are concerned, their use was reported in 14.5% of 643 patients at St Christopher's Hospice (Walsh et al 1981) compared with 25% of the 158 patients in this series.

A fundamental difference between this continuing care unit and a

hospice is its place as an integral part of the hospital, benefitting from close and easy access to specialist oncological teams. This is reflected in the considerable proportion of patients who had specific tumoricidal therapy either initiated or continued whilst in the Unit. In each case this was for control of specific symptoms. In total 46 patients (29%) received either radiotherapy, hormone therapy, chemotherapy or had surgery. This contrasts with data from St Christopher's Hospice reporting the use of radiotherapy in 5% of inpatients (Saunders 1986), hormone therapy in 6% and chemotherapy in 1.6% (Bates and Vanier 1984).

This retrospective study confirms that for most patients with pain due to advanced cancer a simple therapeutic regimen using a three step analgesic ladder and a limited number of co-analgesic drugs is appropriate. In addition, almost one-third of patients benefitted from specific selected anti-tumour therapy. In particular radiotherapy or hormone therapy can be used to optimise symptom control without additional treatment-related toxicity.

CHAPTER 7 CONCLUSIONS

7.a Assay methods

7.b Pharmacokinetics of morphine

7.c Morphine metabolites

7.d Controlled release morphine tablets

7.e Enterohepatic circulation of morphine

7.f Clinical use of opioid drugs

7.g Future studies

CHAPTER 7

CONCLUSIONS

7.a. Assay Methods

A sensitive and specific assay for morphine and its metabolites is an important prerequisite for the pharmacokinetic studies presented here. Two principle assay methods have been assessed in this work, HPLC and RIA, and neither has proven to be ideal. HPLC, whilst providing the optimum in specificity, has proven extremely unreliable in regular day to day use despite meticulous laboratory techniques. In contrast, RIA has been both reliable and much more efficient in handling the large numbers of samples generated in a pharmacokinetic study. It has also proved to be highly flexible in adjusting the technique for blood samples to other body fluids, in particular CSF, bile and pleural fluid, and much more sensitive in detecting levels of morphine < 10 ng/ml which are present after single doses of 5-10mg.

A major concern in the use of RIA for morphine is in ensuring its specificity. In Chapter 2 a large series of samples analysed by both HPLC and RIA have shown that using the current "specific" antiserum, accurate estimation of morphine separate from its major metabolites can be obtained, and that theoretical cross-reactivity with normorphine appears unimportant in clinical samples. However, the discrepancy obtained in the estimates of bioavailability for MST tablets (Chapter 4.b), using the two assay methods, highlights the potential problems that may occur, even when good correlation between individual samples has been demonstrated.

Greater caution is required when interpreting the metabolite data obtained by differential RIA. However, limited comparison with HPLC and results of recovery experiments in spiked samples, suggest that a

reasonable estimation of M3G and M6G may be obtained by this method, although absolute accuracy may be less than with HPLC. It is likely that M3G levels measured by RIA are underestimated and that M6G levels are overestimated. Furthermore, since on the basis of the recovery data presented in chapter 2.f the relative amounts of morphine and metabolite are an important determinant of the degree of over- or under-estimation, between subject comparisons of metabolite levels may be misleading, whilst within subject comparisons are less likely to be significantly affected.

In conclusion, the gold standard for morphine assay remains HPLC but its poor reliability and inflexibility make RIA a more appropriate technique for routine use. Current specific antisera produce comparable accuracy for morphine concentrations over a wide range. Differential RIA provides a useful estimate of metabolite concentrations but may not approach the absolute accuracy obtained by HPLC.

7.b. Pharmacokinetics of Morphine

Marked individual variation in the pharmacokinetics of morphine was seen within both healthy subjects receiving a single dose and in patients receiving multiple doses.

The bioavailability of oral morphine was between 23% and 34%. There was no significant difference in bioavailability apparent between a single dose or chronic dosing and no demonstrable effect of impaired liver function was seen. No difference in bioavailability between morphine in simple aqueous solution, and controlled release tablets (MST Continus) has been demonstrated. The median t_{max} after oral solution was 30-45 minutes, and after MST was 2.4 to 2.5 hours.

The pharmacokinetic parameters derived after intravenous administration show a significantly longer half life and lower clearance of morphine in patients receiving regular repeated oral doses compared with a single oral dose administered to healthy volunteers.

The administered dose of morphine shows consistent correlation with the AUC of morphine in plasma.

Morphine is widely distributed with a mean volume of distribution after single IV injection of 5.0 litres/kilogram. Significant concentrations in CSF, bile, pleural fluid and ascitic fluid have been demonstrated after repeated doses.

7.c Morphine metabolites

The principal metabolites of morphine found in plasma are M3G and M6G. After single oral doses in healthy volunteers the ratio of morphine to M6G is approximately 1:11, which is similar to the ratio of between 1:6 and 1:9 seen after repeated doses.

A mean elimination half-life of 2.2 hours and volume of distribution of 3.6 litres/kg has been calculated for M6G after a single dose of morphine given to healthy volunteers.

These metabolites can also be demonstrated in the CSF, bile, pleural fluid and ascitic fluid.

A relationship between both morphine and M6G and certain pharmacodynamic parameters has been demonstrated in healthy volunteers. This supports the hypothesis that M6G as well as morphine is important in producing the observed clinical effects in man.

7.d. Controlled release morphine tablets

Controlled release morphine tablets are a popular and convenient means of delivering regular oral morphine chosen in preference to other strong opioid formulations in a large postal questionnaire. In an inpatient population within a specialist continuing care unit, 25% of patients received morphine in the form of controlled release tablets.

Controlled release morphine tablets have been shown to be dose equivalent to oral morphine solution, having an absolute bioavailability of 22.4% (compared to 23.8% for oral solution) and a relative bioavailability of between 80 and 94%. The relative amounts of M3G and M6G seen in plasma are also the same after MST as after morphine elixir.

The controlled release nature of the preparation is demonstrated by the later t_{max} and attenuation of the C_{max} when compared with the plasma profile after oral solution.

When transferring a patient from MST to oral solution, a theoretical period of 2 - 3 hours after the first dose of MST exists when inadequate amounts of morphine may be available. Despite this, both clinical assessment of pain and pharmacokinetic data suggest that adding a loading dose of morphine solution with the first dose of MST is unnecessary.

7.e Enterohepatic circulation of morphine

Morphine and its two major metabolites, M3G and M6G, are excreted in bile. Considerable individual variation in both the relative and absolute amounts found in bile is seen. The influence of antibiotics (with resultant loss of gut flora) has not been investigated but circumstantial evidence for reabsorption of morphine excreted in bile,

comes from the demonstration of secondary peaks in the plasma profiles after both single and repeated doses of morphine.

The relative importance of this proposed enterohepatic circulation is unclear but it may account for a significant pool of recirculating morphine.

7.f Clinical use of opioid drugs

76% of a wide cross-section of medical practitioners surveyed in a postal questionnaire chose morphine or diamorphine as their drug of choice for the treatment of severe pain due to advanced cancer. Controlled release morphine tablets (MST) emerged as the most popular morphine formulation and was particularly favoured by those most recently qualified. The oral route and regular administration were chosen by most respondents and over 80% were prepared to titrate the dose of morphine or diamorphine without a preconceived upper dose limit. In general, drug addiction, respiratory depression and a relatively long prognosis were not major concerns limiting the use of strong opioid drugs, but troublesome side effects, in particular nausea and vomiting, were cited as a significant contraindication to their use.

In a population of inpatients in a specialist continuing care unit dealing with symptoms from advanced cancer, morphine or diamorphine was required in 83%. A wide range of dose requirements was demonstrated, the dose being defined by titration against the patient's symptoms, in most cases this being pain. The only factor shown to influence dose to a significant degree was age, with older patients requiring significantly lower doses of morphine, although a trend towards lower doses in patients with renal and/or hepatic impairment

was also seen. Morphine, or diamorphine for parenteral use, was the only strong opioid required for all but 3% of patients studied and concurrent antiemetic therapy was required in 56% of patients.

Overall, the regular use of oral morphine or diamorphine titrating the dose against the patient's pain appears to be the method of choice for pain control in advanced cancer for the majority of medical practitioners.

7.g. Future Studies

The morphine assay remains a major concern in developing further work in the pharmacokinetics of morphine. The specific RIA employed in these studies appears sensitive and specific for morphine, giving comparable accuracy to HPLC with greater sensitivity at low concentrations and being more rapid and reliable in day to day use. However, with increasing recognition of the active role for metabolites accurate quantitation of, in particular, M6G is becoming of increasing importance in any study of morphine. Further development and refinement of the HPLC is required for this to be a viable means of routine measurement of M6G, although at present it remains the most accurate means of doing so. An alternative approach is to develop a specific RIA for M6G and work on the development of a suitable antiserum has been initiated.

The studies presented here establish basic pharmacokinetic parameters for the standard morphine formulations currently used, ie parenteral injection, oral solution and controlled release tablets, and have compared single doses to multiple doses. There remains, however, little information on the pharmacokinetics of morphine during continuous subcutaneous infusion and after rectal administration, both

being common means of administration in a patient unable to take oral medication. Particular factors requiring investigation are the influence of infusion site, local inflammation, duration of use, and the addition of other drugs to the infusate. Other routes of administration include sublingual and inhaled morphine, both of which have been described but require further systematic study.

The role of M6G requires further evaluation as does consideration of other possible active metabolites such as normorphine and morphine ethereal sulphate. Basic animal studies have recently been repeated defining the analgesic activity of M6G but further work looking at its pharmacokinetics, in particular the characteristics of its entry into the central nervous system and binding to opioid receptors is required, together with evaluation of the concentration-effect relationship in experimental pain models. In man, further data on its production and distribution is required , particularly in patients receiving regular doses of morphine and those with hepatic or renal impairment. Early work has recently been reported (Osborne et al 1988) describing its analgesic activity after intravenous administration in man, and again further systematic carefully documented studies in this area are required. This should include both comparison with placebo and with morphine itself, together with attempts to correlate the pharmacokinetic and pharmacodynamic characteristic after intravenous injection.

There remain little data on the distribution and concentration of M6G in the CNS in man. Whilst opportunities for study of drug distribution in this situation in man are limited, the increasing use of indwelling intrathecal catheters may enable dynamic studies of morphine and M6G levels in CSF. Post-mortem studies on human brain

tissue and spinal cord, and possibly other indirect methods such as positron emission should be explored to enable measurement of absolute and relative amounts not only in CSF but also in CNS tissue itself.

Enterohepatic circulation of morphine and its metabolites has been established in this work, but further studies are required to determine the kinetics of these substances in bile, both after a single dose and multiple doses of morphine. The effect of antibiotics and small bowel resection also requires further investigation.

Whilst there has been a definite improvement in the appropriate use of morphine for the control of symptoms due to advanced cancer, as documented here, further work in the continued education of medical and nursing staff is essential. Particular areas which emerge from the study presented here as requiring attention are in the appropriate manipulation of dose once morphine has been initiated in order to gain optimum pain control, and in the control of associated symptoms, in particular drowsiness, nausea and vomiting. Careful documentation and observation in the clinical use of morphine with particular attention to the dose range required and the influence on this of factors such as the aetiology of the patient's pain, concommitant medication and renal and hepatic function, alongside further pharmacokinetic studies in these patients are needed if further progress is to be made in defining and understanding more clearly the role of morphine in these situations.

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CHAPTER 2.b

Standard curves for HPLC assay (figure 2.b.4)

a) Morphine

Concentration (ng/ml by weight)	Peak height
8	5
20	11
40	19
80	38
160	80

b) Morphine - 3 - glucuronide

Concentration (ng/ml by weight)	Peak height
80	1054
160	2561
200	3189
300	4797
400	6851

c) Morphine - 6 - glucuronide

Concentration (ng/ml by weight)	Peak height
8	5
20	9
40	14
80	28
160	52

Comparison of HPLC vs HPLC vs RIA (figure 2.e.2)

Morphine concentrations ng/ml

HPLC (Barts)	HPLC (Hackney)	RIA
34.7	34.8	21.8
35.5	18.1	19.1
64.9	51.8	39.8
87.0	65.4	61.9
94.7	76.8	86.0
121.3	87.6	108.0
87.8	84.8	82.0
100.5	66.8	61.8
100.1	67.9	72.3
97.4	54.9	55.0

CHAPTER 2.f

Influence of method of blood sample collection.

(a)Morphine concentration ng/ml

Patient	Serum		Plasma			
	Glass	Plastic	Glass Heparin	Plastic Heparin	Glass Citrate	Glass Oxalate
1	42.22	36.97	29.68	31.70	26.45	31.70
2	115.82	115.82	113.18	121.07	110.56	115.81
3	189.41	178.90	-	-	-	-
4	129.36	81.06	94.85	36.80	60.35	46.55
5	488.16	474.36	522.66	533.01	488.16	508.86
6	350.16	336.36	350.16	339.81	329.46	329.46
7	112.11	108.66	108.66	115.56	98.30	94.86
8	77.61	81.06	87.96	81.06	82.06	88.61
9	46.56	39.66	39.66	39.66	46.56	53.46
10	419.16	332.56	322.56	339.46	329.46	329.46
11	191.46	184.56	184.56	198.56	177.66	156.96
12	67.26	46.56	39.56	39.56	46.56	108.56

(b) M3G concentration ng/ml

1	2195.5	2183.07	2170.62	2170.63	1921.57	2083.45
2	1161.98	1193.11	1193.11	1211.79	1012 55	1130.85
3	937.84	925.38	925.38	944.06	800.86	875.57
4	4930.89	4666.17	4930.89	4460.28	3401.42	3695.55
5	13460.65	13166.52	12872.38	12548.8	12195.88	11901.75
6	11225.20	10989.90	10784.06	10695.82	10695.83	10666.42
7	10578 10	10460.50	9578.1	9460.48	9372.25	9248.4
8	5225.02	5401.50	4989.70	5048.54	4401.46	5195.61
9	9048.70	9107.53	8754.57	8754.57	7813.36	8695.74
10	9460.48	9519.31	9519.31	9519.31	9284.00	9519.31
11	4901.48	4901.48	4695.59	4636.76	4048.50	3401.42
12	3283.70	3166.11	3107.29	3166.11	2695.50	2871.90

(c) M6G concentration ng/ml

1	350.40	344.33	350.40	350.33	295.78	320.10
2	204.74	201.71	195.06	198.68	180.47	186.54
3	141.02	137.97	150.12	174.39	156.19	168.33
4	862.47	840.56	884.38	805.50	617.07	660.89
5	2304.20	2532.67	2435.67	2514.54	2488.35	2546.84
6	2654.77	2646.01	2628.48	2549.60	2435.66	2610.96
7	2619.72	2549.60	2575.89	2575.89	2409.37	2488.26
8	489.99	489.99	472.45	452.93	393.58	446.16
9	1278.78	1286.30	1234.95	1208.60	1129.78	1234.95
10	1129.78	1050.90	1015.85	1077.20	1007.08	1068.43
11	590.78	595.16	595.16	568.86	525.05	446.16
12	270.87	270.87	279.64	279.64	235.82	253.35

Chapter 3
Morphine pharmacokinetics in healthy volunteers

Intravenous route

Morphine concentration ng/ml

	1	2	3	4	5	6
2min	315	138	157	287	137	144
5min	53.0	34.3	31.6	80.9	34.0	32.0
10min	23.5	22.9	17.2	24.6	20.9	17.5
15min	16.0	20.2	12.1	17.3	14.7	13.2
30min	11.6	13.9	15.6	10.9	9.53	9.15
45min	10.5	11.1	6.68	8.58	6.15	6.52
60min	8.50	10.1	4.83	7.62	5.50	5.73
1.5h	3.28	8.84	4.93	4.45	3.71	3.68
2hrs	3.56	5.64	3.93	3.87	2.99	2.93
2.5h	3.12	5.37	2.99	3.28	2.96	3.66
3hrs	2.32	5.72	2.71	2.57	2.47	2.48
4hrs	2.07	2.81	1.58	2.15	1.65	1.92
6hrs	1.00	0.83	1.05	0.69	0.66	0.66
8hrs	1.07	0.43	0.64	N.D.	N.D.	N.D.
12hrs	0.39	N.D.	N.D.	N.D.	N.D.	N.D.

M6G concentration ng/ml

2min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
5min	N.D.	N.D.	6.4	N.D.	N.D.	N.D.
10min	N.D.	N.D.	7.0	N.D.	N.D.	N.D.
15min	6.52	N.D.	9.1	18.4	6.5	7.8
30min	18.4	9.4	16.7	19.7	12.4	10.0
45min	8.0	11.0	15.2	23.3	19.4	6.8
60min	20.1	12.8	15.6	21.1	14.6	10.1
1.5h	15.6	17.4	13.4	16.0	17.5	10.4
2hrs	15.5	13.9	13.6	14.0	7.6	9.5
2.5h	13.3	12.2	11.2	11.3	7.0	7.2
3hrs	11.7	7.0	10.4	10.0	7.8	6.5
4hrs	10.7	10.2	7.0	4.6	5.2	3.9
6hrs	5.7	4.94	5.1	5.0	3.2	2.4
8hrs	3.8	3.6	2.8	3.3	2.5	2.5
10hrs	2.5	2.8	1.9	2.4	1.6	1.6
12hrs	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

N.D. = None Detected

Oral Solution

Morphine concentration ng/ml

	Subject					
	1	2	3	4	5	6
15min	16.2	1.98	8.85	5.65	3.38	4.66
30min	13.9	2.15	16.4	9.45	4.88	6.49
45min	11.7	3.58	10.7	12.7	6.45	7.80
1hr	11.0	3.92	5.42	5.11	4.34	4.66
2hrs	6.80	2.33	2.90	5.26	2.35	2.57
2.5h	4.63	1.41	2.67	3.64	1.60	1.13
3hrs	3.53	1.23	2.35	3.15	1.43	1.31
3.5h	3.41	-	1.57	1.87	1.19	0.85
4hrs	2.85	0.93	1.30	1.62	0.89	0.70
5hrs	2.31	0.65	1.23	0.88	0.71	0.36
6hrs	1.61	-	0.83	0.58	0.43	0.34
8hrs	0.93	0.25	0.68	0.31	0.41	N.D.
10hrs	0.71	0.17	0.58	0.22	N.D.	N.D.
12hrs	0.88	0.25	0.36	0.27	N.D.	N.D.

M6G concentration ng/ml

	Subject					
	1	2	3	4	5	6
15min	24.1	3.57	4.85	3.96	3.32	6.14
30min	45.0	14.2	17.1	9.95	8.52	13.9
45min	61.6	23.7	42.2	35.7	37.5	22.1
1hr	56.6	46.3	50.4	53.1	66.2	33.7
2hrs	52.5	59.9	32.0	51.9	50.9	22.4
2.5h	42.6	31.4	19.3	47.1	42.3	23.5
3hrs	34.0	25.8	18.3	31.2	35.0	14.5
3.5h	31.6	21.6	13.1	33.4	25.6	11.7
4hrs	18.1	17.5	12.2	27.3	20.9	9.70
5hrs	14.3	10.0	5.62	14.2	15.2	7.34
6hrs	13.3	8.40	6.80	11.5	9.05	5.06
8hrs	6.88	4.19	2.61	5.31	5.32	4.40
10hrs	7.56	3.09	1.78	3.16	3.84	3.18
12hrs	7.19	2.31	3.10	2.80	2.36	2.62

Controlled Release tablet

Morphine concentration ng/ml

	Subject					
	1	2	3	4	5	6
15min	6.20	1.11	N.D.	3.20	1.42	1.89
30min	3.80	1.12	0.97	2.65	2.41	1.45
45min	3.60	1.66	3.93	2.38	3.03	1.97
1hr	3.50	1.51	4.50	3.03	2.08	2.05
2hrs	4.23	1.35	2.60	3.23	2.28	1.41
2.5h	2.95	1.33	1.81	2.80	2.19	1.55
3hrs	2.65	1.51	2.12	2.49	3.93	1.03
3.5h	2.81	1.77	2.29	2.98	2.54	1.09
4hrs	2.95	1.59	2.41	-	2.66	0.99
5hrs	2.41	1.17	1.83	2.25	2.33	2.42
6hrs	2.50	0.63	1.32	1.51	1.02	0.92
8hrs	1.49	0.43	1.02	0.78	1.38	0.41
10hrs	0.85	0.37	0.44	0.46	0.66	0.33
12hrs	0.71	0.27	0.37	0.48	0.46	0.38

M6G concentration ng/ml

	Subject					
	1	2	3	4	5	6
15min	N.D.	2.24	N.D.	0.47	0.78	1.61
30min	8.90	8.40	1.32	5.10	5.69	9.95
45min	13.5	14.0	7.97	8.62	26.0	16.8
1hr	16.6	26.4	16.7	16.9	47.4	25.7
2hrs	29.8	30.6	20.9	41.6	28.0	34.0
2.5h	26.4	22.6	20.3	29.7	28.3	42.6
3hrs	23.8	28.4	20.0	31.4	29.0	25.3
3.5h	21.5	27.0	20.2	31.1	37.8	22.2
4hrs	21.4	23.1	16.8	26.0	36.0	24.8
5hrs	18.5	19.9	14.9	20.8	32.5	18.9
6hrs	17.0	16.3	13.6	14.2	24.9	18.5
8hrs	12.7	9.27	7.63	8.07	14.5	10.0
10hrs	7.50	6.43	4.13	3.47	8.84	6.67
12hrs	4.69	3.83	3.65	3.45	1.14	5.02

Buccal tablet

Morphine concentration ng/ml

	Subject					
	1	2	3	4	5	6
15min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
30min	N.D.	N.D.	N.D.	N.D.	0.29	N.D.
45min	N.D.	N.D.	N.D.	N.D.	1.50	0.44
1hr	N.D.	0.64	N.D.	N.D.	1.19	0.45
2hrs	0.09	0.47	0.39	N.D.	0.61	0.70
2.5h	0.51	0.99	0.87	0.79	3.75	0.94
3hrs	0.32	1.93	-	1.05	1.62	1.43
3.5h	0.33	1.96	0.97	0.62	2.22	2.09
4hrs	0.46	2.00	1.63	1.88	2.11	-
5hrs	0.51	1.97	1.91	2.25	1.93	1.96
6hrs	0.79	1.27	2.53	3.01	1.95	2.28
8hrs	0.66	0.64	2.12	1.15	1.61	1.13
10hrs	0.82	0.30	1.19	1.42	1.11	N.D.
12hrs	1.40	0.42	0.67	1.25	0.56	N.D.

M6G concentration ng/ml

	Subject					
	1	2	3	4	5	6
15min	N.D.	0.58	0.28	N.D.	N.D.	N.D.
30min	N.D.	0.51	0.34	N.D.	0.16	0.27
45min	N.D.	1.03	0.42	0.30	2.85	1.29
1hr	0.25	1.87	0.52	1.80	7.81	2.13
2hrs	0.43	4.45	0.54	2.47	13.0	4.59
2.5h	2.21	4.56	3.20	2.76	14.7	7.73
3hrs	3.49	15.3	4.36	6.32	22.2	8.42
3.5h	4.77	23.1	5.53	7.31	24.4	10.4
4hrs	6.42	24.7	8.14	10.2	28.2	12.0
5hrs	6.62	21.7	12.6	15.0	26.0	15.1
6hrs	12.5	16.7	24.0	15.6	31.3	18.0
8hrs	11.3	7.51	16.9	13.0	23.0	12.8
10hrs	19.3	4.77	16.3	16.4	17.6	9.14
12hrs	20.5	4.29	4.11	14.1	8.94	5.50

Chapter 3.c.1
(i) Dry Mouth scores for individual subjects
(Based on a four point categorical scale from 1 to 4)

(i) Intravenous administration

Time (hours)	Subject 1	2	3	4	5	6	Mean
0	1	1	1	1	1	1	1.00
0.5	4	4	2	2	3	1	2.67
1	3	3	4	3	3	1	3.00
2	2	3	4	3	3	1	2.83
3	3	3	3	2	3	1	2.50
4	2	4	3	2	3	1	2.50
5	1	3	1	2	3	1	1.83
6	1	2	1	2	2	1	1.50
8	1	1	1	1	2	1	1.17
10	1	1	1	1	2	1	1.17
12	1	1	1	1	2	1	1.17
(ii) Oral solution							
0	1	1	1	1	1	1	1.00
0.5	2	3	1	2	2	1	1.83
1	2	3	3	3	3	1	2.50
2	3	3	3	3	4	1	2.83
3	1	3	3	3	3	1	2.33
4	1	1	3	3	3	1	2.00
5	1	1	1	1	3	1	1.33
6	1	1	1	1	2	1	1.17
8	1	1	1	1	1	1	1.00
10	1	1	1	1	1	1	1.00
12	1	1	1	1	1	1	1.00

(ii) Relaxation scores for individual subjects (using100mm visual analogue scale; decreasing score denotes increasing relaxation)

Time (hours)	Subject 1	2	3	4	5	6	Mean
(i) Intravenous administration							
0	18	50	50	50	50	50	44.67
0.5	3	12	50	40	8	50	26.83
1	13	3	50	38	0	50	25.33
2	3	3	50	43	0	50	24.83
3	7	2	50	50	0	50	26.50
4	12	18	50	44	5	50	29.83
5	14	40	50	42	5	50	33.50
6	13	42	50	50	15	50	36.67
8	17	50	50	50	26	50	40.50
10	3	50	50	50	38	50	40.17
12	6	50	32	50	46	50	45.00
(ii) Oral Solution							
0	46	5	50	56	50	50	42.83
0.5	21	4	50	50	46	50	36.83
1	19	2	32	50	10	50	27.17
2	35	2	50	39	2	50	28.83
3	39	1	50	50	6	50	32.17
4	44	10	50	50	36	50	39.50
5	48	4	50	50	25	50	37.67
6	43	16	50	50	29	50	39.67
8	46	45	50	50	42	50	47.17
10	49	33	50	48	47	50	46.62
12	42	9	50	50	46	50	41.17

(iii)Drowsiness scores for individual subjects
(using 100mm visual analogue scale ; increasing score denotes increasing drowsiness)

Time (hours)	Subject 1	2	3	4	5	6	Mean
(i) Intravenous administration							
0	1	11	19	0	0	7	6.33
0.5	5	74	26	18	72	7	33.66
1	1	84	7	0	93	4	31.50
2	1	97	0	2	100	18	36.33
3	1	93	0	12	98	0	34.00
4	1	94	0	0	66	0	26.83
5	1	39	0	7	60	0	17.83
6	1	27	6	6	21	0	10.17
8	1	43	0	0	34	0	13.00
10	1	19	0	0	4	0	4.00
12	1	7	15	0	0	0	1.27
(ii) Oral solution							
0	1	0	10	9	0	11	5.16
0.5	5	19	12	5	0	21	20.66
1	17	3	6	5	71	28	21.66
2	1	63	4	1	93	20	30.33
3	1	75	30	2	75	3	32.50
4	1	35	37	0	53	0	21.00
5	2	11	16	0	56	0	14.17
6	1	4	97	0	35	0	22.80
8	17	1	0	0	18	0	6.00
10	1	1	0	0	0	0	0.33
12	6	2	0	0	0	0	1.33

Chapter 4.a
Morphine bioavailability in patients with advanced cancer

(i) Plasma morphine concentrations ng/ml

	Patient									
Time	1	2	3	4	5	6	7	8	9	10
ORAL										
0	48.0	14.1	82.3	9.03	230	363	77.7	111	31.1	109
15min	48.5	162	79.0	18.9	479	409	143	149	31.1	144
30min	62.0	112	87.0	29.3	739	476	251	260	29.1	216
45min	68.5	79.0	121	26.7	366	437	135	263	29.7	174
60min	64.0	71.0	108	25.5	364	406	114	347	38.7	169
75min	50.5	64.0	160	28.9	485	632	114	485	45.1	117
90min	65.5	52.0	202	26.0	292	867	112	217	-	148
105min	50.5	52.3	110	23.7	305	743	127	245	40.7	155
120min	36.5	56.3	82.5	18.4	335	623	137	235	35.3	146
2.5hrs	43.8	49.0	60.0	13.1	206	615	76.0	170	35.2	170
3hrs	49.0	47.3	52.8	12.1	207	517	68.0	136	36.2	125
4hrs	44.8	23.0	47.0	9.8	162	415	75.0	105	45.6	96.7
IV										
0	44.8	23.0	47.0	9.8	162	415	75.0	105	45.6	
5min	253	1760	279	281	843	7420	311	648	251	
10min	115	181	1608	74.5	499	1210	183	290	138	
15min	94.7	123	563	64.5	417	837	134	233	93.3	
20min	130	84.0	166	46.1	332	765	135	258	108	
30min	84.7	65.5	112	43.5	259	693	136	187	98.5	
45min	60.7	73.4	70.0	29.3	270	556	121	143	66.6	
60min	60.9	55.9	58.7	27.9	254	548	111	140	59.2	
90min	52.8	47.2	63.3	22.6	218	434	95.0	123	53.3	
120min	44.6	30.0	40.8	14.9	188	341	92.7	121	43.3	
3hrs	31.8	26.3	30.7	12.1	157	270	76.7	79.3	25.3	
4hrs	31.8	26.4	33.8	11.1	120	267	63.7	69.7	22.8	

M6G concentrations ng/ml

	Patient									
	1	2	3	4	5	6	7	8	9	10
Time										
ORAL										
0	457.0	755.9	370.7	214.0	1336	1393	246.3	110.0	338.9	1594
15min	446.5	1019	329.0	243.1	1523	1419	280.0	119.0	240.9	1636
30min	404.0	1069	324.0	196.7	1121	1580	218.0	97.0	308.9	1889
45min	626.5	1311	480.0	269.3	1589	1075	251.0	138.0	322.3	2296
1hr	503.0	1469	325.0	295.5	1706	1403	310.0	152.0	299.3	2081
1.25h	510.5	1251	387.0	268.1	1621	1532	338.0	91.0	342.9	1743
1.5h	570.5	1330	464.0	280.0	1670	1935	324.0	82.0	-	1932
1.75h	466.5	1250	591.0	254.3	1743	1997	288.0	212.0	351.3	2225
2hrs	511.5	1009	474.5	-	1341	1988	273.0	125.0	296.7	2064
2.5h	530.2	924.0	622.0	304.9	1147	1754	338.0	199.0	309.9	1797
3hrs	518.0	1114	456.2	284.9	1295	1797	443.0	182.0	368.8	1815
4hrs	503.2	1060	434.0	249.2	1062	1634	276.0	138.0	351.4	1600
IV										
0	503.2	1060	434.0	249.2	1062	1634	276.0	138.0	351.4	
5min	890.0	743.0	434.0	79.0	1147	8713	494.0	131.0	361.0	
10min	758.0	897.0	724.0	231.5	981.0	2635	353.0	347.0	372.0	
15min	665.3	767.0	484.0	276.5	988.0	1765	527.0	223.0	394.7	
20min	639.0	1001	422.0	244.9	1323	2548	387.0	170.0	381.0	
30nmin	813.3	1056	427.0	301.5	866.0	2029	264.0	166.0	389.0	
45min	714.3	779.6	368.0	233.9	1050	1853	372.0	203.0	386.4	
1hr	603.1	883.1	422.3	206.1	961.0	1740	309.0	219.0	361.8	
1.5h	583.2	751.8	327.7	204.4	959.0	1581	416.0	234.0	376.7	
2hrs	622.4	758.0	327.2	94.1	1094	1657	282.3	225.0	303.7	
3hrs	471.2	409.7	272.3	95.9	772.0	1384	242.3	180.7	302.7	
4hrs	419.2	412.6	216.2	86.6	827.0	1567	325.5	174.3	324.2	

CHAPTER 4.b

Relative bioavailability of morphine elixir and MST tablets

(a) HPLC

(i)Morphine concentration ng/ml

Elixir

	Patient									
Time	1	2	3	4	5	6	7	8	9	10
0	7.44	4.99	9.50	8.25	17.5	25.0	28.5	38.9	54.7	53.9
0.5h	19.3	19.4	15.4	23.4	17.5	50.3	49.9	62.1	122	115
1hr	11.1	14.8	16.7	25.8	25.8	42.1	50.7	96.8	115	96.9
1.5h	9.9	10.3	34.2	31.6	15.2	25.3	44.9	92.9	105	90.1
2hrs	11.7	11.6	36.9	24.7	13.2	34.4	32.7	71.7	73.2	69.5
2.5h	16.0	10.3	26.1	26.4	15.6	19.3	47.1	52.5	42.8	72.7
3hrs	16.8	13.3	18.5	29.5	10.0	25.6	21.7	48.5	54.6	95.4
3.5h	10.8	8.75	24.7	25.0	9.3	20.6	21.2	40.6	54.4	45.8
4hrs	7.45	10.3	16.7	25.0	10.5	15.9	20.7	40.8	49.2	43.0
4.5h	7.10	13.3	19.4	19.7	10.4	16.7	25.9	69.8	124	96.5
5hrs	7.19	12.5	27.4	21.8	8.40	29.0	47.7	77.6	72.1	69.3
6hrs	10.6	15.6	23.4	12.1	9.70	24.9	38.5	37.0	50.1	53.5
8hrs	3.65	10.3	16.7	9.49	7.95	24.4	37.0	29.3	67.2	37.4
10hrs	5.07	7.23	15.4	8.01	10.2	20.3	37.1	58.2	36.5	47.2
12hrs	2.90	41.6	14.0	3.04	2.94	12.8	30.0	15.7	24.0	52.0

MST

0	7.10	0	4.76	15.6	9.90	17.2	22.0	1.17	34.6	34.2
0.5h	6.43	9.36	3.17	20.4	12.3	17.3	27.9	128	38.8	18.1
1hr	7.43	11.3	2.37	14.2	18.5	29.3	24.4	117	67.4	51.7
1.5h	9.37	13.3	7.15	16.5	16.9	45.0	31.2	95.4	81.1	65.4
2hrs	12.7	15.2	20.7	14.5	9.15	40.0	20.8	89.4	91.9	76.8
2.5h	19.4	13.3	51.8	14.1	27.7	38.3	104	85.4	123	87.7
3hrs	19.2	9.17	48.6	8.62	21.7	38.8	79.9	67.5	135	84.8
3.5h	15.5	7.39	29.5	12.2	17.5	35.0	50.7	63.5	111	66.6
4hrs	12.9	5.43	11.9	10.8	15.9	66.7	50.8	51.5	113	67.9
4.5h	11.5	6.41	11.1	19.6	17.8	32.5	39.0	41.6	104	55.0
5hrs	9.90	5.40	16.7	14.8	16.3	30.6	43.6	59.4	96.3	54.7
6hrs	7.35	4.43	6.32	11.6	11.0	25.5	29.6	33.6	60.3	30.4
8hrs	8.10	3.47	5.56	8.92	7.07	24.9	43.6	39.6	69.7	40.8
10hrs	5.55	2.49	3.97	11.5	4.98	14.2	29.6	19.6	43.6	26.8
12hrs	5.47	1.50	2.51	9.07	2.89	14.6	25.5	15.6	34.9	54.7

(ii) M3G concentration ng/ml

Elixir

Time	Subject				
	1	2	3	4	5
0	219.6	379.4	386.0	1879.8	455.9
0.5h	436.0	414.8	440.0	1688.5	550.4
1hr	300.8	426.1	495.0	2617.9	726.3
1.5h	476.6	409.7	642.9	2783.3	752.4
2hrs	415.7	419.8	727.7	2748.8	653.0
2.5h	436.0	267.7	609.7	3133.3	826.9
3hrs	463.1	224.8	609.7	2968.4	560.2
3.5h	287.2	199.8	708.8	3282.1	503.7
4hrs	408.9	247.1	333.1	2933.2	402.7
4.5h	422.4	219.3	650.1	3395.4	512.9
5hrs	321.0	245.6	749.8	2446.7	410.9
6hrs	503.6	317.1	910.6	2586.9	400.0
8hrs	231.4	287.3	831.1	2647.9	431.1
10hrs	476.5	197.7	873.8	2693.7	472.8
12hrs	408.9	632.0	272.9	2403.8	350.6

	Subject				
	6	7	8	9	10
0	1167.2	2473.5	1745.4	2798.4	2422.3
0.5h	1167.2	2481.3	2571.3	2860.1	2459.8
1hr	1212.7	2886.1	3093.7	2847.8	3085.0
1.5h	2446.5	2791.3	3548.8	3072.6	3251.9
2hrs	1303.6	2728.7	3481.3	2998.5	2751.2
2.5h	1320.7	2844.3	3228.6	2521.5	2746.4
3hrs	808.9	2715.6	3447.7	2512.5	2655.7
3.5h	996.9	2360.3	2958.9	2457.3	2533.6
4hrs	621.3	2528.4	2621.8	2884.2	2331.6
4.5h	791.9	2161.1	2958.9	2830.5	3093.5
5hrs	2173.6	2235.6	3601.8	3050.5	2508.2
6hrs	2685.3	2505.1	2790.4	2771.2	2716.2
8hrs	1661.8	2503.9	1711.7	2313.9	2861.3
10hrs	2139.5	2275.0	2790.4	2620.4	2426.7
12hrs	1934.8	2104.5	1153.9	2400.4	2146.6

MST

	Subject				
	1	2	3	4	5
0	179.1	0	373.6	1671.8	46.0
0.5	300.8	484.4	126.1	1416.5	224.1
1hr	408.9	1038.8	330.5	1919.8	419.6
1.5h	503.6	1267.1	344.5	1867.1	455.4
2hrs	625.3	1365.0	546.1	1871.1	654.1
2.5h	665.9	1356.8	1049.9	1723.0	571.6
3hrs	855.2	1413.9	1138.9	1723.6	717.6
3.5h	503.6	1201.9	1129.7	1683.5	782.3
4hrs	652.4	1234.5	337.2	1631.2	773.0
4.5h	638.9	1104.1	410.6	1738.5	688.9
5hrs	476.6	908.4	540.3	1749.3	670.4
6hrs	517.1	794.2	770.9	1868.4	439.1
8hrs	571.2	517.0	929.4	1853.5	312.6
10hrs	300.8	370.2	847.8	1283.5	175.2
12hrs	97.9	207.2	169.8	1299.3	116.6

	Subject				
	6	7	8	9	10
0	781.2	2335.2	364.8	846.3	300.0
0.5h	2170.1	1830.2	3239.8	792.3	333.2
1hr	2873.9	2003.7	3827.8	1011.1	614.5
1.5h	3965.6	1942.7	4121.9	1317.9	647.6
2hrs	3286.9	1914.3	4497.6	1559.5	796.6
2.5h	3422.9	2455.0	4481.2	1727.2	813.3
3hrs	3775.4	3300.4	4448.6	2076.7	1408.9
3.5h	3878.1	3205.0	3991.2	2079.5	697.2
4hrs	4480.1	3022.6	3517.5	2082.3	667.2
4.5h	4099.1	2969.3	3321.4	2062.5	382.9
5hrs	4114.1	3258.1	3566.5	1994.3	498.7
6hrs	3992.6	2275.6	2945.7	1562.3	382.9
8hrs	3488.9	2834.8	2341.3	1761.3	631.1
10hrs	2705.8	2274.9	1678.0	1252.6	473.9
12hrs	2270.1	2178.4	1167.4	1085.0	449.0

(iii) M6G concentration ng/ml

Elixir

	Subject				
	1	2	3	4	5
0	46.9	23.5	29.3	338.0	105.5
0.5h	53.2	39.7	31.9	308.3	105.1
1hr	52.6	59.0	34.6	394.3	145.5
1.5h	55.0	46.1	42.5	427.7	144.5
2hrs	55.2	42.9	61.0	426.2	142.6
2.5h	71.8	38.1	50.4	467.3	136.2
3hrs	65.7	21.9	50.4	445.0	114.2
3.5h	60.3	31.6	55.7	506.9	96.1
4hrs	60.1	25.2	45.1	465.2	92.3
4.5h	62.9	54.2	37.2	526.7	80.3
5hrs	62.2	38.0	47.8	357.4	65.9
6hrs	77.8	29.9	58.4	416.2	79.9
8hrs	63.1	18.7	50.4	397.7	75.5
10hrs	73.9	9.03	49.1	432.4	82.2
12hrs	27.3	3.66	47.8	366.7	53.2

	Subject				
	6	7	8	9	10
0	289.8	382.5	249.3	443.2	415.7
0.5h	225.5	344.2	351.6	466.4	414.8
1hr	316.6	446.5	532.8	557.7	606.0
1.5h	491.2	473.2	574.2	549.2	616.9
2hrs	358.1	434.8	552.5	521.4	545.0
2.5h	323.5	443.3	540.7	434.7	502.2
3hrs	238.7	443.0	536.1	424.7	484.4
3.5h	262.7	349.3	517.1	399.7	425.4
4hrs	170.9	382.8	436.3	401.2	402.7
4.5h	171.4	301.5	469.8	432.8	541.4
5hrs	391.9	306.8	564.3	551.4	411.3
6hrs	511.6	399.9	446.2	423.8	508.7
8hrs	192.6	360.3	340.2	381.8	408.3
10hrs	421.4	353.8	422.4	466.3	432.4
12hrs	360.4	295.7	147.9	357.5	378.3

MST

	Subject 1	2	3	4	5
0	35.6	0	29.1	366.2	63.2
0.5h	38.0	30.1	23.3	369.3	56.1
1hr	57.2	53.2	24.7	396.5	84.9
1.5h	64.9	57.0	23.3	420.1	119.8
2hrs	69.3	58.9	30.6	440.3	152.4
2.5h	87.6	72.4	52.4	402.3	157.8
3hrs	110.4	74.3	77.4	397.4	189.2
3.5h	111.6	53.2	75.9	378.3	183.5
4hrs	113.8	49.3	64.2	367.3	177.9
4.5h	106.9	41.7	45.2	378.4	176.0
5hrs	85.4	39.7	52.5	380.3	163.6
6hrs	85.9	34.0	29.1	422.0	106.4
8hrs	70.1	22.5	27.7	391.0	80.7
10hrs	43.0	16.7	20.4	305.4	58.2
12hrs	40.0	12.9	17.4	308.0	47.0

	Subject 6	7	8	9	10
0	382.1	238.2	611.0	224.6	181.6
0.5h	384.8	261.4	500.8	211.7	91.6
1hr	399.6	257.6	683.1	269.0	137.8
1.5h	505.2	269.7	711.1	383.7	163.2
2hrs	628.1	229.4	847.3	461.2	200.6
2.5h	672.8	340.8	907.4	514.2	218.3
3hrs	691.8	518.6	851.5	629.2	336.1
3.5h	693.0	539.2	775.2	649.2	203.0
4hrs	717.6	494.3	639.0	631.1	180.9
4.5h	682.4	481.1	611.0	612.2	128.7
5hrs	681.0	472.4	655.0	583.4	134.2
6hrs	663.6	311.6	536.9	448.9	111.8
8hrs	616.8	380.8	388.7	526.3	77.2
10hrs	402.1	350.8	220.4	347.4	66.1
12hrs	360.6	333.5	202.4	288.6	65.2

RIA

Morphine concentration ng/ml

Elixir

	Subject									
	1	2	3	4	5	6	7	8	9	10
0	7.6	6.1	11.0	11.5	9.3	14.5	21.0	36.9	114.0	46.5
0.5h	15.5	24.0	14.0	20.1	18.9	52.6	37.0	102.0	155.0	88.1
1hr	11.4	12.0	17.8	17.9	20.7	43.3	63.7	111.0	114.0	103.0
1.5h	10.1	11.4	37.9	20.2	13.8	32.4	38.0	108.0	81.3	78.5
2hrs	9.6	10.4	38.6	18.8	13.1	30.1	27.9	66.8	82.5	71.7
2.5h	11.3	8.8	27.3	16.6	9.6	21.4	37.7	50.9	68.0	67.5
3hrs	11.6	7.3	20.3	12.2	8.1	17.9	26.0	46.0	79.0	54.6
3.5h	10.1	5.6	19.7	14.0	6.9	17.0	18.3	46.7	70.3	48.6
4hrs	9.0	6.7	14.8	10.9	7.6	15.5	18.9	36.9	73.3	40.9
4.5h	10.2	17.5	14.2	20.3	6.6	14.1	18.6	64.9	225.0	57.9
5hrs	10.4	12.9	28.2	15.9	4.5	23.6	47.4	68.4	115.0	87.5
6hrs	9.2	7.3	26.6	12.2	6.6	18.4	37.2	38.7	59.8	41.0
8hrs	8.8	6.0	17.3	8.8	5.0	16.9	29.9	35.4	83.8	55.8
10hrs	9.3	5.1	17.9	10.4	8.6	16.8	36.6	54.2	75.3	42.3
12hrs	8.9	4.0	14.5	6.6	7.3	17.0	25.0	7.8	61.2	38.9
3wks	16.8	-	26.4	32.3	-	-	56.6	-	-	95.3

MST

	Subject									
	1	2	3	4	5	6	7	8	9	10
0	4.4	5.9	8.0	11.0	5.7	19.7	12.6	28.7	43.3	21.8
0.5h	6.8	14.3	8.4	24.8	5.0	19.0	20.2	130.0	42.5	19.1
1hr	9.9	10.8	7.5	33.6	17.5	29.7	17.7	152.0	77.0	39.8
1.5h	8.1	14.2	13.3	38.9	14.8	53.7	26.3	127.0	102.0	61.9
2hrs	11.8	18.0	26.5	26.6	12.3	47.8	32.3	107.0	100.0	86.0
2.5h	18.0	14.8	68.2	27.2	29.4	43.2	121.0	84.4	140.0	108.0
3hrs	14.7	11.6	48.4	41.3	23.1	49.0	84.6	86.5	159.0	82.0
3.5h	14.8	11.0	34.3	38.3	17.4	40.2	54.6	72.6	116.0	61.8
4hrs	12.2	8.7	23.5	26.8	15.8	65.4	49.5	87.5	106.0	72.3
4.5h	11.0	8.9	17.5	28.2	12.3	36.5	38.3	69.1	127.0	55.0
5hrs	11.8	6.6	16.9	27.5	10.5	37.3	55.0	73.4	100.0	54.6
6hrs	8.3	6.3	9.8	17.1	6.0	33.4	36.3	35.9	62.3	45.8
8hrs	6.2	5.4	8.7	14.6	5.5	25.4	44.3	45.9	86.0	60.9
10hrs	4.6	4.4	4.3	8.8	3.2	16.6	23.3	22.3	55.3	21.5
12hrs	5.2	3.6	3.6	9.6	2.7	13.6	24.7	21.3	39.7	48.5

Chapter 4.c

Evaluation of a loading dose when starting MST

a) Placebo

	Patient								
	1	2	3	4	5	6	7	8	9
Time									
0	6.2	206.0	116.1	23.0	137.6	7.6	24.9	28.3	7.1
30min	5.1	286.0	147.0	45.6	216.4	8.6	50.6	34.3	10.5
1hr	12.8	293.7	115.2	74.3	172.2	41.5	34.4	25.3	15.1
1.5h	23.3	352.3	159.9	429.1	223.6	38.5	48.6	32.9	17.0
2hrs	26.0	309.1	275.2	94.2	210.1	40.9	48.2	26.7	16.1
2.5h	18.5	456.2	204.2	86.1	238.0	37.7	30.9	21.8	16.5
3hrs	17.8	366.5	159.0	84.1	308.7	35.3	42.0	29.8	15.7
3.5h	20.6	334.1	169.4	83.3	593.4	34.2	50.1	25.7	15.6
4hrs	18.2	277.2	137.0	90.8	385.1	31.0	40.7	29.6	10.8
4.5h	13.2	265.0	135.5	79.9	368.3	26.9	32.0	69.8	11.3
5hrs	15.3	304.5	140.9	62.4	364.6	25.4	41.6	55.4	12.4
5.5h	11.0	278.4	141.4	51.6	304.8	22.0	37.2	59.3	12.7
6hrs	10.8	275.3	83.9	51.0	302.4	26.9	33.3	41.9	10.4
6.5h	9.1	223.8	105.4	46.3	270.4	22.3	26.5	46.2	11.3
7hrs	6.2	218.2	89.6	38.4	262.9	21.4	25.2	39.7	10.1
8hrs	5.5	193.6	71.4	28.6	199.7	29.8	21.5	33.4	7.1
9hrs	5.8	123.9	40.1	26.3	147.7	20.9	17.1	25.9	6.0
10hrs	5.1	144.9	40.8	29.0	137.2	15.6	12.3	24.4	6.5
11hrs	4.2	103.2	49.2	22.8	100.0	21.5	10.9	21.2	6.1
12hrs	4.6	91.6	43.2	20.2	103.2	25.8	11.6	16.7	6.1

Active loading dose

	Patient									
	10	11	12	13	14	15	16	17	18	19
Time										
0	32.9	174.5	9.6	24.9	18.3	55.5	5.8	24.5	29.5	64.1
30min	61.2	511.6	19.7	50.6	41.3	163.6	7.4	64.1	27.5	348.5
1hr	95.2	489.4	42.5	34.4	60.1	161.8	8.9	134.5	33.7	251.1
1.5h	131.0	99.7	48.8	48.6	55.9	168.2	18.6	72.9	35.8	156.9
2hrs	203.4	342.7	31.9	48.2	49.7	173.4	11.4	56.4	36.7	152.2
2.5h	107.2	266.9	34.1	30.9	43.9	152.6	17.0	57.6	40.1	161.7
3hrs	112.4	-	29.0	42.0	42.1	161.2	17.4	61.5	46.8	173.9
3.5h	109.2	432.0	34.0	50.1	43.3	198.0	26.6	61.8	56.4	161.3
4hrs	76.7	452.6	23.8	40.7	39.0	183.0	22.2	36.8	52.7	197.7
4.5h	77.3	418.1	32.2	32.0	36.2	170.8	11.8	39.6	50.2	189.9
5hrs	86.5	463.5	29.5	41.6	39.5	159.8	13.3	36.9	40.6	130.8
5.5h	102.8	445.1	27.0	37.2	27.7	187.8	34.0	39.5	51.1	151.5
6hrs	91.2	390.2	26.5	32.3	22.1	161.5	16.2	30.1	40.3	139.1
6.5h	69.0	309.5	25.5	26.5	20.2	174.5	17.1	42.0	43.6	119.1
7hrs	65.0	368.5	21.2	25.2	22.1	130.4	20.4	54.5	38.7	132.7
8hrs	54.3	328.0	16.4	21.5	21.0	132.4	6.6	40.8	38.5	72.2
9hrs	55.4	328.7	14.2	17.1	16.2	85.9	4.6	35.4	34.0	56.3
10hrs	49.3	287.1	14.1	12.3	13.8	70.5	3.6	19.3	29.1	54.3
11hrs	39.1	259.8	13.7	10.2	16.4	58.1	3.9	22.4	30.2	61.9
12hrs	32.8	241.2	14.6	11.6	10.6	49.4	3.8	20.5	27.0	55.5

APPENDIX 2

COPY OF QUESTIONNAIRE USED IN STUDY DESCRIBED IN CHAPTER 6.a

No [| | | | | |]

QUESTIONNAIRE

BIOGRAPHICAL DETAILS

Number of years since graduation (please tick)

- < 5 years ☐
- 5-10 years ☐
- 11-20 years ☐
- > 20 years ☐

Present Post:

- General Practitioner ☐
- Consultant ☐
- Senior Registrar ☐
- Registrar ☐
- Senior House Officer ☐
- House Physician/House Surgeon ☐
- Other ☐

Current Speciality: _____

Extent of Specialist Oncology Experience:

- None ☐
- < 6 months ☐
- 6 months - 1 year ☐
- 1 - 3 years ☐
- > 3 years ☐

Q.1 What would be your first choice analgesic drug in the management of chronic severe cancer pain? (assuming that the pain is constant)

Answer: _____

Optional: Please state briefly the reason for your choice:

_____

_____

_____

_____

Q.2 What other analgesics of equivalent strength would you use? (Maximum choice of 4)

1. _____
2. _____
3. _____
4. _____

Q.3 Would you administer your analgesic of choice (in Q.1)

A. Regularly ☐ (please tick one box only.)

or

B. As required ☐

How often?

A. 2 hourly ☐
B. 4 hourly ☐
C. 6 hourly ☐
D. 8 hourly ☐
E. 12 hourly ☐

Other (please insert) F. _____

Q.4 Please state the dose at which you would start this drug (single dose)

Starting Dose

..... (mgs) OR ..... No. of tablets

How high would you go?

Maximum Dose

..... (mgs) OR ..... No. of tablets

(Either state maximum dose or tick box)

☐ No limit

Q.5 Please rank, in order of importance, which of these factors define the choice of your analgesic dose (most important = 1, least important = 5).

A. Body weight ☐
B. Age ☐
C. Co-existent chronic obstructive airways disease ☐
D. Severity of pain ☐
E. Significant impairment of hepatic or renal function ☐

If other, please state: _____

Q.6 Which is your preferred route of administration when prescribing analgesics to relieve severe cancer pain? (tick one box only)

A. Intermittent intravenous injection ☐
B. Intermittent intramuscular/subcutaneous injection ☐
C. Continuous parenteral infusion ☐
D. Oral ☐
E. Rectal ☐

Q.7 If the degree of pain relief afforded by your analgesic of choice (in Q.1) is inadequate, what action would you take? (Tick one box only)

A. Increase dose of analgesic ☐
B. Increase frequency of administration ☐
C. Prescribe "breakthrough pain" analgesia in addition to existing schedule ☐
D. Change from "as required" to "regular" schedule ☐
E. Change to equivalent alternative analgesic ☐
F. Change to stronger analgesic ☐

Q.8 If the duration of pain relief afforded by your analgesic of choice (in Q.1) is inadequate what action would you take? (Tick one box only)

A. Increase dose of analgesic ☐

B. Increase frequency of administration ☐

C. Prescribe "breakthrough pain" analgesia in addition to existing schedule ☐

D. Change from "as required" to "regular" schedule ☐

E. Change to equivalent alternative analgesic ☐

F. Change to stronger analgesic ☐

Q.9 Do you consider any of the following a contraindication to using narcotic analgesics in cancer pain? (please tick one box in each line)

	Yes	No	Possibly
A. Possibility of sedation	☐	☐	☐
B. Possibility of respiratory depression	☐	☐	☐
C. Possibility of nausea/vomiting	☐	☐	☐
D. Possibility of addiction	☐	☐	☐

Q.10 Would you consider any of the following a contraindication to using narcotic analgesics in cancer pain? (please tick one box in each line)

	Yes	No	Possibly
A. Prognosis >6 months	☐	☐	☐
B. Prognosis 1-6 months	☐	☐	☐
C. Prognosis <1 month	☐	☐	☐

Thank you for your co-operation

APPENDIX 3

Publications arising from work related to this thesis

Hanks GW, Hoskin PJ
Pain control in advanced cancer: pharmacological methods
Journal of the Royal College of Physicians (1986); 20: 276-281

Hanks GW, Hoskin PJ
Opioid analgesics in the management of pain in patients with cancer. A review.
Palliative Medicine (1987); 1: 1-25

Hoskin PJ, Hanks GW
Bone Pain
Clinical Oncology (1987); 1: 399-416

Hanks GW, Hoskin PJ, Aherne GW, Turner P, Poulain P
Explanation for potency of repeated oral doses of morphine
Lancet (1987) ii: 723-725

Hoskin PJ, Hanks GW
Opioid therapy in malignant disease
Clinical Anaesthesiology (1987); 1: 883-904

Hanks GW, Hoskin PJ
Diamorphine stability and pharmacodynamics
Anaesthesia (1987); 42: 664

Hanks GW, Hoskin PJ, Aherne GW, Turner P, Poulain P
Enterohepatic circulation of morphine
Lancet (1988) i: 469

Walker VA, Hoskin PJ, Hanks GW, White ID
Evaluation of the WHO analgesic guidelines for cancer pain in a specialist cancer hospital
The Journal of Pain and Symptom Management
(1988) 3: 145-149

Hoskin PJ, Hanks GW
The management of symptoms in a hospital-based continuing care unit
Journal of the Royal Society of Medicine (1988); 81: 341-344

Hoskin PJ, Dicks B
Symptom Control
In: Oncology for Nurses and Health Care Professionals
Volume 2, Ed Tiffany R
Harper and Row, London (1988)

Hoskin PJ, White ID, Hanks GW
Syringe drivers
Anaesthesia (1988); 43: 708

Hoskin PJ, Hanks GW, Walker VA
Sterile abcess formation by continuous subcutaneous infusion of diamorphine
British Medical Journal (1988); 296: 1605

Poulain P, Hoskin PJ, Hanks GW, Omar OA, Walker V, Johnston A, Turner P, Aherne GW
The relative bioavailability of controlled release morphine tablets (MST-Continus) in cancer patients
British Journal of Anaesthesia (1988); 61: 569-574

Hoskin PJ, Hanks GW, Heron CW, Aherne GW, Chapman D
Morphine and morphine-6-glucuronide (M6G) in human cerebrospinal fluid
The Clinical Journal of Pain (In Press)

Hoskin PJ, Hanks GW, Aherne GW, Chapman D, Littleton P, Filshie J
The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers
British Journal of Clinical Pharmacology (In Press)

Hoskin PJ, AlSayed O, Hanks GW, Johnston A, Turner P
The influence of blood sample preparation on measured levels of morphine and its major metabolites
Annals of Clinical Biochemistry (In Press)

Omar OA, Hoskin PJ, Johnston A, Hanks GW, Turner P
Diamorphine stability in aqueous solution for subcutaneous infusion
Journal of Pharmacy and Pharmacology (In Press)

Pain Control in Advanced Cancer: Pharmacological Methods

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Consultant Physician

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Pain is a major symptom in some 60 per cent of patients managed in a general oncology unit[1] and up to 85 per cent of patients referred for hospice care[2]. Pain control is therefore an essential component of the modern management of malignant disease.

Pain is a complex subjective experience, combining the perception of a painful stimulus with a variable emotional response to it. Chronic pain associated with progressive malignancy is quite different from acute pain following trauma or surgery, or the minor acute pains (headache or toothache) of normal day to day life. Unlike acute pain, chronic pain is of unpredictable duration and is maladaptive: it has no positive function. Thus a major component of chronic cancer pain is the associated emotional reactions of fear, anxiety, anger or depression. Invariably the patient is also troubled by other symptoms such as anorexia, nausea, constipation, fatigue and sleep disturbance, all contributing to a lowered pain threshold and impaired pain tolerance. The clinical picture of the patient with chronic cancer pain is a summation of the physical effects of the original nociceptive stimulus, the patient's emotional response to this, and other symptoms associated with the underlying malignancy or caused by the pain. The situation is further complicated by the fact that 80 per cent of patients in pain will have more than one pain and approximately 20 per cent will have four or more separate pains[3].

Management of Chronic Cancer Pain

As the nature of chronic cancer pain is so complex it is necessary before embarking upon treatment to identify each individual pain and its underlying aetiology, to appraise the patient's mental state and to evaluate any associated physical symptoms. A body chart is often helpful and will also provide a valuable baseline for future assessments.

Once the underlying nature of the patient's pain has been identified a logical treatment strategy can be devised. The mainstay of treatment will be pharmacological. It is, however, important not to neglect the role of other treatment modalities and at this early stage to identify those pains which may respond to specific non-drug measures, such as the use of radiotherapy for localised bone pain.

A further important step at the outset of treatment is careful explanation to the patient and reassurance that pain control can be achieved. Realistic goals should be set, with three stages of pain control in mind: to be pain free at night, pain free at rest and pain free on movement. The first two of these will almost always be possible to achieve and confidence will be built up as each objective is realised. Complete pain control on movement may be more difficult and sometimes simple modifications to life style, in addition to specific treatment, are needed.

Drug Treatment of Chronic Cancer Pain

Effective drug treatment is founded on the regular use of an appropriate analgesic given in an adequate dose. Initial choice of drug is based on the severity of the pain and its response to previous treatment. In general, a simple scheme using a limited number of drugs familiar to the prescriber is recommended, ranking drugs according to analgesic strength with a range from simple non-opioid analgesic, to weak opioid, to strong opioid. One drug in each class should be used routinely, for example paracetamol, dextropropoxyphene/paracetamol, and morphine; only rarely will an alternative be necessary. If a drug is no longer effective there is no value in using alternatives from the same group, and it is inappropriate to use two drugs of similar strength in the hope of an additive or synergistic action. Proprietary tablets containing combinations of drugs, in particular those combining several simple analgesics, are best avoided unless careful consideration has been given to the individual constituents and their doses.

There is no place for intermittent 'as required' analgesia in the management of chronic cancer pain. The aim of treatment is to control and prevent further symptoms by regular medication, maintaining constant effective blood concentrations in the steady state. A recommended scheme of drug use in chronic cancer pain is outlined in Table 1.

Table 1. Recommended scheme of drugs for use for chronic cancer pain.

Pain	*Mild pain*	*Unresponsive to simple analgesics*	*Unresponsive to weak opioids*
Analgesic group	Simple peripherally-acting analgesic	Weak opioid	Strong opioid
Drug of choice	Paracetamol 1 g 4-hourly	Dextropropoxyphene/paracetamol 2 tabs. 4-hourly	Morphine or diamorphine orally 5–200 mg 4-hourly
Alternative drugs	Soluble aspirin 600–1200 mg 4-hourly	Dihydrocodeine 30–60 mg 4-hourly	Phenazocine, levorphanol, oxycodone suppositories
Drugs to avoid	Compound preparations	Pentazocine	Short-acting opioids, combinations, opioids with cumulative toxic effects
Other measures	Co-analgesic	Co-analgesic	Co-analgesic

Simple Analgesics

Paracetamol is the preferred simple analgesic where no anti-inflammatory action is required. A derivative of para-aminophenol, it has analgesic and antipyretic effects similar to those of aspirin at equivalent doses up to 1 g. Paracetamol is rapidly absorbed from the small bowel but hardly at all in the stomach: hence gastric emptying may significantly affect the overall rate of absorption. Peak plasma concentrations are reached at 30 to 60 minutes after a single oral dose[4]. In addition to tablets a suppository for rectal use is available for those patients unable to take drugs by mouth. The plasma elimination half-life is 1.5–3.0 hours[5], and regular 4-hourly oral administration of 1 g (two tablets) is the recommended dose.

The principal advantage of paracetamol over other simple analgesics is that it is well tolerated by most patients with no gastric irritant effect. Serious toxicity is not seen when it is used in the above doses. The alkylating metabolite responsible for hepatotoxicity in overdosage is produced only in small amounts at normal therapeutic doses and is rapidly detoxified by conjugation with reduced glutathione[6].

Alternative simple analgesics are not usually required since intolerance to paracetamol is unusual. Failure of a simple analgesic to control pain is an indication for a drug with a stronger analgesic action.

Aspirin (acetylsalicylic acid) is recommended by some authors[3] as the simple analgesic of choice. It has the advantage, in high dosage (4-6 g/day), of additional anti-inflammatory action which may be of value, particularly in the treatment of bone metastases. However, side-effects, including gastric intolerance and metabolic disturbances, are much more common at these doses and the use of one of the newer non-steroidal anti-inflammatory drugs is generally preferable when an anti-inflammatory action is required. At low doses aspirin has no advantage over paracetamol and is generally less well tolerated.

Weak Opioids

These drugs are recommended where simple analgesics are ineffective or in mild to moderate visceral pain which often does not respond to paracetamol.

Dextropropoxyphene/paracetamol (Coproxamol) is our drug of choice in this group, despite continued controversy over its efficacy and potential dangers[7,8]. Dextropropoxyphene is a synthetic opioid structurally related to methadone and a weak opioid agonist. It is readily absorbed from the gastrointestinal tract with peak serum levels at about two hours after administration. The mean elimination half-life is about 15 hours with steady state levels being reached after three to four days of regular 6 to 8-hourly administration. In elderly patients the half-life may be very long (over 50 hours)[9]. Dextropropoxyphene undergoes extensive first pass metabolism, its principle metabolite being norpropoxyphene which also has analgesic activity and a longer half life (about 23 hours) than dextropropoxyphene itself. This metabolite therefore accumulates in plasma[10]. Both dextropropoxyphene and norpropoxyphene reach plasma concentrations in the steady state which are five to seven times greater than those found after the first dose.

It follows from this that studies using single doses of dextropropoxyphene are assessing a very different situation to that which exists in the steady state during regular administration for chronic pain[11]. This may explain why extensive clinical experience with a dextropropoxyphene/paracetamol combination in patients with chronic pain due to malignant disease and in patients with rheumatic disorders[12] suggests that the preparation is effective and well tolerated, but controlled clinical trial data are conflicting. There is, however, substantial evidence to support the efficacy of dextropropoxyphene itself[13] and a single published controlled study in rheumatology patients[14] which indicates the superiority of a dextropropoxyphene/paracetamol combination over paracetamol alone.

The recommended dose is up to two tablets of Coproxamol 4-hourly (each tablet contains dextropropoxyphene 32.5 mg and paracetamol 325 mg). At these doses serious side effects are unusual but confusion, dysphoria and lightheadedness may occur, particularly in the elderly. Nausea and vomiting are infrequent and constipation is less troublesome than with other opioids. Addiction has been reported[15] but is rare and does not arise in the treatment of chronic pain. Coproxamol will potentiate the effects of warfarin, carbamazepine and central nervous system depressants.

Alternative weak opioids should be restricted to pure opioid agonists such as codeine or dihydrocodeine.

Dihydrocodeine is probably the alternative drug of choice being a semi-synthetic analogue of codeine and approximately 30 per cent more potent than the parent drug. Both drugs are chemically closely related to morphine (codeine is 3-methylmorphine). After an oral dose of codeine some 10 per cent is converted by demethylation to morphine, which may contribute to the analgesic effect. The principal disadvantage of codeine or dihydrocodeine compared with Coproxamol is that they tend to be more constipating at equi-analgesic doses[3].

Pentazocine is a mixed opioid agonist and antagonist which, although in common use, is not recommended for chronic pain due to malignant disease. It is a derivative of phenazocine, a strong opioid agonist. An evaluation in patients with chronic pain[16] showed an analgesic potency of one sixth that of morphine, and another single dose study[17] has suggested that standard doses are less effective than standard doses of dextropropoxyphene with paracetamol. Thus no clear advantage of pentazocine exists in terms of analgesic efficacy and there are two major drawbacks; first, it may antagonise opioid agonists and, second, there is a high incidence of psychotomimetic effects, occurring in 20 per cent of patients in one series[18], half of which resulted in a major disturbance.

Strong Opioids

When pain is no longer controlled by a weak opioid in standard doses, then a strong opioid should be used in its place, titrating the dose to the patient's pain.

Morphine sulphate is the drug of choice for oral use, most readily taken in aqueous solution or in chloroform water as morphine elixir. Morphine is the pharmacologically active constituent of opium. Despite its widespread use, dating from the third century B.C., accurate data on the pharmacokinetics of morphine are sparse, primarily due to the difficulties in measuring morphine distinct from its metabolites in serum[19]. Absorption from the gastrointestinal tract occurs readily (mainly in the upper small bowel) but oral bioavailability varies considerably (between 15 and 64 per cent in one study in cancer patients[20]). The effect of an oral dose is significantly less than that of the same dose given intravenously due to a considerable first pass effect. In rats, 85 per cent of an oral dose is eliminated due to metabolism in both gut wall and liver[21]. While a role for the kidney has been recently proposed[22], the relative importance of renal glucuronidation is disputed[23]. Almost certainly the metabolism of morphine is principally hepatic, the main pathway resulting in the formation of morphine-3-glucuronide and morphine-6-glucuronide. The elimination half life also shows considerable variation from one to $7\frac{1}{2}$ hours after low single oral doses in cancer patients[20], although it is not clear how this relates to steady state conditions after chronic high dosage. During chronic dosing, accumulation of the main metabolites occurs, the average ratio for morphine-3-glucuronide to morphine being 35:1 and for morphine-6-glucuronide 4:1[24]. There is evidence to suggest that morphine-6-glucuronide also has significant analgesic activity[25]. The presence of high concentrations of morphine-6-glucuronide may explain the apparent increased sensitivity to morphine of patients with renal impairment and the possible misinterpretation of kinetic data obtained using an assay method which could cross react with this metabolite[26, 27].

Despite the variation in plasma half-life, in clinical practice regular 4-hourly administration provides constant analgesia in doses ranging from 5 mg to 200 mg every four hours, although occasionally much higher doses are required. The dose is titrated to achieve pain control and around 70 per cent of patients will not require more than 30 mg 4-hourly[28]. The need for a dose to be given in the middle of the night can usually be avoided by a double dose at bedtime.

The use of a slow release preparation of morphine sulphate (MST Continus) has gained increasing popularity over recent years. Peak concentrations of morphine in the blood are not achieved until up to four hours after administration[29], but there are claims that overall bioavailability may be better than with 4-hourly oral morphine sulphate[30]. Although a useful means of delivering regular morphine in a stable situation, it is important to emphasise that this preparation should not be used for acute exacerbations of pain, nor, because of uncertainty over the time to achieve steady state plasma levels, is it ideal for patients starting morphine or requiring regular dose adjustments. MST does appear to be effective when given twice a day, and used appropriately it allows a more convenient regimen for patients requiring long-term morphine therapy[31].

The principal side effects of morphine in chronic use are drowsiness, constipation, nausea and vomiting. Most patients experience drowsiness initially which may cause considerable concern for both patients and relatives, particularly if associated with confusion. However, this is usually transient and not an indication to reduce an effective pain-relieving dose of morphine, but rather should be dealt with by careful explanation and reassurance. Constipation is universal and regular laxatives such as Dorbanex (containing a faecal softener, poloxamer, and a peristaltic stimulant, danthron) should be given from the outset. Nausea and vomiting are not inevitable, up to one third of patients receiving regular oral morphine requiring no anti-emetics[32]. In those patients who do become nauseated, haloperidol taken once or twice daily is usually effective with fewer side effects than the phenothiazines. Where a more sedative anti-emetic is required, prochlorperazine or chlorpromazine taken 8- or 4-hourly is suitable.

Other reported side effects, including pupillary constriction, biliary spasm, increased bladder tone and peripheral vasodilatation, do not usually present a clinical problem in chronic cancer pain patients. Respiratory depression does not occur in patients who are in pain[28] and is not a justification for using inadequate doses.

Addiction does not occur in patients receiving long term opioids for chronic cancer pain. Addiction is based on three separate components: physical dependence, psychological dependence and habituation (Fig. 1). Despite prolonged treatment with high doses of opioids

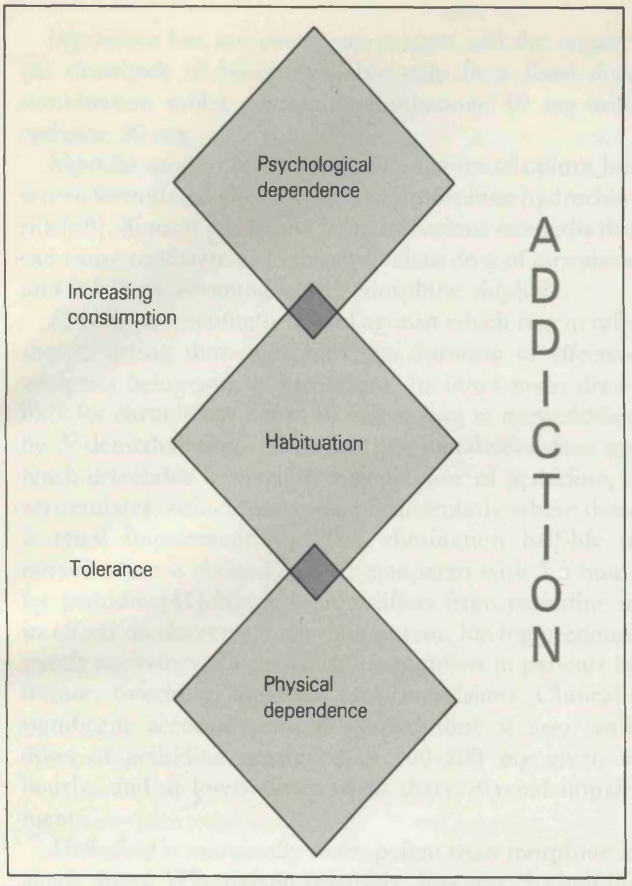

Fig. 1. *The components of addiction.*

neither psychological dependence nor habituation is seen. Tolerance to the physical effects of opioids may occur and physical dependence may develop after continuous use for periods of longer than about two weeks. Despite this, in patients whose pain improves or resolves, dose reductions and discontinuation of the opioid may be achieved without difficulty[3].

Diamorphine (diacetylmorphine) is the strong opioid of choice for use by subcutaneous or intravenous administration, and may also be substituted for morphine orally. It is a semi-synthetic derivative of morphine and is rapidly deacetylated in the body to monoacetyl-morphine and morphine. Its onset of action after intravenous injection is more rapid than that of morphine and it is associated with less vomiting and less sedation. There is some evidence that diamorphine is better absorbed from the gastrointestinal tract than morphine. However, diamorphine is essentially a prodrug for morphine, diacetylmorphine and monoacetylmorphine being undetectable in blood after an oral dose[33]. Diamorphine has no unique advantages or disadvantages for the relief of pain[34, 35] and its effects are indistinguishable from those of morphine when given 4-hourly for chronic pain[36].

The principal advantage of diamorphine lies in its much greater degree of solubility, enabling high doses to be administered by injection in small volumes suitable not only for intravenous use but also for subcutaneous injection or infusion. The limit of solubility is about 400 mg/ml although a concentration of 250 mg/ml (25 per cent w/v) is probably the maximum that should be used for continuous subcutaneous infusion[37].

It is important to consider the differences in bioavailability when changing from an oral morphine preparation to parenteral diamorphine, dividing the oral dose of morphine by three to obtain an equivalent parenteral dose of diamorphine. Because of the better oral bioavailability of diamorphine, an oral dose of diamorphine should be divided by two to obtain the equivalent parenteral dose.

Alternative Strong Opioids

None of the alternative strong opioids possess particular advantages which make them preferable to oral morphine or parenteral diamorphine. Commonly used drugs in this group are shown in Table 2 together with their equivalent oral morphine doses. As can be seen, some are considerably more potent than morphine and this can cause problems in changing from one to another.

Table 2. Alternative strong opioids.

Drug	*Dose (mg)*	*Oral morphine sulphate equivalent dose (mg)*
Buprenorphine (Temgesic)	0.2*	10–15
Dextromoramide (Palfium)	5	10
Dipipanone (Diconal when combined with cyclizine 30 mg)	10	5
Nepenthe	1ml (10ml of 10% solution)	12
Papaveretum (Omnopon)	10	5
Pethidine	50	6
Phenazocine (Narphen)	5	25
Methadone (Physeptone)	5†	5

*Usually given 8-hourly; the equivalent dose of morphine indicated is a 4-hourly dose.
†In single doses only; due to accumulation considerably more potent in chronic usage.

Buprenorphine is a partial opioid agonist which means that it may have both agonist and antagonist effects. It may be given sublingually or by injection. In acute pain postoperatively it appears effective, but in chronic use it has a high incidence of side effects, in particular nausea and vomiting, dizziness and drowsiness[38]. This limits its effective dose range and together with its potential antagonist action outweighs the advantage of sublingual absorption which may in any case be delayed and unreliable in patients with malignant disease who frequently have dry sore mouths.

Dextromoramide is a potent analgesic but usually has an effective duration of action of only 1½–2 hours. It is unsuitable for the treatment of chronic cancer pain.

Dipipanone has no specific advantages and the important drawback of being available only in a fixed dose combination tablet containing dipipanone 10 mg with cyclizine 30 mg.

Nepenthe used to be an alcoholic tincture of opium but is now formulated almost entirely as morphine hydrochloride[39]. Since it can be made up in various strengths this can cause confusion as to the equivalent dose of morphine and it has no advantages over morphine sulphate.

Pethidine is a synthetic opioid agonist which is generally shorter acting than morphine, its duration of effective analgesia being two to four hours. Its other main drawback for chronic use lies in its conversion to norpethidine by *N*-demethylation. Although this metabolite does not reach detectable levels after a single dose of pethidine, it accumulates with chronic usage, particularly where there is renal impairment[40]. The elimination half-life of norpethidine is about 17 hours compared with 3.5 hours for pethidine[41].Norpethidine differs from pethidine in its effects on the central nervous system, having predominantly excitatory effects which are manifest in patients by tremor, twitching, agitation and convulsions. Clinically significant accumulation of norpethidine is seen with doses of pethidine greater than 200–300 mg given 3-hourly, and at lower doses when there is renal impairment.

Methadone is marginally more potent than morphine in single doses. When given regularly, however, its half life increases considerably, with cumulation; plasma concentrations may take two to three weeks to reach a steady state[42]. Furthermore, no clear relation exists between plasma levels and analgesic activity. This tendency to cumulation in regular use can be particularly troublesome in the debilitated and elderly in whom sedation, confusion and, occasionally, respiratory depression may be seen.

Opioid mixtures have been advocated in the past, based on the traditional 'Brompton Cocktail', and the current British National Formulary[43] still contains four such formulations containing morphine or diamorphine with cocaine in a sweetened alcoholic base. Use of such cocktails confers no advantages but has a number of disadvantages. The inclusion of cocaine appears to increase side effects particularly in the elderly, and the use of any combination preparation reduces flexibility in dosage.

Route of Administration

The majority of patients will have their pain well controlled on oral medication until the final hours or days of their illness, and over 50 per cent will never require an injection[44]. Some patients, however, will be unable to tolerate oral drugs, because of nausea and vomiting, general debility, or impaired consciousness.

Rectal administration is a good alternative but may be unacceptable to some patients. Morphine suppositories are given 4-hourly in the same dose used by mouth and are widely available in a range of strengths. Oxycodone suppositories are an alternative which have the advantage of a longer duration of action (6 to 8 hours). Oxycodone 30 mg is equivalent to morphine 20 mg.

As discussed above, when parenteral medication is required, diamorphine is preferred. The optimum means of administration is by subcutaneous infusion using a syringe driver which avoids the need for repeated skin punctures. An anti-emetic such as haloperidol can be included in the subcutaneous infusion if necessary.

Parenteral opioid analgesics are not inherently better than oral medication when given in equi-analgesic doses, and in practice the indications for the use of subcutaneous infusions are relatively limited.

Co-analgesics

A co-analgesic is any therapeutic agent which may not have intrinsic analgesic activity but which will contribute significantly to pain relief when used with a conventional analgesic[45]. Table 3 gives some common examples.

Table 3. Co-analgesics.

Drug	*Type of pain*
NSAID	Musculoskeletal pain, e.g. bone metastases or soft tissue infiltration.
Corticosteroid	Raised intracranial pressure
	Nerve root compression
	Soft tissue infiltration
	Hepatomegaly
Diuretic (+ compression sleeve, massage)	Lymphoedema
Antibiotic	Infected ulcer
	Discharging sinus
Muscle relaxants	Muscle spasm
Anticonvulsants	Nerve root pain
	Post herpetic neuralgia

Non-steroidal anti-inflammatory drugs (NSAIDs) do not have a place as primary therapeutic agents but when used in conjunction with an opioid may be very effective particularly in the relief of bone pain. Prostaglandins are involved in peripheral nociceptive mechanisms, sensitising free nerve endings to pain-inducing vasoactive amines and kinins and hence facilitating pain transmission. They are also specifically involved in the development of bone metastases, stimulating osteoclastic bone resorption. Some tumours produce prostaglandin-like substances which may promote their metastatic potential in bone; the use of a prostaglandin synthetase inhibitor has a rational basis in the treatment of bone pain.

NSAIDs have a considerable potential, however, for producing adverse effects particularly on the gastrointestinal tract and in elderly patients[46]. It is important to closely monitor the therapeutic response of each patient and discontinue the drug at an early stage if no clear-cut benefit is seen. Despite a wide range of drugs in this class, none appears to have specific advantages in this indication. Soluble aspirin 600–1200 mg 4-hourly, may be appropriate for patients receiving 4-hourly morphine. In general, drugs which require less frequent administration are preferable for other patients, such as piroxicam 20 mg nocte or flurbiprofen 100 mg b.d.

Benorylate is an ester of paracetamol and aspirin which can be administered as an oral suspension. It has fewer side effects than aspirin used alone and has the additional advantage of 12-hourly dose intervals. It is de-esterified *in vivo,* each gram of benorylate producing 600 mg aspirin and 440 mg paracetamol. It may be a suitable alternative in certain patients where gastrointestinal tolerance is a problem with anti-inflammatory doses of aspirin, or with other NSAIDs. A dose of 10 ml (4g) b.d. is equivalent to 4.8 g/day of aspirin.

Corticosteroids are of use in headache due to raised intracranial pressure, nerve root pain due to compression or tumour infiltration, and may also reduce pain due to soft tissue infiltration. Dexamethasone has advantages over prednisolone because of its weaker mineralocorticoid (salt and water retaining) effects, with a lesser tendency to cause oedema and weight gain.

Diuretics may be useful in conjunction with massage and compression for painful lymphoedema.

Antibiotics are helpful for pain from an infected ulcer or discharging sinus, and for dysuria due to a urinary tract infection.

Muscle relaxants are indicated where pain is due to increased muscle tone, spasm or clonus. Baclofen 5–20 mg three times daily is the preferred drug, having less sedative action than diazepam. Some patients, however, have intolerable gastrointestinal side effects and in these diazepam 2 to 5 mg t.d.s. may be used as an alternative.

Anticonvulsants may be helpful in some patients with lancinating or stabbing dysaesthetic pains associated with nerve compression or infiltration, and post-herpetic or post-traumatic neuralgias. Carbamazepine 100 mg t.d.s., sodium valproate 200 mg t.d.s. or clonazepam 0.5–2.0 mg once or twice daily, may all be helpful. Individual patients may respond better to one particular drug. Clonazepam tends to cause more sedation and the choice of drug should be tailored to the individual patient.

Conclusion

The principles of effective pain control are: make a diagnosis; individualise the treatment; and keep it simple. Familiarity with a simple analgesic ladder will facilitate rational changes in analgesic and dose modifications as appropriate. Predictable side effects such as constipation should be prevented. The appropriate use of co-analgesics including non-drug treatments such as radiotherapy or nerve blocks should also be considered. With this approach it should be possible to control pain in almost all patients with malignant disease without the need for exceptional measures.

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Review article

Opioid analgesics in the management of pain in patients with cancer. A review

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Key words: opioids, analgesia, receptors, tolerance, addiction, pain, cancer.

Introduction

The relief of pain in patients with cancer is largely achieved by pharmacological methods. Effective symptom control is based on an analytical approach and the intelligent and informed use of drugs. However, analgesics cannot ever be sufficient by themselves. Pain and suffering in the cancer patient are invariably compounded by anxiety, fear, depression, hopelessness and misunderstanding. Empathy, explanation and reassurance may have a profound pain-relieving effect, and anxiety and depression may require specific treatment.

Of the analgesics, the main group of drugs used in cancer pain are the opioids. In this review we describe our choice of individual drugs and discuss the reasons for using them in preference to the available alternatives. We also focus on current areas of controversy relating to the use of strong opioid analgesics.

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Terminology

In recent years there has been much confusion about the meaning of the terms opiate, opioid, and narcotic, and agonist and antagonist. This is often compounded by the misuse of the words efficacy and potency.

Opiate is a specific term which is used to describe naturally-occurring compounds derived from the juice of the opium poppy[1] (codeine, morphine and papaveretum (Omnopon) are the most common opiates in clinical use).

Opioid is a general term which includes both naturally-occurring and synthetic drugs with opiate-like or morphine-like activity that are antagonised by naloxone (all of the drugs discussed

in this review). Diamorphine is a synthetic opioid.

Narcotic is a term derived from the Greek word 'narke' meaning numbness or torpor. 'Narcotic analgesics' are agents which produce naloxone-reversible *analgesia*. Thus 'opioid' is not interchangeable with narcotic because it has a broader meaning and encompasses many other pharmacological effects in addition to analgesia.

The word narcotic has assumed notoriety because of its widespread general use and association with drug abuse. It is somewhat misleading to use it in a pharmacological sense and the term opioid is preferable. While some authorities believe 'narcotic' to be already obsolete[2] it is still used in works of reference[3]. We shall use the terms weak opioid and strong opioid rather than weak narcotic and strong narcotic.

Receptors are specialized areas of the cell membrane which are highly specific for certain drug or hormone molecules. A drug which binds to the receptor and induces changes in the cell and other systems to produce the pharmacological response associated with that drug is called an agonist. Some drugs, however, have no intrinsic pharmacological action but can interfere with the action of the agonist: these are called antagonists. 'Competitive antagonist' is a specific term referring to antagonists which bind to the receptor and compete for receptor sites. The blocking effect of a competitive antagonist can be overcome by increasing the concentration of the agonist. Non-competitive antagonists prevent the agonist from producing its pharmacological effect, but may act in various ways other than by merely competing for the receptor.

Opioids are agonists at highly specific receptor sites, and there is general agreement on the existence of at least three types of opioid receptor[4]: μ (mu) the classical morphine receptor; κ (kappa) at which the prototype agonist is a drug called ketocyclazocine; and σ (sigma) at which the prototype agonist is a compound called SKF 10,047 (N-allyl normetazocine). Other receptors (δ, delta and ϵ, epsilon) have been proposed and a recent development has been the further subdivision of μ receptors into μ_1 (high affinity) and μ_2 (low affinity)[5]. The concept of different receptors ('receptor dualism') is helpful in understanding the differences between various opioid analgesics. Table 1 shows the functions attributed by Martin and his colleagues to the three main opioid receptors[4]. This classification remains the basis of our current understanding.

Table 1 Putative effects mediated by main classes of opioid receptor

Mu	Kappa	Sigma
Supraspinal analgesia	Spinal analgesia	Dysphoria
Euphoria	Sedation	Hallucinations
Miosis	Miosis	Delusions
Respiratory depression	Respiratory depression	Respiratory stimulation
Physical dependence		Vasomotor stimulation

Opioid receptors are found in several areas of the brain, particularly in the periaqueductal grey matter, and also throughout the spinal cord. Animal studies indicate that there may be some functional differentiation of nociceptive stimuli between receptor types, with μ receptors being selective for heat stimuli and κ receptors selective for pressure stimuli[6]. This is a controversial area and there is still debate about the existence and the function of so many opioid receptors.

Stereospecificity

Most opioids can exist in two chemical forms (laevorotatory and dextrorotatory) known as optical isomers because they have opposite effects on polarized light. One form is usually much more active pharmacologically than the other. This is because opioid receptors exhibit a high degree of stereospecificity (structural specificity) and only interact with either the l- or the d- stereoisomer of a particular opioid. For example, d- propoxyphene or dextropropoxyphene accounts for the analgesic action of propoxyphene.

Potency and efficacy

Figure 1 illustrates diagrammatically the dose response curves for two drugs, A and B. By plotting the log of the dose against response an agonist will produce a typical 'S'-shaped or sigmoid curve. The two drugs illustrated are both agonists but they differ in potency. A is more potent (it will produce the same response but at a lower dose than B) but A and B are equally effective (the

curves are parallel: the same range of response and maximum response can be produced by both drugs using the appropriate dose).

Potency is a measure of the affinity of a drug for receptors: the more potent the drug the greater the affinity.

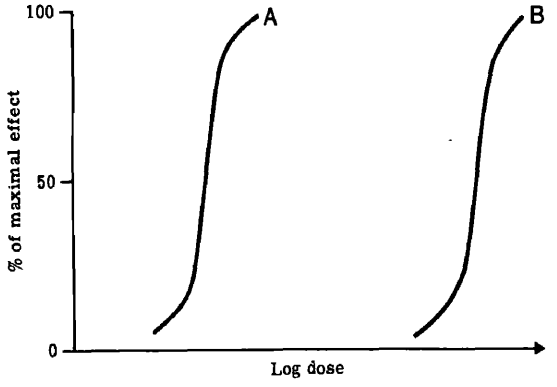

Figure 1 Dose response curves for two opioid agonists (A and B)

Figure 2 illustrates a third type of drug: drug C. This drug is not as effective as drugs A and B because there is a limit to the response it can produce, a 'ceiling effect'. This means that increasing the dose above a certain level does not result in any further increase in response. Such a drug is called a *partial agonist*. In this particular example drug C is *more potent* than drug B (in the lower part of the curve it will produce the same response at a lower dose) but it is *less effective* because of its ceiling effect.

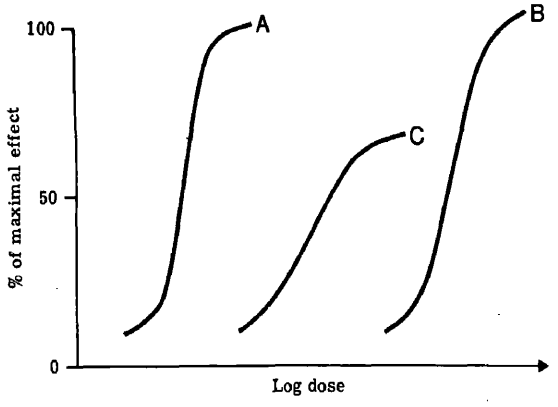

Figure 2 Dose response curves for two opioid agonists (A and B) and a partial agonist (C)

Buprenorphine is an example of a partial opioid agonist. If a partial agonist is administered together with a pure agonist it may antagonise the effects of the agonist. This applies to buprenorphine when it is administered with morphine. Buprenorphine, the more potent drug, displaces morphine from the receptors. At low doses this merely means that the buprenorphine is now producing the μ receptor effect rather than the morphine, so that nothing changes. If, however, a patient is receiving high doses of an agonist, such as morphine, and buprenorphine is added, the morphine will be displaced from the receptors and because of buprenorphine's ceiling effect the net pharmacological action will be reduced. This is the mechanism of the antagonist action of buprenorphine. It may be sufficient to produce an acute withdrawal syndrome in a patient physically dependent on opioids. Though this interaction is only likely to occur at high doses, in principle it is inadvisable to use an agonist at the same time as a partial agonist or a mixed agonist antagonist.

The pharmacological treatment of cancer pain

Table 2 shows our recommended scheme of drug use in chronic cancer pain. Initial choice of drug is based on the severity of the pain and its response to previous treatment. A simple scheme using a limited number of drugs works well in practice. Drugs are ranked according to analgesic strength with a range from simple non-opioid analgesic to weak opioid to strong opioid. One drug in each class should be used routinely and only rarely will an alternative be necessary. If the drug is no longer effective there is no value in using alternatives from the same group. The next step is to move up to a higher level of analgesia.

There is no place for intermittent 'as required' analgesia in chronic cancer pain. The aim of treatment is to control and prevent further symptoms by regular medication, maintaining constant effective blood concentrations in the steady state. Individualisation of dose and route of administration, and simplicity, are the principles of the effective use of analgesics in cancer pain.

Table 2 Recommended scheme of analgesic drug use in chronic cancer pain

	Mild pain	Pain unresponsive to simple analgesics	Pain unresponsive to weak opioids
Analgesic group	Simple, peripherally-acting analgesic	Weak opioid	Strong opioid
Drug of choice	Paracetamol 1 g 4-hourly	Dextropropoxyphene/paracetamol 2 tabs 4-hourly	Morphine or diamorphine orally 5–200 mg 4-hourly
Alternative drugs	Soluble aspirin 600–1200 mg 4-hourly	Dihydrocodeine 30–60 mg 4-hourly	Phenazocine, levorphanol oxycodone suppositories
Drugs to avoid	Compound preparations	Pentazocine	Short-acting opioids, combinations, opioids with cumulative toxic effects
Other measures	Co-analgesics	Co-analgesics	Co-analgesics

Weak opioid analgesics

When pain is not controlled with a peripherally-acting analgesic such as paracetamol the next step is to move to a weak opioid.

Dextropropoxyphene/paracetamol

Dextropropoxyphene in combination with paracetamol (coproxamol) is our drug of choice in this group. The proprietary preparation Distalgesic was for long the most commonly prescribed analgesic in Britain, but received much adverse publicity because of its lethal effects in overdose[7] and because of fears about its addiction potential[8].

Coproxamol is the commonest cause of fatal poisoning from drug overdose in the United Kingdom[9]. Respiratory depression may develop rapidly, often within an hour, so that patients may die before they reach medical attention. As few as 15 tablets may be sufficient to produce a fatal outcome particularly if combined with alcohol[10],

Addiction has also been reported[11,12] but is rare. However, these two factors, coupled with doubts about the efficacy of dextropropoxyphene have resulted in repeated calls for its proscription[13,14,15]. Others have taken a more pragmatic view[16] and the preparation remains popular and widely used. It is noteworthy that coproxamol was omitted from the United Kingdom's provisional limited list of drugs for NHS prescription, but was eventually included.

Chemistry and pharmacology

Propoxyphene is a synthetic derivative of methadone[17] and its dextrorotatory stereoisomer, dextropropoxyphene, is responsible for its analgesic activity[18]. Dextropropoxyphene has weak opioid activity in animal models, and receptor studies have shown a low affinity for μ sites, of a similar order to that of codeine[19]. The opioid effects of dextropropoxyphene (analgesia, sedation, nausea, vomiting, constipation, hypotension and respiratory depression) are reversed by naloxone.

Pharmacokinetics

Dextropropoxyphene is readily absorbed from the gastrointestinal tract with peak serum levels at about two hours after administration. The mean elimination half-life is about 15 hours with steady state levels being reached after three to four days of regular six to eight hourly administration. In elderly patients the half-life may be very long (over 50 hours)[20].

Dextropropoxyphene undergoes extensive first pass metabolism, its principal metabolite being norpropoxyphene which is active but penetrates the brain to a much lesser extent and has much weaker opioid effects[19]. Norpropoxyphene has a longer half life (about 23 hours) than dextropropoxyphene itself and accumulates in plasma[21]. Both dextropropoxyphene and norpropoxyphene reach plasma concentrations in the steady state which are five to seven times greater than those found after the first dose.

Clinical use

In man the analgesic efficacy of dextropropoxyphene hydrochloride in doses of 65 mg or more has been established in a number of placebo-con-

trolled studies[22]. Beaver equates lower doses with aspirin and estimates that the relative potency of dextropropoxyphene is 1/2 to 2/3 that of codeine[23]. Dextropropoxyphene napsylate is less potent than the hydrochloride (in a ratio of 5:3).

In comparative single dose studies against aspirin, paracetamol, and non-steroidal anti-inflammatory drugs including ibuprofen 400 mg, mefenamic acid 250 mg and fenoprofen 50 mg, dextropropoxyphene appears to be a slightly less effective analgesic[22]. However these studies used acute pain models such as rheumatoid and osteoarthritis, dysmenorrhoea, and pain after oral surgery which are generally less responsive to centrally-acting analgesics than peripherally-acting drugs[22]. Also the pharmacokinetic profile of dextropropoxyphene after a single dose is not comparable to that in chronic use. When given orally a significant percentage of the dose will be converted on 'first pass' to the weaker norpropoxyphene before it reaches the systemic circulation. This presystemic metabolism is dose dependent: the systemic availability of dextropropoxyphene increases with increasing oral dose[24]. Thus with regular administration there is enhanced bioavailability, and some degree of accumulation because of the long elimination half-lives of the parent drug and main metabolite. The drug is likely to be more effective when given in repeated doses, and the results of *single dose* efficacy studies of dextropropoxyphene may be misleading.

Dextropropoxyphene in combination with paracetamol

The use of a centrally- and a peripherally-acting analgesic together can achieve greater analgesia with a reduction in dose-related side effects associated with each individual constituent[25].

The combination of dextropropoxyphene and paracetamol (coproxamol) is the usual form of administration in the United Kingdom. However, evidence from controlled studies that the combination is more effective than paracetamol by itself is sparse, and only two studies have shown that the combination is significantly superior to paracetamol alone[26,27]. In assessing data from studies where no difference has been shown between paracetamol alone and in combination with dextropropoxyphene, the comments above relating to the type of pain model and the use of single doses are again relevant.

Other criticism is based on the pharmacokinetic incompatibility of the combination[28]. Dextropropoxyphene and norpropoxyphene have long elimination half-lives whereas paracetamol does not. However, no problems attributable to persistent effects of dextropropoxyphene in the body have been reported in clinical use even after chronic dosing. Thus this seems a theoretical objection which is of little clinical significance.

In summary, dextropropoxyphene is an effective weak opioid analgesic. In combination with paracetamol it is a useful intermediate between simple peripherally-acting analgesics and morphine. The recommended dose is up to two tablets of coproxamol four-hourly (each tablet contains dextropropoxyphene 32.5 mg and paracetamol 325 mg). At these doses serious side effects are unusual but confusion, dysphoria and lightheadedness may occur, particularly in the elderly. Nausea and vomiting are infrequent and constipation is less troublesome than with other opioids but is common and needs to be anticipated and treated. Coproxamol will potentiate the effects of warfarin[29], carbamazepine[30], and central nervous system depressants, including alcohol[31].

Other weak opioid analgesics

Codeine and dihydrocodeine

Codeine (methylmorphine) is the standard weak opioid analgesic. It is a naturally-occurring alkaloid in opium, chemically closely related to morphine (Figure 3) and has μ receptor effects. Codeine phosphate is well absorbed from the gastrointestinal tract and is metabolised to norcodeine and morphine. Some 10% of an oral dose is converted to morphine and this may partly account for its analgesic effect[32].

The usual oral dose of codeine is 30 to 60 mg and its duration of action is four to six hours. Its oral to parenteral potency ratio is 2:3[33] which is much more favourable than for other opioids, but parenterally codeine is less than one-twelfth as potent as morphine[34]. There is disagreement about the effective dose range of codeine. Whilst it is widely believed that there is a levelling off in analgesia at doses above 60 mg by mouth, there is

evidence from studies of IM codeine that a progressive increase in analgesia is obtained with doses up to 360 mg[23]. Such doses are rarely, if ever, used.

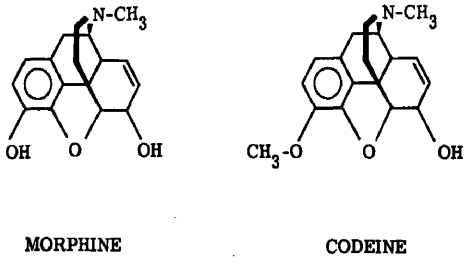

Figure 3 The chemical structures of morphine and codeine

Dihydrocodeine (DF 118) is a semi-synthetic analogue of codeine and approximately 30% more potent[35]. There is a dearth of controlled clinical trial data on the use of oral dihydrocodeine. The usual dose is 30 to 60 mg (one to two tablets) four- to six-hourly.

Coproxamol versus codeine and dihydrocodeine

We prefer coproxamol because of its theoretical advantage in having equal efficacy to codeine and dihydrocodeine, but with less potential for causing opioid side-effects (particularly constipation). There are no clinical trial data either to substantiate or refute this putative advantage, and some authorities prefer to use codeine or dihydrocodeine.

Combination preparations of codeine and dihydrocodeine together with aspirin or paracetamol are also available. Without exception these preparations contain low doses of the opioid (e.g. Codis (cocodaprin), with 8 mg codeine and 500 mg soluble aspirin; Panadeine (cocodamol) with 8 mg codeine and 500 mg paracetamol; Paramol with 10 mg dihydrocodeine and 500 mg paracetamol). These doses of the opioid, even when two tablets are given, are subtherapeutic. In contrast, two tablets of coproxamol give a therapeutic dose of dextropropoxyphene.

We would use dihydrocodeine as our *alternative* weak opioid analgesic if for some reason patients are unable to take coproxamol.

If pain is insufficiently controlled with a weak opioid analgesic in maximum dose (two tablets four-hourly of coproxamol, or 60 mg four-hourly of dihydrocodeine) the starting dose of oral morphine should be 10 mg four-hourly.

Agonist/antagonist opioid analgesics

This is a group of drugs which falls between the weak opioids and strong opioids in terms of their analgesic activity. Drugs included in this category are a heterogenous group including the partial agonist buprenorphine, the nalorphine-like agonist antagonists pentazocine, butorphanol and nalbuphine, and the more recent μ_1 selective agonist antagonist meptazinol. All of these drugs are characterised by having analgesic activity but at the same time are capable of antagonising the effects of morphine or other opioid agonists. The motive for developing such drugs was to produce powerful analgesics which lacked the addictive properties, respiratory depression and other major side-effects associated with the strong opioids. Unfortunately this objective has never been achieved.

Nalorphine-like agonist antagonists

Nalorphine, N-allylnormorphine, was synthesized in 1941 and was found to antagonise the effects of morphine[36]. Surprisingly nalorphine was also found to have powerful analgesic activity[37] but in man this was accompanied by a high incidence of dysphoric side-effects. For this reason attention was switched to a series of benzomorphan derivatives, of which two appeared to have clinical potential: cyclazocine and pentazocine[38].

Pentazocine

Pentazocine was the first mixed agonist antagonist analgesic to be used in widespread clinical practice. Pentazocine is a weak competitive antagonist at μ receptors and an agonist at κ and σ receptors[4].

Early studies with pentazocine indicated that given parenterally it is a potent analgesic. Estimates of its potency relative to morphine range from 1/6[39] to 1/3[40]. The drug undergoes extensive first pass metabolism and the oral to parenteral potency ratio is 1/3 to 1/4[41]. Comparative studies

with standard analgesics have produced conflicting results. In postoperative patients pentazocine 50 mg (two tablets) appeared to be as effective as codeine 60 mg[42] or dihydrocodeine 60 mg[43]. However, in other studies in patients with cancer pain pentazocine 50 mg was less effective than aspirin 650 mg[44] or than combinations of codeine 8 mg with aspirin 500 mg, and dextropropoxyphene 32.5 mg with paracetamol 325 mg[45]. A study in rheumatoid patients also indicated that pentazocine 50 mg was less effective than aspirin 500 mg and the two combination preparations mentioned above[26]. The duration of analgesia produced by pentazocine in these studies was about three hours.

The other major drawback of pentazocine is that it produces a high incidence of psychotomimetic side-effects, most commonly hallucinations, euphoria and depersonalisation, which can occur in some patients at very low doses. The incidence of psychotomimetic effects has been variously reported as 1%[46] to 20%[47] with most estimates being in the region of 10%[48]. There is some evidence that the incidence is higher in chronic pain patients[49] and patients with cancer may be particularly at risk[3].

Initially pentazocine was believed to be non-addictive, but pentazocine abuse is now well recognised[50,51,52]. The abuse potential of pentazocine and other agonist antagonists is however less than that of morphine and other strong agonists, and may be less than that of codeine or propoxyphene[53].

In summary, pentazocine has weak analgesic activity when given by mouth, appears to be closer in analgesic efficacy to the peripherally-acting simple analgesics than the weak opioids, and its use is associated with a high incidence of unpleasant side effects. Pentazocine has no advantages over other weak opioid analgesics to balance these major disadvantages and has no place in our management of cancer pain.

Butorphanol

Butorphanol is another nalorphine-like agonist antagonist which is structurally related to pentazocine and which is a weak μ antagonist and a κ and σ agonist. It is a potent analgesic, three and a half to seven times as potent as morphine and twenty times as potent as pentazocine[54]. It was introduced in the United Kingdom in 1978 but was only available for parenteral administration. Butorphanol did not appear to have any particular advantages over other more established drugs and was withdrawn from the market in 1983 because of poor sales.

Nalbuphine

Nalbuphine is chemically closely related to naloxone, the specific opioid antagonist, and to oxymorphone, a strong agonist. It is a weak μ antagonist and a κ agonist. Nalbuphine is approximately equipotent with morphine after intramuscular injection[55] and its duration of action is three to six hours.

Nalbuphine is also only available for parenteral administration (IM, SC or IV) and this formulation has no obvious place in the management of chronic cancer pain. Studies of oral nalbuphine in postoperative pain have shown it to be 1/4 to 1/3 as potent as intramuscular nalbuphine in total analgesic effect, but only 1/10 as potent in terms of peak analgesic effect[56]. No oral formulation of nalbuphine has yet been registered for general clinical use.

Morphine-like agonist antagonists

Buprenorphine

Buprenorphine is a semi-synthetic derivative of thebaine and chemically closely related to the potent agonist etorphine. Buprenorphine is a partial agonist and exhibits a ceiling or plateau effect in various animal models, and in some a 'bell-shaped' dose response curve is seen[57]. This means that at doses above a certain level the pharmacological response actually decreases with increasing dose.

Buprenorphine has potent agonist activity, being some thirty times as potent as morphine[58]. It undergoes extensive first-pass metabolism and inactivation and is not therefore effective by the oral route. However, a sublingual tablet (0.2 mg) is available and sublingual buprenorphine is almost as effective as parenteral buprenorphine (0.3 mg IM = 0.4 mg sublingually)[59]. The duration of analgesia is six to nine hours[59].

A bell-shaped dose response curve has not been shown for any opioid effect of buprenorphine *in man* nor has the maximal effective dose been unequivocally demonstrated. However there does

appear to be a ceiling effect for subjective responses to buprenorphine at about 1 mg subcutaneously (and therefore probably a little higher sublingually)[60]. There is a more practical 'ceiling' with respect to the number of tablets a patient will tolerate. The administration of more than three or four tablets (0.6 to 0.8 mg) in a single dose is impractical.

The use of buprenorphine perioperatively, given both parenterally and sublingually is well established[61]. It is potent and long acting but with a slow onset and slow peak effect. A major practical advantage in this setting is that it is not a Controlled Drug and therefore not subject to the same restrictions on prescribing and dispensing as other strong opioid analgesics.

There are limited clinical trial data on the use of sublingual buprenorphine in cancer pain. In one open study 94 of 141 patients discontinued the drug within one week: 50 because of side-effects (dizziness, nausea, vomiting, drowsiness, light-headedness) though not all of these may have been directly attributable to the buprenorphine. The other 47 patients appeared to have satisfactory relief of their pain using doses ranging from 0.15–0.8 mg at varying dose intervals[62]. In another open study over half of 70 patients obtained pain relief with total daily doses of 0.4 to 4 mg, but 'most' patients withdrew from the study because of unwanted effects or inadequate relief[63].

In two controlled studies in cancer patients buprenorphine appeared better overall than pentazocine[64,65] and others have confirmed the clinical efficacy of chronic sublingual administration[66,67].

Buprenorphine has a much lower abuse potential than other strong opioid analgesics. It has little capacity to produce physical dependence[68] and acute withdrawal even after high doses causes only mild abstinence phenomena[69]. However, abuse of buprenorphine has been reported and in some centres is a growing problem[70].

The opioid effects of buprenorphine are relatively resistant to reversal by naloxone, possibly due to the very high binding affinity of the drug to μ receptors. Even large doses of naloxone are only partially effective[60] and on the basis of studies in healthy volunteers the manufacturers recommend the use of the respiratory stimulant doxapram in the treatment of respiratory depression resulting from overdosage of buprenorphine.

In summary, buprenorphine is a potent opioid analgesic with several potential advantages: it is effective when given sublingually, has a long duration of action (six to nine hours) and is less likely to cause physical dependence and abuse than other strong opioids. Against this must be weighed a number of limitations: buprenorphine has a narrow effective dose range because of its ceiling effect; it has the potential to antagonise the actions of pure opioid agonists and precipitate abstinence phenomena; and its chronic use is associated with the same range of side-effects as other strong opioids with some indications that these unwanted effects are more frequent.

We would see the place of buprenorphine in the management of cancer pain as an alternative to oral morphine in the lower dose range. Since progression to morphine will invariably be required the usefulness of buprenorphine in cancer pain is limited.

Patients may be converted directly from buprenorphine to a pure agonist, though there may be a delay in achieving the optimum dose level of the new drug. No problems are likely to be encountered in the transition period. The conversion ratio to oral morphine suggested by Twycross and Lack[3] works well in practice: multiply the total daily dose of buprenorphine by 100 and convert into a convenient four-hourly regimen.

Meptazinol

Meptazinol is a synthetic hexahydroazepine derivative with opioid agonist and antagonist properties. However, it is unlike either the nalorphine-type agonist antagonists or buprenorphine. In animal models it has potent analgesic effects which are almost completely reversed by naloxone, but has low dependence liability[71]. Meptazinol also antagonizes morphine-induced respiratory depression and precipitates abstinence phenomena in morphine-dependent rats[71]. Studies in man have confirmed that meptazinol is effective in the relief of moderate to severe acute pain associated with surgery, trauma, renal colic, and childbirth[72,73].

Unlike other opioids, both optical isomers possess analgesic activity and the drug has central

cholinergic properties which may account at least in part for its analgesic effects[74]. This differentiates meptazinol from all conventional analgesics. Receptor binding studies show it to be a specific μ_1 agonist[75].

An oral formulation of meptazinol is available in the United Kingdom but is not yet registered elsewhere. The effective dose range of meptazinol appears to be narrow[76] and there are few comparative data. In terms of analgesic efficacy, oral meptazinol comes into the same category as the weak opioids, but it does not seem to compare favourably with coproxamol either in terms of efficacy or side-effects.

The use of meptazinol is restricted to "short term treatment of moderate pain"[77] and we do not see, therefore, any particular place for it at present in the management of cancer pain.

Opioid antagonists

Naloxone

Naloxone is a synthetic derivative of oxymorphone, a strong opioid agonist, and therefore structurally closely related to morphine. It competitively antagonises the effects of opioids but in contrast to other opioid antagonists has no intrinsic agonist activity of its own. Naloxone has greatest affinity for the μ receptor but also binds to κ and σ receptors[78]. It thus antagonises not only morphine-like drugs acting primarily through μ receptors but also drugs with agonist activity at other receptors (such as pentazocine at the κ receptor).

The most common clinical use for naloxone is in opioid overdosage to reverse coma and respiratory depression[79], though other uses have been proposed including shock and schizophrenia[80,81].

Naloxone is in general well tolerated though predictably may provoke symptoms similar to those of opioid withdrawal, in particular sweating, agitation or vomiting. Naloxone-induced hypertension and cardiac arrhythmias have also been reported[82].

Strong opioid analgesics

Most patients with chronic cancer pain will eventually require a strong opioid analgesic to achieve pain control, and morphine is regarded as the strong opioid agonist of choice[3,83].

Morphine

Morphine is extracted from opium and is its principal alkaloid, constituting about 10% by weight. The chemical structure of morphine base is shown in Figure 3.

Chemistry and pharmacology: pharmaceutical preparations

Morphine sulphate in aqueous solution (chloroform water) is the usual preparation for oral use. The addition of ethylene diamine tetracetic acid and benzoic acid to the solution prolong the shelf-life from two weeks when made up in chloroform water alone to six months. This formulation has the advantage that elixir of any given strength can be prepared for an individual patient as necessary, maintaining a constant volume convenient for administration, usually 10 mls. The limit of solubility is 400 mg in 10 mls. The principal disadvantage of the elixir is its characteristic bitter taste which is difficult to disguise.

Nepenthe was originally an alcoholic tincture of opium but is now formulated as an elixir containing anhydrous morphine 8.4 mg/ml of which only 500 microgrammes is as opium tincture[84]. It is therefore essentially an alternative morphine elixir with no advantages over morphine sulphate. 1ml of undiluted Nepenthe (10 mls of 10% solution) is equivalent to 12 mg morphine sulphate by mouth. A parenteral preparation of Nepenthe is also available.

Slow release morphine sulphate tablets (MST-Continus) are available in four strengths: 10 mg (brown), 30 mg (purple), 60 mg (orange) and 100 mg (grey) tablets. A higher strength tablet is planned.

For parenteral use, *morphine sulphate injection* is available in concentrations of 10, 15, 20 and 30 mg/ml. There is also a long-acting aqueous suspension containing 64 mg/ml for subcutaneous or intramuscular use (Duromorph), and a preservative-free injection for spinal use in strengths of 2.5 mg in 5 mls and 2 mg in 10 mls. *Cyclimorph injection* contains either 10 or 15 mg morphine tartrate with 50 mg cyclizine tartrate per ml.

Morphine may also be administered rectally and *suppositories* containing morphine sulphate or

morphine hydrochloride are available commercially in strengths of 15 mg and 30 mg, but most hospital pharmacies are able to prepare a variety of other strengths according to need.

Two *buccal morphine* preparations are under development and early studies suggest that good absorption by this route is achieved[85].

Combination elixirs based on the traditional Brompton Cocktail are still available but are not recommended.

Pharmacodynamics

The clinical effects of morphine in man are well recognised and include an inhibitory action on the central nervous system accounting for analgesia, respiratory depression and somnolence; an excitatory action on the CNS accounting for miosis, vomiting and convulsions; a stimulant action on peripheral smooth muscle accounting for constipation, bronchoconstriction and increased bladder and uterine tone; and a number of other associated peripheral effects including itching, sweating and dry mouth.

At opioid receptors in the CNS morphine is a pure agonist with a predominant action at the μ receptor, but also binds to κ receptors. Opioid receptors have also been demonstrated outside the central nervous system[86]. The relative role of central and peripheral receptors in the actions of morphine in man remains unclear, as does their putative physiological role in relation to endogenous opioids.

The active substance binding to these receptors has in the past been assumed to be morphine itself. There is, however, now some evidence to suggest that metabolites of morphine may be important in producing its effects. In rats morphine-6-glucuronide (M6G) has been shown to be a very potent analgesic with an effect 45 times greater than morphine when injected intracerebrally and 3.7 times greater than morphine when injected subcutaneously[87]. Morphine-3-glucuronide (M3G) does not cross the blood brain barrier but has demonstrable analgesic activity when it is injected intracerebrally[88].

A role for M6G in mediating the effects of morphine in man has been postulated[89]. Prolonged respiratory depression following morphine has been observed in the presence of negligible plasma concentrations of morphine but very high levels of both M6G and M3G[89].

Pharmacokinetics of morphine

Despite having been used in clinical practice for many years, the pharmacokinetics of morphine, particularly in chronic use, remain poorly understood. A fundamental difficulty until recently has been the inability of assay techniques to reliably distinguish morphine from its metabolites. This is a particular problem in chronic use because of the accumulation of the glucuronide conjugates M3G and M6G to a concentration many times greater than that of unconjugated morphine. Only a small degree of non-specificity is required in the assay for the concentrations of unconjugated morphine to be considerably overestimated. Recent developments in assay techniques now enable reliable measurements of morphine in tissue fluids using either a specific radioimmunoassay[90] or high performance liquid chromatography (HPLC)[91]. The latter assay has the advantage of enabling quantitative estimation of the main metabolites as well as morphine.

In addition to assay specificity there are other factors to be considered in the interpretation of the available pharmacokinetic data. Most studies in which the pharmacokinetics of morphine have been described use single doses of morphine, rarely more than 10 mg, administered parenterally or orally to normal volunteers or morphine-naive patients. This reflects a very different situation to that encountered in the treatment of chronic cancer pain where morphine is given regularly over a period of weeks or months in much higher doses.

When comparing normal volunteers or healthy post-operative patients with patients having advanced cancer it is also important to consider the influence of the disease upon drug handling. Hepatic and renal impairment are common in advanced malignancy and may well influence the pharmacokinetics of a drug.

Absorption

Absorption from the gastrointestinal tract is virtually complete, occurring predominantly in the proximal small bowel[92]. Morphine is a basic compound (pKa 9.85) and becomes unionised (lipid soluble and diffusible) as the pH rises in this region. A similar pH dependence has been demon-

strated at the buccal mucosa[93] where morphine is also readily absorbed. Absorption through the rectal mucosa is rapid and blood levels similar to that after oral administration are achieved[94].

Distribution

Pharmacokinetic data derived from single dose studies in both rats and man suggest that a three-compartment model for the distribution of morphine is most likely[95,96,97,98,99,100]. There is rapid distribution from the plasma compartment to brain, liver, lung, muscle and bile[101,102]. Some 30-40% of the morphine present in plasma is protein bound, predominantly to albumin[103].

Metabolism

Morphine undergoes extensive biotransformation by synthetic and oxidative reactions (Figure 4)[104]. Extensive presystemic elimination is thought to account for the poor bioavailability of morphine after oral administration, ranging from 15% to 64% in one study in cancer patients[105]. The main metabolites found in plasma following administration of morphine are M3G and M6G. During long-term treatment the conjugation of morphine with glucuronic acid is proportional to the dose, with no evidence of saturation of the system or autoinduction as the dose is increased[106].

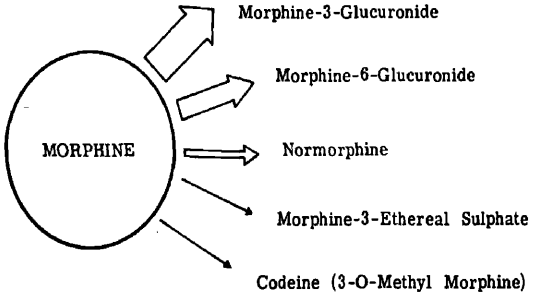

Figure 4 The metabolites of morphine

Controversy has developed over whether the liver or kidney is the main site of morphine metabolism in man. Data from animal studies show conclusively that both *in vitro*[107] and *in vivo*[108] conjugation of morphine with glucuronic acid occurs in the liver. In rats up to 85% of an oral dose is metabolised on 'first pass' and of this 46% is calculated to take place in the small bowel mucosa.

In man there is also good evidence to support hepatic metabolism. *In vitro* work on human liver obtained immediately after death has demonstrated the ability of hepatic microsomes to glucuronidate morphine[109]. A study in six cancer patients submitted to laparotomy at which liver biopsies were obtained, followed by *in vivo* pharmacokinetic profiles after administration of single doses of morphine showed a clear correlation between UDP-glucuronyl transferase activity in the liver biopsy specimens and morphine-3-glucuronide/morphine ratios in plasma[110]. The poor oral bioavailability of morphine[105] is further clinical evidence for a major role for the gut or liver in morphine metabolism.

Conflicting data were obtained in a study of patients with impaired liver function related to moderate to severe cirrhosis which showed no difference in the disposition and elimination of morphine compared with healthy volunteers following a single intravenous dose[111]. However, a more recent study in patients with cirrhosis showed a much higher oral bioavailability and long elimination half-life of morphine compared with patients with normal liver function[112].

Extrahepatic metabolism of morphine has been demonstrated in animal models. Isolated rabbit kidney proximal tubules have been shown to glucuronidate morphine *in vitro*[113]. In two chronically cannulated cows, hepatic extraction of morphine was seen only at plasma concentrations greater than those found in most patients with advanced cancer receiving morphine[114,115].

In man the evidence for renal metabolism is based mainly upon observations in patients with impaired renal function. A study performed in patients undergoing renal transplantation in which a single intravenous dose of morphine was given following induction of anaesthesia, showed elevated morphine concentrations compared with a control group. Of greater significance was a plateau phase during which morphine levels remained constant during the period of cold ischaemia, followed by a steady fall which correlated with the recovery of renal function in the transplanted kidney[116]. Further evidence that hepatic extraction may not be important was suggested by

the finding of a relative bioavailability for oral morphine of over 100% in another study by the same authors[117]. Further evidence for the importance of the kidney in the elimination of morphine was provided by a retrospective analysis of patients with advanced cancer which suggested that those with impaired renal function (serum creatinine greater than 180 micromoles/1) required lower doses of morphine (median 5 mg 4-hourly) than those with impaired hepatic function (median 20 mg 4-hourly)[118].

The findings in the two experimental studies above have been criticised[119] on the basis that both used a radioimmunoassay subsequently shown to cross react significantly with M6G, resulting in considerable overestimation of what was thought to be unconjugated morphine. Three further studies have now been performed in patients with renal failure, including anephric patients, using highly specific assay techniques. None of these show evidence of impaired elimination of morphine but do show accumulation of glucuronides[99,120,121].

The weight of evidence in man therefore at present seems to be in favour of hepatic metabolism as the principal route of morphine elimination. There are animal data to show that both the small bowel and kidney can metabolise morphine and it may well be that in chronic high dosage these sites have considerable significance, particularly where hepatic impairment is present.

Excretion

The main route of excretion for morphine is through the kidney by glomerular filtration, and possibly to a minor extent by tubular secretion[104]. Morphine glucuronides are the major excretory metabolites accounting for 60–70% of an administered dose, with smaller amounts of normorphine and normorphine conjugates being detectable. Seventy to eighty per cent of an administered dose is excreted within 48 hours of administration, with most of this appearing within the first 24 hours[122]. In dogs a dose-related reduction in morphine clearance has been demonstrated[123] but there is no evidence of dose-dependent metabolism or excretion in man.

In rats, biliary excretion and enterohepatic circulation of morphine has been clearly demonstrated[95,124]. After subcutaneous administration, half of the administered dose was excreted in the bile, predominantly as morphine glucuronide.

The evidence for enterohepatic circulation in man is sparse. Morphine can be detected in the faeces after non-oral administration and morphine and its conjugates have also been detected in bile[102,104] accounting for up to 7.4% of the administered dose. Enterohepatic circulation could make an important contribution to the plasma morphine concentrations in patients receiving chronic oral morphine[125,126].

Clinical use

Morphine is the strong opioid agonist of choice for treating cancer pain which is not controlled by weak opioids in full dose. When confronted by patients taking other opioid analgesics which are ineffective an appropriate equivalent dose of morphine must be chosen (Table 3). Dose escalation will often then be required, titrating the dose against pain relief, with no arbitrary upper limit whilst evidence of a dose-response effect is seen[127]. The majority of patients will achieve control at doses of 30 mg four-hourly or less, and rarely will doses in excess of 200 mg four-hourly be required.

Side effects of morphine may be predictable, such as constipation and drowsiness, or unpredictable such as nausea with or without vomiting, confusion, itching, sweating and dry mouth. Predictable side effects should be anticipated, constipation being avoided with regular laxatives. The possibility of drowsiness should be discussed with the patient and relatives in the expectation that this will resolve within a few days in the majority of patients. Antiemetics are not recommended routinely in hospital or hospice practice since one-third of patients will not require them[128], but if nausea does develop then haloperidol is our drug of choice (in a dose of 1.5–5 mg *nocte*). Prophylactic antiemetics are recommended for patients starting on morphine at home.

The respiratory depressant effect of morphine is utilized in many patients with advanced cancer to relieve troublesome respiratory symptoms and in particular cough and dyspnoea due to parenchymal lung disease. Ventilatory failure does not occur when morphine is used for cancer pain even where there is longstanding chronic lung disease[129]. This may reflect in part physical tolerance to the effects of morphine at the respiratory centre but also the principle that pain is the physiological

Table 3 Equivalent oral doses of morphine relative to other opioid analgesics

Drug and Dose (4-hourly unless stated)		Equivalent 4-hourly dose of morphine
a) *Weak opioids*		
Coproxamol (dextropropoxyphene 32.5mg + 325 mg paracetamol)	2 tablets	<10 mg
Dihydrocodeine	60 mg	<10 mg
b) *Strong opioids*		
Pethidine	50 mg	6 mg
Methadone	5 mg *8-hourly*	5 mg*
Dipipanone (with cyclizine 30 mg in Diconal)	10 mg	5 mg
Dextromoramide	5 mg	10 mg
Papaveretum	10 mg	7 mg
Nepenthe 1:10	10 ml	12 mg
Phenazocine	5 mg	25 mg
Oxycodone suppository	30 mg *8-hourly*	20 mg
Buprenorphine	0.4 mg *8-hourly*	20 mg

* Probably considerably more in chronic dosage due to accumulation of methadone.

antagonist of the respiratory depressant effects of opioid analgesics[127].

Oral morphine sulphate elixir remains the preparation of choice for initial oral use, given regularly at four-hourly intervals. Frequent dose adjustments may be required until pain relief is achieved. A double dose may be given on retiring to bed, to avoid the need to wake in the middle of the night.

Slow release morphine sulphate tablets (MST-Continus) provide a means of maintaining plasma concentrations of morphine and its metabolites within the therapeutic range, using only twice daily administration. This may have considerable advantages to the ambulant patient whose morphine requirements are stable using regular four-hourly elixir. Where morphine treatment is being initiated, or frequent dose adjustments are required, the slow absorption and long half-life of this preparation become a considerable disadvantage in monitoring the effects of changes in dose.

Rectal administration provides a suitable alternative route for patients unable to take oral drugs, and the same dose is used. Regular four-hourly administration of suppositories is, however, not ideal and may be unacceptable to some patients. Oxycodone suppositories may be preferable because they require only six- or eight-hourly administration. A 30 mg oxycodone suppository appears equivalent to 20 mg morphine sulphate.

Parenteral administration may be necessary where oral or rectal preparations cannot be used. Diamorphine has advantages over morphine for parenteral use as discussed below. However, morphine is effective parenterally and in most countries diamorphine is not available. The principal disadvantage of morphine lies in its relatively poor solubility so that concentrations greater than 30 mg/ml cannot be used. This problem can be overcome to some extent by using continuous subcutaneous infusion[130] which produces plasma concentrations similar to those after intravenous infusion[131].

Patient controlled analgesia using intravenous opioids is an effective technique in post-operative pain[132,133], providing immediate analgesia when required, without additional side-effects or serious complications. The technique has also been used in the treatment of cancer pain but its utility in this indication requires further investigation. In general the intravenous route is best avoided in the treatment of chronic cancer pain, unless there is no alternative[134].

When changing from the oral or rectal route to parenteral administration of morphine it is important to take into consideration the poor oral bioavailability of morphine and reduce the parenteral dose. There remains controversy as to the appropriate dose change to be made. Conventionally oral morphine has been considered to be one-sixth as potent as intramuscular morphine[135]. However, clinical experience with chronic oral use suggests that a ratio of 1:3 or 1:2 is more appropriate[136]. It

has been suggested that the single dose data and clinical experience with chronic dosage are not incompatible and may merely reflect the wide confidence intervals which exist in such studies or the effect of four-hourly analgesia compared to total or peak analgesia[137]. Further well-designed trials in the setting of chronic dosage are required, but at present a ratio of 1:2 appears to work satisfactorily in most patients.

Spinal administration

Morphine and diamorphine achieve their analgesic effects by interaction with opioid receptors in the central nervous system and direct administration of the drug into the CNS would be expected to produce effective analgesia and perhaps reduce systemic side effects. Since the discovery of opioid receptors in the spinal cord[138] it has been demonstrated that both epidural and intrathecal administration of opioids in very small doses will produce effective and long-lasting analgesia[139]. Diamorphine has a considerably shorter elimination half-life than morphine when given intrathecally[140] and has been recommended as the drug of choice for intrathecal use on this basis. A larger dose is required epidurally than intrathecally: morphine 5 mg epidurally appears to be equivalent to 1 mg intrathecally and produces analgesia for 12–18 hours[141].

The putative advantage of spinal opioids is that equivalent or better analgesia may be achieved with a reduction in side-effects by avoiding systemic administration. For both post-operative pain and chronic cancer pain there is increasing evidence to confirm the efficacy of spinal opioids[142] but it is less clear whether this route of administration does have any significant advantages over oral or parenteral use. The introduction of an extradural or intrathecal catheter through which repeated injections may be given is a potentially hazardous procedure and can only be undertaken by skilled personnel in units experienced in their use. If routine use of this technique is to be recommended for the treatment of chronic cancer pain significant advantages must be demonstrated and are not yet apparent. There are also specific hazards associated with spinal opioid administration. Marked respiratory depression has been reported occurring some time after intrathecal injection, due to rostral spread of the opioid to the respiratory centres[143]. Itching may be more common after intrathecal opioids[144] though this is disputed[142]. The relative incidence of sedation, nausea, vomiting and constipation remains unclear.

Buccal administration

Buccal administration of morphine avoids the first pass metabolism responsible for its poor oral bioavailability. At present two buccal tablet formulations are undergoing evaluation. They may provide a useful alternative route for patients with advanced cancer unable to take oral medication.

Tolerance and addiction

Misconceptions about addiction resulting from the therapeutic use of opioids have arisen partly because of confusion about the terms addiction and dependence: they are not interchangeable. Dependence is an altered physiological and/or psychological state produced by the repeated administration of a drug, which necessitates continued administration to prevent the appearance of a withdrawal syndrome[145]. Tolerance refers to the need for increasing doses of a drug to produce the same effect and may be due to changes in pharmacokinetics (such as enzyme induction or increased excretion), or adaptive changes in responding tissues, possibly mediated by reduction in receptor sensitivity[145]. In many patients receiving regular opioids some degree of tolerance and physical dependence will be seen, but neither is of clinical consequence.

Addiction encompasses physical and psychological dependence and tolerance (Figure 5) and is defined by a behavioural pattern of drug use, characterised by overwhelming compulsion to take the drug, securing its supply, and a high tendency to relapse after withdrawal[146].

Addiction is not seen in patients taking regular strong opioid analgesics for cancer pain. The evidence for this comes not only from extensive clinical experience[147] but also from carefully documented cases where reducing doses of morphine, and even complete withdrawal has been achieved following definitive treatment such as radiotherapy or a local nerve block[148,149]. A large retrospective review of medical inpatients receiving strong opioid analgesics found only four out of 11,882 cases of subsequent addiction, of which only two were described as severe[150].

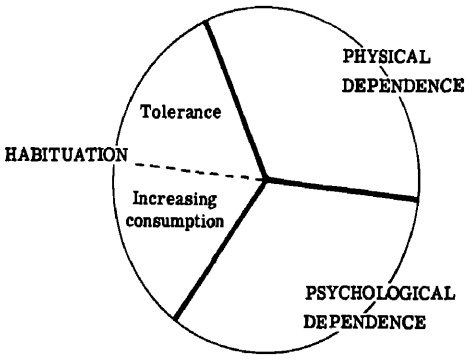

Figure 5 The components of addiction

Tolerance may be seen as an increase in dose requirements during the first few weeks of morphine treatment. However, as treatment proceeds and pain control is achieved a slower rate of rise in dose with long periods of dose stability is seen with even dose reduction and drug withdrawal becoming possible.

Florid withdrawal symptoms will not occur with gradual dose reduction, but inadvertent sudden discontinuation of medication or introduction of a drug with opioid antagonist activity may provoke the typical syndrome of morphine withdrawal.

Diamorphine

Diamorphine (diacetylmorphine) is a synthetic analogue of morphine produced by acetylation in the 3 and 6 positions, generally used in the form of diamorphine hydrochloride. Diamorphine is highly soluble in water and chloroform, the maximum solubility in both being 1 in 1.6, i.e., 1 gram will dissolve in 1.6 ml of diluent[151]. This has been erroneously interpreted as meaning that 1.6 ml of solution can contain 1 g diamorphine. However the solution of diamorphine will have a greater volume than this, namely 2.4 ml, giving a maximum possible concentration of 416.6 mg/ml[152].

There is a strong tendency for diamorphine in solution to dissociate into 6-monoacetylmorphine and morphine. For oral use, diamorphine elixir is formulated in chloroform water and should be protected from light. Degradation is both temperature and pH dependent, and independent of the concentration of chloroform used[153,154]. A similar temperature dependent effect can be demonstrated with a simple aqueous diamorphine solution used for subcutaneous infusion, with progressive degradation occurring over eight weeks[155]. Clinically this degradation of diamorphine is probably insignificant except perhaps in the case of prolonged infusions where a change in the potency of the infused drug may cause problems. None have so far been reported.

Chemistry and pharmacology: pharmaceutical preparations

Diamorphine tablets contain diacetylmorphine hydrochloride 10 mg.

Diamorphine elixir contains diacetylmorphine hydrochloride in chloroform water, in varying concentrations depending upon individual requirements.

For parenteral use *diamorphine injection* is available in 5 mg, 10 mg, 30 mg, 100 mg and 500 mg ampoules containing diamorphine powder. Sterile water only should be used for making up the injection since precipitation occurs with saline. For continuous subcutaneous infusion pumps varying concentrations can be prepared and a standard solution of 250 mg/ml has been advocated, avoiding confusion and enabling very small volumes to be infused[152].

Combination elixirs are still available as for morphine, but again are not recommended.

Pharmacodynamics

In the light of its rapid conversion to morphine, and the similar spectrum of clinical effects seen, there is some controversy as to the role of diamorphine and its metabolite 6-monoacetylmorphine in these effects. Since, after oral administration, significant levels of diamorphine and 6-monoacetylmorphine are absent from plasma it is highly unlikely that they exert any effect when given by this route. Following intravenous administration, however, both diamorphine and 6-monoacetylmorphine are present for up to one hour. This may account for the distinction between diamorphine and morphine when these drugs are given intravenously, with diamorphine having a greater analgesic potency and a more rapid onset but shorter duration of action. This has been attributed to the greater lipid solubility of diamorphine resulting in more rapid and extensive passage across the blood-brain barrier. However, following entry

into the central nervous system, it remains unclear whether the diamorphine or 6-monoacetylmorphine binds to the opioid receptor, or whether morphine – or even one of its metabolites – is the active substance at the receptor.

There are data from studies measuring affinity to opioid receptors in rat brain to suggest that 6-monoacetylmorphine has approximately 40% greater binding affinity than morphine, the same study showing total absence of binding affinity for diamorphine[156]. In contrast, when injected into the cerebroventricular system in mice, diamorphine and 6-monoacetylmorphine are equally potent analgesics. These apparently conficting results can be reconciled if continued rapid biotransformation of diamorphine into the active products of deacetylation occurs in the central nervous system.

In man, pharmacokinetic data support the possibility that 6-monoacetylmorphine is active: analgesic activity has been shown to correlate with concentrations of this substance and declines as transformation into morphine occurs[157].

Pharmacokinetics of diamorphine

The study of diamorphine pharmacokinetics has been subject to the same limitations imposed by assay sensitivity and specificity which have been discussed above with respect to morphine. Specific antisera are not available but a specific HPLC assay with UV detection has now been developed enabling determination of diamorphine and its two metabolites, 6-monoacetylmorphine and morphine[158].

A further problem exists in the study of diamorphine because of its rapid deacetylation in blood with a half-life of approximately 15 minutes *in vitro*[157]. Stabilisation of diamorphine during sample collection and storage is essential.

Absorption and distribution

Diamorphine readily passes across the mucosa of the upper gastrointestinal tract, and is quickly taken up from the plasma. It rapidly crosses the blood brain barrier, resulting in highly efficient uptake into the brain following parenteral administration[159].

Metabolism

Diamorphine is deacetylated to 6-monoacetylmorphine and morphine. There is evidence from animal studies that biotransformation can occur in liver, kidney, brain and blood with a half-life *in vitro* of less than 20 minutes. *In vitro* studies in human tissue homogenates from the same sites confirm similar activity in man[160]. Following intravenous injection a rapid decline in blood concentrations of diamorphine is seen with disappearance after 15 minutes[161] and a mean apparent half-life of three minutes. This is paralleled by a rapid rise in levels of metabolites which are present within two minutes of injection. The rapid rise in 6-monoacetylmorphine levels is followed by a rapid decline and at 60 minutes after injection only morphine can be detected. Steady state levels of diamorphine can only be achieved with continuous intravenous infusion.

Following oral administration of diamorphine neither morphine nor 6-monoacetylmorphine can be detected in plasma[157] inferring complete presystemic metabolism in the liver. It would appear, therefore, that diamorphine is essentially a prodrug for morphine when given orally.

Excretion

The rapid biotransformation of diamorphine after parenteral administration and complete first pass metabolism after oral administration results in extremely small amounts being detected in urine[162]. Following administration of diamorphine, significant levels of morphine can be detected in saliva for up to 12 hours[157], but the role of this route in the excretion of diamorphine is unclear.

Clinical use

Oral administration of diamorphine, whether as tablets or elixir, offers no advantages over morphine[163,164] which is compatible with the pharmacokinetic data demonstrating no detectable levels of diamorphine or 6-monoacetylmorphine in the plasma, following oral administration. Disadvantages include the fact that tablets are available in only 10 mg strength, and the limited stability of diamorphine elixir.

Parenteral administration of diamorphine has advantages over morphine because of its greater solubility. It is for this reason, rather than its more rapid and potent analgesia after parenteral administration that diamorphine is considered the strong opioid of choice for injection. Continuous sub-

cutaneous infusion is preferable to repeated injections if prolonged parenteral administration is necessary.

It is important to emphasise that parenteral opioids are not intrinsically more effective than oral or rectal opioids, and should only be used where these routes are not available. The common indications for parenteral administration are severe nausea or vomiting; dysphagia; patients whose rectum has been removed; patients for whom suppositories are unacceptable or impractical for other reasons; and in those situations where rapid pain relief is desired prior to stabilisation of oral therapy.

Relative potency of morphine and diamorphine

Where morphine is the strong opioid of choice for oral administration and diamorphine is the drug of choice for parenteral administration it is inevitable that many patients will have their medication changed from morphine to diamorphine and vice versa during the course of their treatment. Just as there is controversy with regard to the relative potency of oral and parenteral morphine, so also are the relative potencies of morphine and diamorphine unclear.

There is some evidence that in chronic administration for advanced malignant disease, oral diamorphine is more potent than oral morphine in a ratio of three to two[165]. Incomplete absorption of morphine in the gastrointestinal tract was proposed as the explanation for this difference in potency, but most evidence suggests that morphine is virtually completely absorbed[92]. In a more recent study[157] using a highly specific HPLC assay and serial blood samples the amount of morphine present after oral diamorphine was 79% of that present after oral morphine in the same dose, implying that oral diamorphine may be *less* potent than oral morphine.

A recent review[166] applying strict methodological criteria to the data available concluded that the relative potency of these two drugs remains unknown and that well-designed prospective randomised studies are required to further evaluate this problem.

In practice a ratio of morphine to diamorphine of 2:3 appears to be appropriate for most patients although a ratio of 1:1 could equally well be correct. Using the ratio of 2:3, and taking into account the required dose reduction of 2:1 when changing from oral to parenteral morphine, the dose of oral morphine should be divided by three to obtain an appropriate dose of parenteral diamorphine.

Other strong opioid agonists

There are a number of drugs other than morphine or diamorphine which have strong opioid agonist activity. None of these drugs possess significant advantages over morphine and several have potential disadvantages in chronic use. These drugs are in general best avoided except for the rare occurrence of true intolerance to morphine or where an alternative route of administration, such as with oxycodone suppositories, is more appropriate.

Oxycodone is a synthetic derivative of morphine which may be given orally or by injection, and is also available as oxycodone pectinate suppositories which have an analgesic action lasting six–eight hours.

Phenazocine is a synthetic opioid structurally related to morphine but considerably more potent in its analgesic action. One 5 mg tablet is equivalent to 25 mg morphine which may present difficulties when changing from a regular dose of morphine to an equivalent dose of phenazocine and means that there is less dose flexibility. Phenazocine is associated with less sedation and psychotomimetic side effects than morphine[167] and may be given sublingually although administration by this route is usually avoided because of its bitter taste and variable absorption.

Papaveretum contains 50% morphine hydrochloride, the remainder being composed of the hydrochlorides of other opium alkaloids (predominantly noscapine with small quantities of codeine and papaverine). Of these, morphine has the strongest analgesic activity and this mixture of alkaloids has no advantages over morphine alone.

Dextromoramide is a strong opioid agonist with potent analgesic effects. Whilst there is a lack of confirmatory pharmacokinetic data, in clinical use for chronic cancer pain it appears to have a much shorter half-life than morphine with an effective duration of only one and a half to two hours. For regular analgesia, therefore, it is unsuitable although its use as a short acting strong analgesic for breakthrough pain between regular doses of morphine has been advocated in some centres.

Dipipanone is a diphenylpropylamine structurally related to both dextromoramide and methadone. As an analgesic it is approximately half as potent as morphine, but its main disadvantage is that it is only available in a combination tablet (Diconal) containing 10 mg dipipanone and 30 mg cyclizine. This results for many patients in excessive sedative and anticholinergic side effects related to cyclizine when adequate analgesic doses are given.

Pethidine is a synthetic drug structurally unrelated to morphine, being a phenylpiperidine. It has opioid agonist activity, with a similar pattern of clinical effects to those of morphine, differing in having a less intense action at smooth muscle and additional anticholinergic effects. In equipotent doses it has equivalent analgesic effects, and similar effects on the vomiting centre and respiratory centre.

Pethidine is unsuitable for use in chronic pain. It has a half-life of effective analgesia of only two to four hours so that its use in a regular four-hourly regimen may result in inadequate analgesia between doses. Its principal route of metabolism is by hydrolysis to pethidinic acid and N-demethylation to norpethidine in the liver. In chronic use, norpethidine accumulates, its half-life being about 17 hours compared with only three and a half hours for pethidine[168]. Unlike pethidine, this metabolite has excitatory effects on the central nervous system, resulting in tremor, twitching, agitation and convulsions. Significant accumulation of norpethidine occurs when doses of pethidine greater than 200–300 mg three-hourly are used. Where there is impairment of renal function toxic effects may be seen at lower doses.

A number of other drugs are structurally related to pethidine and have opioid agonist activity. Anileridine and alphaprodine are closely related to pethidine with similar effects and duration of action. Fentanyl and alfentanil are both synthetic opioids structurally related to pethidine with agonist activity primarily at μ receptors and are used primarily as anaesthetic agents because of their short duration of action. Diphenoxylate and loperamide are piperidine derivatives with opioid agonist activity, used primarily as antidiarrhoeal agents.

Methadone is a synthetic opioid agonist acting primarily at μ receptors. In single doses methadone is slightly more potent than morphine, but in chronic use appears considerably more potent. This may be related to the difference in pharmacokinetics in chronic use when the half-life increases from 15 hours to 2–3 days. It may take 2–3 weeks for plasma concentrations to reach a steady state[169]. Methadone is also firmly protein bound, not only in plasma where about 90% is bound to plasma protein but also in various tissues. This pool of bound drug is then slowly released maintaining plasma concentrations for some time following discontinuation of the drug. Accumulation of methadone occurs to varying degrees in patients taking the drug regularly at the recommended six to eight hourly dosage intervals, and appears to be a particular problem in the debilitated and elderly when excessive sedation, confusion and even respiratory depression may be seen.

Oxymorphone and hydromorphone are semisynthetic derivatives of morphine with similar activity, but dose for dose are more potent analgesics. They are little used in the United Kingdom but more so in the United States.

Levorphanol is structurally closely related to morphine, differing only in the loss of an hydroxyl group at the 6-position. Predictably, its actions also closely resemble those of morphine, though it possibly causes less nausea and vomiting. Levorphanol has a longer duration of action (six to eight hours) due to its greater lipid solubility with a tendency to accumulate in body fat. It is also metabolized relatively slowly with a half-life of about 11 hours, so that problems of cumulation and excessive sedation may arise, particularly in the elderly.

Conclusions

Table 2 illustrates our recommended scheme of analgesic drug use in the treatment of chronic cancer pain. Of the weak opioids our drug of choice is dextropropoxyphene (in the form of coproxamol). In patients whose pain is inadequately controlled by full doses of coproxamol we would use aqueous morphine by mouth, and controlled release morphine tablets once stabilisation has been achieved. Diamorphine by subcutaneous injection or infusion is used when parenteral drugs are required. We see no particular place for the mixed agonist antagonist

opioid analgesics, but do occasionally use other strong opioids as alternatives to morphine if there are specific indications.

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9

Bone pain

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The skeleton is a common site for metastases to develop from a variety of primary tumours. Bone metastases are estimated to occur in 73% of patients dying from breast cancer, 32% of those with lung cancer and 85% of those with prostatic cancer (Abrams et al, 1950; Jacobs, 1983), and since these three sites alone account for approximately 40% of all patients with cancer, local bone pain and nerve compression pain caused by bone metastases are common problems. In a detailed analysis of the causes of pain in patients with advanced cancer, bone pain and nerve compression pain accounted for 38% of the pains detected (Twycross and Fairfield, 1982). The principle of management in patients with metastatic bone pain is careful analysis of individual sites of pain and their specific cause, on the basis of which rational treatment, individualized for each patient, can be instituted. In planning a treatment strategy it is important to consider both specific tumoricidal treatment and non-specific measures to control pain.

PATHOLOGY

Whilst direct invasion of bone by adjacent tumour may occur, skeletal metastases are usually the result of blood-borne dissemination of tumour cells. Tumour emboli take seed in the medullary cavity of the bone and only at a later stage is the cortex involved (Galasko, 1981). From studies of direct bone invasion in head and neck tumours (Carter, 1985) two phases of bone resorption in response to tumour cells have been described. Initially there is activation of osteoclasts causing bone resorption together with osteoblastic activity which results in focal production of osteoid and new bone. This is followed by a decline in osteoclastic activity, and tumour cells enter the areas of bone resorption and new bone formation. These processes are reflected in the familiar morphological features seen at post mortem and on X-ray, in which a combination of both bone destruction and new bone formation is invariably seen in association with bone metastases. The predominant picture of either lytic or sclerotic metastases on X-ray reflects the balance of these two processes; the finding of both lytic and sclerotic deposits within a single bone demonstrates the wide variation which can occur under apparently similar

conditions. Pure lytic lesions, with no demonstrable new bone formation, are seen only in myeloma, the lymphomas and leukaemias (Galasko, 1981).

The factors controlling the initiation of this process in response to the presence of tumour cells are of considerable interest and have therapeutic implications. It seems likely that a chemical mediator is responsible for activating osteoclasts, but its precise nature remains unclear. Prostaglandins have been extensively investigated in this respect, and bone-resorbing activity can be clearly demonstrated in vitro for prostaglandins E_1, E_2, and $F_{1\alpha}$. Other non-prostaglandin osteolysins have also been demonstrated, including the lymphokine osteoclast activating factor (OAF), epidermal growth factor (EGF), and several other tumour-associated growth factors (Galasko, 1981; Carter, 1985). In vitro studies have demonstrated that both prostaglandin inhibitors such as indomethacin or ibuprofen and direct osteoclast inhibitors, in particular the diphosphonates, significantly reduce tumour-induced osteolysis (Powles, 1976; Galasko, 1981).

The underlying mechanism by which the process of tumour invasion results in bone pain remains poorly understood. It is a familiar clinical finding that one patient may have widespread bone metastases with little or no pain, whereas another may have only equivocal evidence for bone involvement by tumour, yet have severe pain. Thus the pathological process described above seems unlikely to account in itself for the pain with which it may be associated.

The cortex and medullary cavity are in general considered to be insensitive to pain though nerve fibres can be demonstrated in bone and its associated blood vessels. It is in the periosteum and joints where pain-sensitive nerve endings are found, and these peripheral nociceptors can be activated by both mechanical and chemical stimuli. The relative role in initiating the neuronal activity of distortion and increased pressure due to the growing tumour causing mechanical stimulation, and of chemical mediators such as prostaglandins, is unknown. Prostaglandins themselves do not produce pain (Horton, 1963) although they do sensitize peripheral nerve endings so that substances such as histamine and bradykinin can activate them and initiate pain transmission (Ferreira, 1972). There is also evidence to suggest that tumour shrinkage *per se* is not required to achieve relief from bone pain, since relief may be obtained with treatments which would not be expected to have a direct tumour-shrinking effect, such as hypophysectomy (Stoll, 1985), small single doses of radiotherapy (Price et al, 1986b), or calcitonin (Hindley, 1982).

MANAGEMENT OF BONE PAIN

Diagnosis

Whilst most bone pain occurring in patients with cancer will be related to metastatic disease, Twycross and Fairfield (1982) found that in 27% of patients admitted to a continuing care unit, musculoskeletal pain of non-malignant origin was present. An accurate diagnosis is therefore essential

before initiating treatment. The presence of bone metastases may be suspected on the basis of the clinical history of pain in one of several bone sites, with associated tenderness, or radiation due to nerve root compression. Examination may reveal localized tenderness to percussion, local swelling, heat, or less frequently, a bruit at the site of a vascular metastasis. Simple investigations will generally confirm the presence of bone metastases in the presence of a clear history and physical findings. On occasions, however, pain may be less well localized and vague in nature with no abnormal findings on examination: more detailed investigations will then be required.

X-rays of the painful area will in many cases confirm the presence of bone metastases but their sensitivity is relatively poor (Edelstyn et al, 1967). Simple biochemical estimations reflecting bone turnover, such as serum alkaline and acid phosphatase, serum calcium, and urinary hydroxyproline/creatinine ratios, may provide further evidence for bone involvement by tumour. Where hepatic dysfunction is also suspected in the presence of a raised serum alkaline phosphatase, measurement of the specific bone isoenzyme will help clarify the situation.

Where plain X-rays are negative or equivocal, an isotope bone scan is the investigation of choice. In carcinomas of breast, bronchus and prostate, sensitivities of 87%, 97% and 99% respectively are reported for the detection of bone metastases using the isotope technetium (^{99m}Tc), with values of about 70% for melanoma, sarcoma, kidney and bladder (Goris and Bretille, 1985). For the common tumours, isotope scans represent the most sensitive method of detecting bone metastases. It is important to interpret results in the light of clinical findings and plain X-ray appearances in order to distinguish benign disease, usually degenerative or traumatic, from tumour invasion.

Only rarely will more sophisticated investigations be required to confirm the presence of bone metastases. Computerized tomography (CT) scanning may be considered for certain sites, in particular the spine, flat bones and sacrum, and is superior in demonstrating associated soft tissue infiltration (Sheedy et al, 1977; Cranston et al, 1984). This may be highly relevant in elucidating the mechanism of local pain in individual patients. The role of magnetic resonance imaging (MRI) in bone is currently under investigation. MRI appears to be superior to CT scanning in showing tumour in medullary cavity and surrounding soft tissues but less effective in detecting pathological fractures and areas of remineralization (Rimmer et al, 1985).

In phaeochromocytoma and neuroblastoma, scanning after administration of ^{131}I-labelled meta-iodo-benzyl guanidine (MIBG) will detect bone lesions not seen with conventional imaging. The use of isotope-tagged monoclonal antibodies for more common epithelial tumours is under investigation (Rainsbury et al, 1983).

Biopsy of a bone metastasis may be indicated where no primary site has been demonstrated, the patient presenting with bone pain and associated changes on X-ray or scan. Where the primary site is known and has been confirmed histologically, further tissue diagnosis of bone metastases is rarely necessary.

Pain assessment

Having confirmed the presence of metastatic bone disease in a site or sites consistent with the patient's pain, a more detailed pain assessment is essential before embarking upon treatment. Pain due to advanced cancer will in most cases have a prominent affective component. This means that in addition to the basic nociceptive input, the patient will exhibit a variable emotional response, incorporating amongst others anxiety, depression, fear and anger, which will modify their pain perception. Furthermore, it is unusual for a patient to have a single pain and it is important therefore to identify each individual pain, its site and likely cause, and also to consider their inter-relationship. For example, a vertebral metastasis may cause not only local bone pain but also nerve root irritation and referred pain within the appropriate dermatome. Weakness and sensory loss due to nerve root compression may result in pressure sores, or involvement of sacral nerves may cause constipation or urinary dysfunction. Thus to consider the vertebral bone pain alone may be a misleading oversimplification of the overall pain which the patient is suffering. A careful assessment of the patient's physical condition together with consideration of their mental state will provide a basis for appropriate treatment.

Treatment

There are a number of treatment options available and it is important to consider the range of these at the outset. The three principal modalities of cancer treatment—radiotherapy, surgery and chemotherapy—may each have a role in selected cases in association with the use of appropriate analgesics and co-analgesic drugs.

Analgesics

In the majority of patients with pain due to advanced cancer the use of regular analgesic drugs will be the mainstay of their management. The basic principles governing analgesic use in this situation are to give the drug on a regular basis, preventing pain rather than treating each recurrence, and to use a drug of appropriate analgesic strength in an adequate dose. This means in practice that three main groups of analgesics are used for mild, moderate and severe pain, choosing one drug from each as shown in Figure 1 and selecting specific adjuvant therapies as appropriate. If a drug given regularly in adequate dosage fails to control pain, it is rarely useful to change to an alternative drug of similar strength, for example from coproxamol to dihydrocodeine. Rather this is an indication to reassess the pain, consider alternative co-analgesics or increase analgesia by moving up the analgesic ladder to a stronger drug. In order to evaluate changes in therapy it is best to make only one change at any one time. In this way, unnecessary medication is avoided and optimum pain control achieved in the most efficient way.

Mild pain. Patients presenting with scattered musculoskeletal pains may not require strong analgesics, and in all such patients who have not received

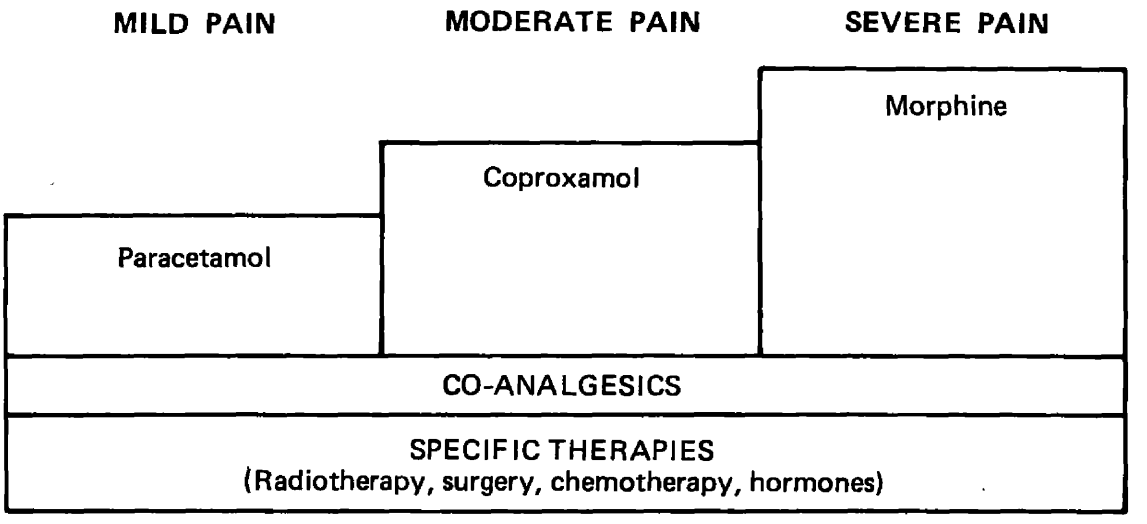

Figure 1. Principles of analgesic use.

regular medication with a simple analgesic this is the initial treatment of choice. Paracetamol or aspirin both have similar potency as simple analgesics and are the recommended drugs in this group. Paracetamol tends to be better tolerated than aspirin, which may be associated with a high incidence of gastro-intestinal side-effects (Hanks, 1983), and for this reason is the preferred drug in a dose of 1 g (two tablets) 4-hourly. Aspirin in high dosage (4–6 g/day) has significant anti-inflammatory as well as analgesic activity, and may therefore achieve a better response than paracetamol in bone pain. Greater flexibility and better tolerance may however be achieved by combining paracetamol with one of the newer non-steroidal anti-inflammatory drugs and this approach is to be preferred in most patients. Proprietary compound tablets have no advantages over either paracetamol or aspirin alone.

Moderate pain. Pain that is unresponsive to simple analgesics is an indication for use of a weak opioid drug. Dextropropoxyphene or dihydrocodeine are the two drugs recommended in this group. Dextropropoxyphene is available as a combination tablet containing dextropropoxyphene 32.5 mg and paracetamol 325 mg (coproxamol) and is recommended in preference to dihydrocodeine because it is theoretically less likely to produce dose-related opioid side-effects, particularly constipation. Whilst dextropropoxyphene has been shown to be an effective analgesic in single doses (Beaver, 1984) there is little evidence from controlled trials that the combination with paracetamol is better than paracetamol alone. When given regularly, however, dose-dependent first pass metabolism and accumulation of its active metabolite norpropoxyphene provide an explanation for the greater clinical efficacy of dextropropoxyphene in both rheumatology (Owen and Hills, 1980) and cancer patients (Hanks and Hoskin, 1986). The usual dose is two tablets of coproxamol 4-hourly, which is in general well-tolerated, though confusion, dysphoria and lightheadedness may occur (particularly in the elderly) and less frequently nausea, vomiting and constipation may become a problem.

Dihydrocodeine given in a dose of 30–60 mg 4-hourly may be used as an alternative but may be accompanied by more prominent opioid side-effects.

Other opioid drugs of similar analgesic strength, including meptazinol, nalbuphine and pentazocine have no particular advantages for use in this situation. Nalbuphine can only be given by injection, meptazinol has a narrow effective dose range with no advantages over coproxamol, and pentazocine is associated with a high incidence of psychotomimetic effects (Hanks and Hoskin, 1987).

Severe pain. For pain that is unresponsive to regular medication with weak opioids, a strong opioid analgesic is required. Morphine is the drug of choice for oral use in this situation, initially in an aqueous formulation given regularly at 4-hourly intervals, and progressing to twice daily controlled-release morphine. A wide dose range is used in patients with advanced cancer, varying from 5 mg to over 1 g 4-hourly. The dose should be titrated against the patient's pain, initiating therapy with 5–10 mg 4-hourly, with no fixed arbitrary upper limit. It is, however, important to note that two-thirds of patients will require no more than 30 mg 4-hourly (Hanks and Twycross, 1984), and careful reassessment to confirm that the pain is morphine-responsive is recommended before escalating the dose beyond these levels. As dose adjustments are made, side-effects may occur and should be anticipated and prevented. Only rarely will true morphine intolerance be encountered provided that active measures are taken to deal with intrusive side-effects. Thus all patients should receive a laxative regularly to avoid constipation, and anti-emetic cover should be provided or made immediately available for the 50–70% of patients who will have associated nausea or vomiting. Drowsiness with poor concentration is a frequent problem on initiating treatment but often resolves spontaneously over a period of a few days so that simple reassurance is usually sufficient.

Respiratory depression does not occur in cancer patients who are receiving oral morphine for pain control, as pain acts as a physiological antagonist to the respiratory effects of opioids (Hanks and Twycross, 1984). Similarly there is no danger of true addiction occurring in these patients despite fears to the contrary. The physical effects of chronic opioid exposure are tolerance (increasing doses of a drug are required to produce the same effect) and physical dependence (physical symptoms of withdrawal ensue if the drug is stopped abruptly). Whilst both tolerance and physical dependence may develop in cancer patients on morphine for periods of weeks or months, the third component of addiction (psychological dependence) is not seen. Psychological dependence accounts for the craving and drug-seeking behaviour seen in addicts, together with their high tendency to relapse back to their addict behaviour patterns when the drug is withdrawn.

The treatment of bone metastases provides a good example of a situation in patients with advanced cancer in which morphine may be used initially to control pain and subsequently be reduced and even discontinued following definitive treatment such as radiotherapy to the site of bone pain. This is illustrated in Figure 2.

There are two formulations of morphine generally available for oral use:

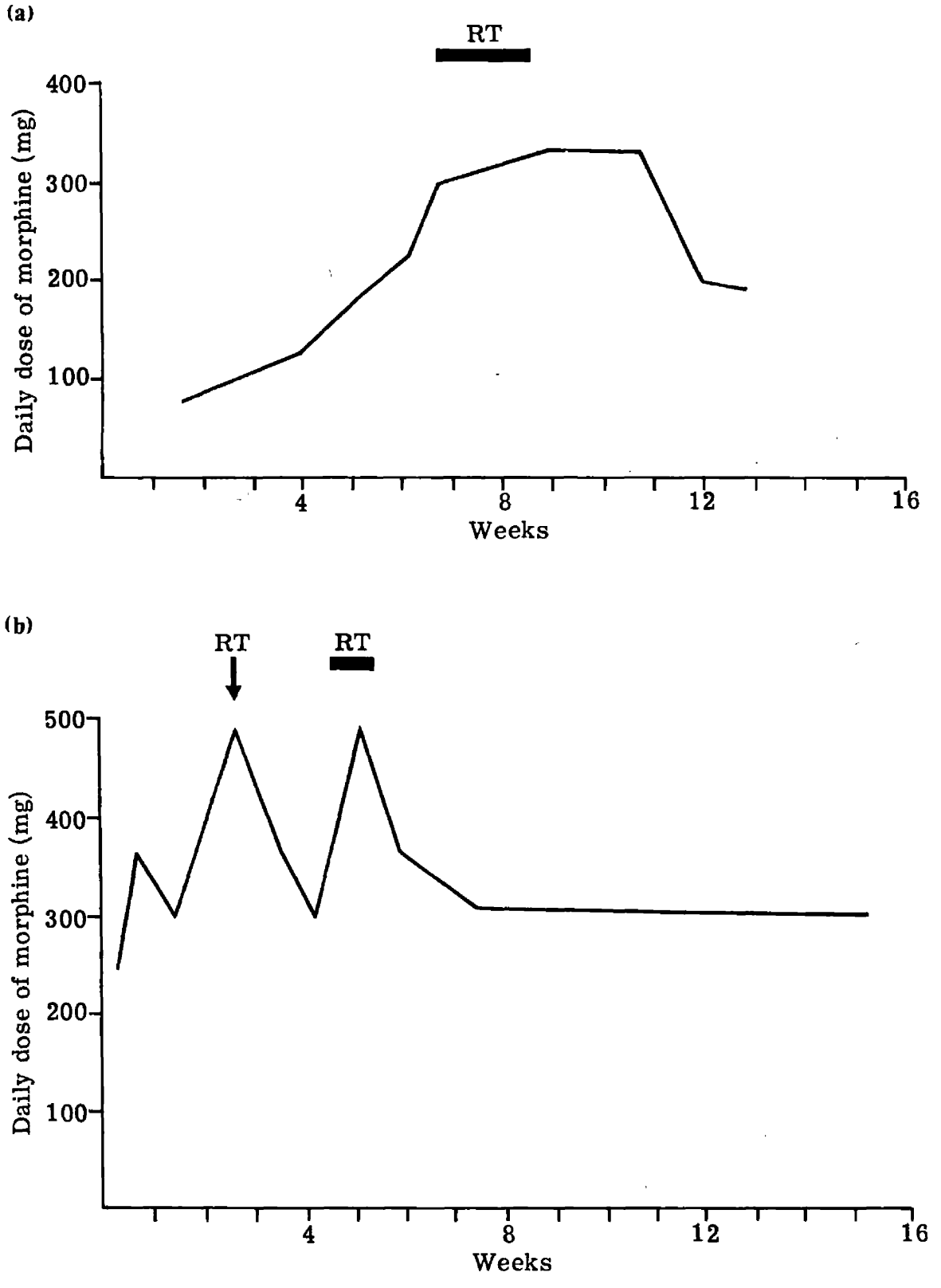

Figure 2. Influence of radiotherapy for local bone pain on morphine requirements. (a) A 61-year-old man with bone metastases from carcinoma of the prostate, who received 30 Gy in 10 daily fractions to the left hip for localized bone pain. (b) A 62-year-old woman with bone metastases from carcinoma of the breast. A single fraction of 8 Gy was given to the right posterior ribs for localized bone pain with good effect. Shortly after this she developed further bone pain in the cervical spine for which she received 20 Gy in five daily fractions. RT = radiotherapy.

morphine elixir, either as a simple aqueous solution or with the addition of a preservative such as chloroform water, and controlled-release morphine tablets (MST-Continus). Whilst the latter provide an ideal means of taking oral morphine when dose requirements are stable, their slow release formulation, resulting in peak concentrations at up to 4-hours after administration (Hanks et al, 1981), makes them unsuitable for patients who are starting treatment with morphine or whose pain is unstable. In these patients dose titration with oral elixir will provide the most rapid pain control and may then be followed by conversion to controlled-release tablets. Bioavailability of morphine from MST is the same as 4-hourly elixir in chronic use in cancer patients (Poulain et al, 1987) and the 12-hourly dose of MST should therefore be the same as the 12-hourly requirement with elixir.

Alternatives to oral morphine will only rarely be required in the treatment of bone pain. If the patient is unable to take oral medication, morphine suppositories are available for rectal use and should be used 4-hourly in the same dose as oral elixir. Oxycodone suppositories are a useful alternative where the rectal route is to be used since they need to be given only 6- to 8-hourly—a 30 mg oxycodone suppository being equivalent to 20 mg oral or rectal morphine.

Where the rectal route is impracticable or unacceptable to the patient, then parenteral medication may be necessary. The subcutaneous route is preferable to intramuscular or intravenous injections, and where parenteral medication is likely to be required for more than 24 hours a continuous infusion using a syringe driver is most appropriate. It is however important to note that injections of strong opioid drugs are not intrinsically more effective in controlling pain than oral medication, and merely provide an alternative means of delivering the drug to opioid receptors in the central nervous system. However, because the drug is well absorbed directly into the systemic circulation, avoiding the extensive first pass metabolism which occurs after oral administration, smaller doses of the drug will be required parenterally. Whilst morphine may be given by this route it has limited solubility in water, the maximum concentration available for injection being 30 mg/ml. Because of this, diamorphine is preferred for parenteral use, being far more soluble with concentrations of up to 250 mg/ml recommended for clinical use (Jones et al, 1985). Whilst there remains controversy over the equivalent doses of oral diamorphine and oral morphine, and of oral versus parenteral morphine or diamorphine during chronic administration, in practice dividing the oral dose of morphine by three will give an appropriate parenteral dose of diamorphine (Hanks and Hoskin, 1987). When given orally, diamorphine has no advantages over morphine, since there is extensive pre-systemic metabolism in the liver, resulting in complete deacetylation of diacetylmorphine to morphine. Following an oral dose of diamorphine, therefore, only morphine can be detected in the systemic circulation (Inturissi et al, 1984).

There are a number of other strong opioid drugs available, none of which have any particular advantage over morphine in the treatment of advanced cancer pain. Potential problems exist in patients who have been receiving these drugs and require a change to morphine since there is a wide range of

equivalent doses which it is important to consider before choosing the appropriate starting dose of morphine. Estimations of these doses together with the principal drawbacks of these drugs are shown in Table 1. Where an alternative oral drug is required then phenazocine is recommended, a 5 mg tablet being equivalent to 25 mg morphine taken 4-hourly.

Table 1. Alternative opioids.

Drug	Usual dose (4-hourly unless stated)	Equivalent 4-hourly dose morphine	Disadvantage compared with morphine
Buprenorphine (Temgesic)	0.2 mg 8-hourly	10 mg	Partial agonist Ceiling effect for analgesia
Dextromoramide (Palfium)	5 mg	10 mg	In chronic use short duration of action (1–2 h) and increasing dose requirements
Dipipanone (Diconal, with cyclizine)	10 mg	5 mg	Only available in combination with cyclizine hydrochloride (Diconal)
Nepenthe	10 ml of 10% solution	12 mg	Alcoholic tincture of morphine Variable concentrations available are confusing
Papaveretum (Omnopon)	10 mg	5 mg	Opium extract—active component is morphine
Pethidine	50 mg	6 mg	Short duration of action (2–3 h) In chronic use metabolite toxic to CNS may accumulate causing excitability, tremor, fits
Methadone	5 mg 8-hourly	5 mg	Long half-life, high protein binding. May accumulate with prolonged action, especially in elderly

Co-analgesics

A number of drugs which do not have intrinsic analgesic activity when tested against conventional pain models, may be useful in controlling pain due to advanced cancer when used with one of the analgesic drugs discussed above. Drugs used in this way are co-analgesics (Twycross and Hanks, 1984) and include a wide range of substances such as diuretics, steroids, anticonvulsants, antidepressants and muscle relaxants. They will only be effective where there are specific indications for their use and so careful assessment of the patient's pain and its underlying cause is essential for their correct use.

In the treatment of bone pain, one of the most useful groups of drugs are the non-steroidal anti-inflammatory drugs (NSAIDs). In considering the pathology of bone metastases the possible role for prostaglandins, both in facilitating bone destruction and tumour invasion through activation of osteoclasts, and in modifying neuronal transmission in pain fibres, was

discussed. NSAIDs inhibit the synthetic pathway by which arachidonic acid is converted to prostaglandins and this is thought to be their principal mode of action. As primary therapeutic agents NSAIDs are not particularly effective in the treatment of bone metastases and relieve pain in only some 20% of patients (Coombes et al, 1979). However, they may produce worthwhile results when used in conjunction with an opioid analgesic in patients with metastatic bone pain. There is no convincing evidence that any particular NSAID is more efficacious than another in this group of patients. Soluble aspirin is as effective as the newer drugs but its anti-inflammatory action is only seen in high doses of 3.6 g per day or more, and at this level its use may be associated with a significant incidence of side-effects, in particular dyspepsia and gastro-intestinal bleeding. Indomethacin is similarly associated with a high incidence of side-effects but does have the advantage that it can be given by twice daily suppository. For oral use the newer propionic acid derivatives such as ibuprofen, naprosyn or flurbiprofen are generally better tolerated; when a liquid preparation is desirable or where gastric intolerance is a potential problem, benorylate, which is a lipid soluble ester of acetylsalicylic acid and paracetamol, is valuable. This has the additional advantage of needing only twice daily administration in a dose of 5–10 ml (2–4 g).

Since these drugs are potentially hazardous, it is important to carefully assess the patient's response to them without, wherever possible, introducing other variables such as changes in analgesic, and to discontinue the drug where it is clearly ineffective. Particular care is required in the elderly and those with a history of dyspepsia. All the NSAIDs are highly protein-bound and therefore may interact with other protein-bound drugs such as anticoagulants. Care is also needed in patients requiring loop diuretics since many NSAIDs will inhibit their diuretic action (L'Orme, 1986).

In addition to NSAIDs, other co-analgesic drugs may have a role in treating bone pain, particularly where nerve irritation or compression and muscle spasm are present. Corticosteroids are particularly valuable where there is nerve root compression, as they reduce associated oedema and inflammation. Dexamethasone is preferred in this setting in divided doses of 8–16 mg per day, since it is associated with less mineralocorticoid activity which causes the oedema and weight gain seen with steroid treatment. It can also be given in fewer tablets.

Anticonvulsants may be indicated where nerve root irritation is resulting in lancinating or stabbing dysaesthesia or paraesthesia. No particular anticonvulsant drug is superior in this indication and choice is based on individual response and tolerance. In general, clonazepam will be associated with more sedative side-effects than sodium valproate or carbamazepine, but these may cause more gastric irritation. Where muscle spasm is present a muscle relaxant such as baclofen or diazepam may be helpful.

There are anecdotal reports of L-dopa (levodopa) being effective in controlling bone pain due to advanced cancer (Nixon, 1975; Minton et al, 1976) but the only systematic study which has been reported failed to find any evidence of an analgesic effect of L-dopa (used in combination with carbidopa) (Sjolin and Trykker, 1985).

Calcitonin has recently been promoted as effective treatment for bone pain and evidence from case reports and one small prospective randomized study (Hindley et al, 1982) suggests that up to 40% of selected patients can receive useful pain relief following treatment with salmon calcitonin. The main disadvantage of this treatment is the need for multiple subcutaneous injections and the possibility of associated nausea and vomiting, for which anti-emetic cover should be considered. Whilst calcitonin cannot be considered for first line treatment of metastatic bone pain, it may be worth trying where pain persists despite local radiotherapy and appropriate analgesic and co-analgesic therapy.

Mithramycin in relatively low doses (15 mg/kg by weekly intravenous infusion) has been reported to successfully relieve bone pain in metastatic breast cancer (Davies et al, 1979) but no prospective randomized studies confirming this are available.

Radiotherapy

Ionizing radiation is well established in the management of bone pain.

Local external beam irradiation is the treatment of choice for localized metastatic bone pain. The pooled data from 16 non-randomized reports of treating patients in this way using a wide range of radiation doses reveals that in a total of 2422 treatments a mean overall response rate of 86% (range 73–100) and mean *complete* response rate of 52% (range 20–90) is found (Hoskin, 1988). No evidence for a dose–response relationship is seen nor any advantage for prolonged multiple fraction therapy. There is no clear difference in response between various types of primary tumour, and, although many patients in these series have only limited survival, response in terms of pain relief is prolonged, being maintained in 78% of patients at five years from treatment in one series (Allen et al, 1976). Many criticisms can however be made of these data in which little detail is given of treatment techniques, criteria for diagnosis, dose definition and correction, or patient selection where more than one dose fractionation schedule has been used. Only four of these 16 reports have employed prospective pain assessments, the remainder using a retrospective assessment of case records, and all use physician rather than patient assessment, which will tend to overestimate response rates.

There are three prospective randomized trials of radiotherapy in metastatic bone pain (Tong et al, 1982; Madsen, 1983; Price et al, 1986a). The results from these trials support the retrospective and non-randomized data with overall response rates of 90%, 48% and 85% respectively. In these three studies, a range of radiation doses have been randomly allocated, including a single fraction of 8 Gy, two fractions of 10 Gy in one week, six fractions of 4 Gy in three weeks and 15 fractions of 2.7 Gy in three weeks. No consistent advantage for any one particular dose fractionation schedule emerges from these three studies, although a re-analysis of the earliest trial has suggested an advantage for multiple fractions (Blitzer, 1985). Duration of response has also been investigated in these studies and overall about one half of patients have response lasting until death. In those surviving up to

one year from treatment 60% were still responding with no significant differential effect of radiation dose or fractionation being seen. Long-term survivors tend to have primary tumours of breast or prostate and Tong et al have suggested that these tumours show better response than other histological types. This is not confirmed in other studies where no difference between histological groups is seen.

There is then little doubt that external beam radiotherapy is a highly effective treatment for localized bone pain due to tumour metastases, where response rates of some 80% can be anticipated. Since a single fraction treatment appears as effective as multiple fractions this will be the preferred means of delivery for most patients where pain relief is the primary aim of treatment. Where irradiation is being performed for prophylaxis of, or stabilization of, pathological fractures then many radiotherapists will prefer to use a fractionated regimen, delivering 30 Gy in 10 daily fractions or its equivalent. Similarly, fractionated regimens are often preferred for large fields such as the pelvis or certain histological types of tumour thought to be relatively radioresistant, such as renal carcinoma, although there are few data to support this approach.

Whilst external beam therapy offers the optimal treatment for localized bone pain, unfortunately most bone metastases arising from blood-borne spread of tumour emboli are multiple, and frequently the patient will have several sites of pain. Isolated treatment of one site in these patients will often serve only to unmask pain in another site which will then require further treatment, and so the cycle will be repeated. In this situation, wide field irradiation, in which the upper, middle or lower hemi-body is encompassed in a single radiation volume, may be appropriate. A review of five reported series in the literature (Hoskin, 1988) shows that single fraction hemi-body irradiation delivering 6–8 Gy mid-plane dose will produce a response in about 75% of patients. Response is often rapid (within 24–48 hours), with a duration of several months or until death. Against this must be balanced the greater toxicity of wide-field irradiation. Virtually all patients suffer mild gastro-intestinal toxicity with nausea and diarrhoea within the first 48 hours after treatment. Bone marrow depression is seen in some 10% of patients unless sequential upper and lower hemi-body irradiation is performed, when most patients will have significant falls in blood count. Pneumonitis from upper hemi-body irradiation in this setting has been reported in 10% or more of patients (Fitzpatrick, 1981; Qasim, 1981) and subsequent treatment-related deaths may be seen from this complication. Toxicity may be minimized by careful preparation, premedication with steroids, anti-emetics and sedatives, and regular monitoring of the blood count with haematological support and treatment of infections in neutropenic patients. Pneumonitis is a dose-related complication and is rare when doses to the upper hemi-body are limited to 6 Gy uncorrected for lung density.

Careful patient selection is therefore necessary for this procedure but in suitable patients with widespread bone metastases, particularly those from myeloma or carcinoma of the prostate, wide field irradiation delivering 6 Gy mid-plane dose to the upper hemi-body or 8 Gy mid-plane dose to the lower hemi-body will provide useful pain relief in some 75% of patients. Isolated

painful areas that persist or arise due to subsequent disease progression may still be treated by local radiotherapy if necessary without additional problems (Epstein et al, 1979).

An alternative approach to the treatment of multiple bone pain from scattered metastases has been the systemic administration of radioisotopes selectively taken up by bone. Early studies with radioactive phosphorus (^{32}P) showed that this method of treatment could be effective in selected patients, but when doses of up to 21 mCi of ^{32}P were given over six weeks, bone marrow suppression was found in most patients (Tong, 1971). More recent work has focused on the use of strontium (^{87}Sr) which is preferentially concentrated and retained in areas of osteoblastic activity but delivers a lower overall dose to the bone marrow (Robinson, 1986). Response rates varying from 51–86% are reported in the literature in selected groups of patients (Hoskin, 1988) with little or no bone marrow suppression, and subsequent treatment to localized sites with external beam radiotherapy was not compromised. This is clearly an area for further research, requiring prospective randomized studies to define the role of such radioisotopes in the management of widespread bone pain and also to explore newer techniques of localization such as the use of labelled diphosphonates.

Surgery

The role of surgery in the management of bone pain due to metastatic cancer is limited but may be invaluable where there is impending pathological fracture or a displaced unstable fracture through a metastatic deposit. Lytic deposits in a weight-bearing long bone carry a high risk of subsequent fracture once there is erosion of cortical bone. Spontaneous healing of such fractures is unlikely despite adequate immobilization. Left untreated the patient will experience severe pain on movement and usually succumb from the consequent immobilization. In these cases internal fixation using an intramedullary nail or prosthetic replacement of the upper femur will stabilize the fracture, enable good pain relief to be achieved and usually allow the patient to become mobile once more.

Chemotherapy and hormone therapy

Since the underlying cause for bone pain due to metastatic cancer is the growing malignant tumour, the most rational response to this is to give treatment which will result in tumour shrinkage and control of its subsequent growth and further spread. Unfortunately, in the population of patients presenting with bone pain, two thirds will have primary tumours such as lung, prostate, or kidney for which no effective chemotherapeutic agents are available (Price et al, 1986a). Therefore chemotherapy will only be appropriate in a minority of patients, predominantly those with breast cancer or myeloma, and in this group treatment with appropriate chemotherapy regimens should be considered for widespread bone pain, particularly if there is active disease elsewhere. In carcinoma of the breast, which may account for up to one third of patients presenting with bone pain (Price

et al, 1986a), chemotherapy will be considered for those patients who have failed to respond to hormone therapy or who are pre-menopausal with oestrogen receptor negative tumours, or those with aggressive widespread disease. Depending upon the drug regimen used, complete response rates for bone metastases ranging from 0 to 84% are reported. A rapid response in terms of pain relief is unusual, the median time to achieve maximal response in bone metastases being 32 weeks, which is considerably longer than in other tissues (Whitehouse, 1985).

The high relative incidence of carcinoma of the breast and prostate amongst patients presenting with bone pain, both of which are hormone sensitive tumours, means that therapy utilizing a form of endocrine manipulation may be considered in these patients. Pain relief may be rapid, within 24 hours of an ablative hormone manoeuvre, and frequently occurs despite no objective changes in either bone or soft tissue tumours (Stoll, 1985). A 'pain flare' may also be seen on initiating or changing hormone therapy, as may hypercalcaemia, but despite this about one half of patients experiencing such a 'flare' will subsequently go on to achieve pain relief. In breast cancer a number of therapeutic options are available, all of which may be effective in bone pain. With older treatments such as oestrogen, androgen or steroid therapy, response rates for bone pain of approximately 25% are found, and a slightly higher response rate of 35% is reported with ablative procedures such as oophorectomy, adrenalectomy or hypophysectomy. Today, hormone manipulation is usually achieved using either tamoxifen, aminoglutethimide or a progestogen. With both tamoxifen and progestogens response rates for bone pain in the region of 20% are reported, but aminoglutethimide given with hydrocortisone, when compared with tamoxifen as first-line therapy in prospective randomized studies, appears to have a consistently higher response rate in bone of about 35% (Smith and Macaulay, 1985).

In carcinoma of the prostate, orchiectomy is the hormone treatment of first choice today, having similar response rates but none of the cardiovascular complications of oestrogen therapy. Some 85% of patients will respond to their first-line endocrine manoeuvre. Subsequent relapse is however more difficult to manage using systemic therapy. Response rates to a second hormone manoeuvre such as stilboestrol, cyproterone acetate or luteinizing hormone releasing hormone (LHRH) analogues are poor. Aminoglutethimide with hydrocortisone has been reported to produce response in about one third of patients when used as a second-line agent (Catalona, 1984), and may be the endocrine treatment of choice for patients with prostatic cancer relapsing after orchiectomy with bone pain, although a recent study has suggested that hydrocortisone alone may produce similar response rates (Plowman et al, 1987). At present 4-hydroxyandrostenedione is under investigation for the treatment of bone pain in advanced prostatic cancer; early results are encouraging (Shearer R.J., 1987, personal communication) but further studies with this agent are required before more widespread use can be recommended.

In addition to these hormone-dependent tumours, relief from bone pain has been reported following hypophysectomy in tumours not generally

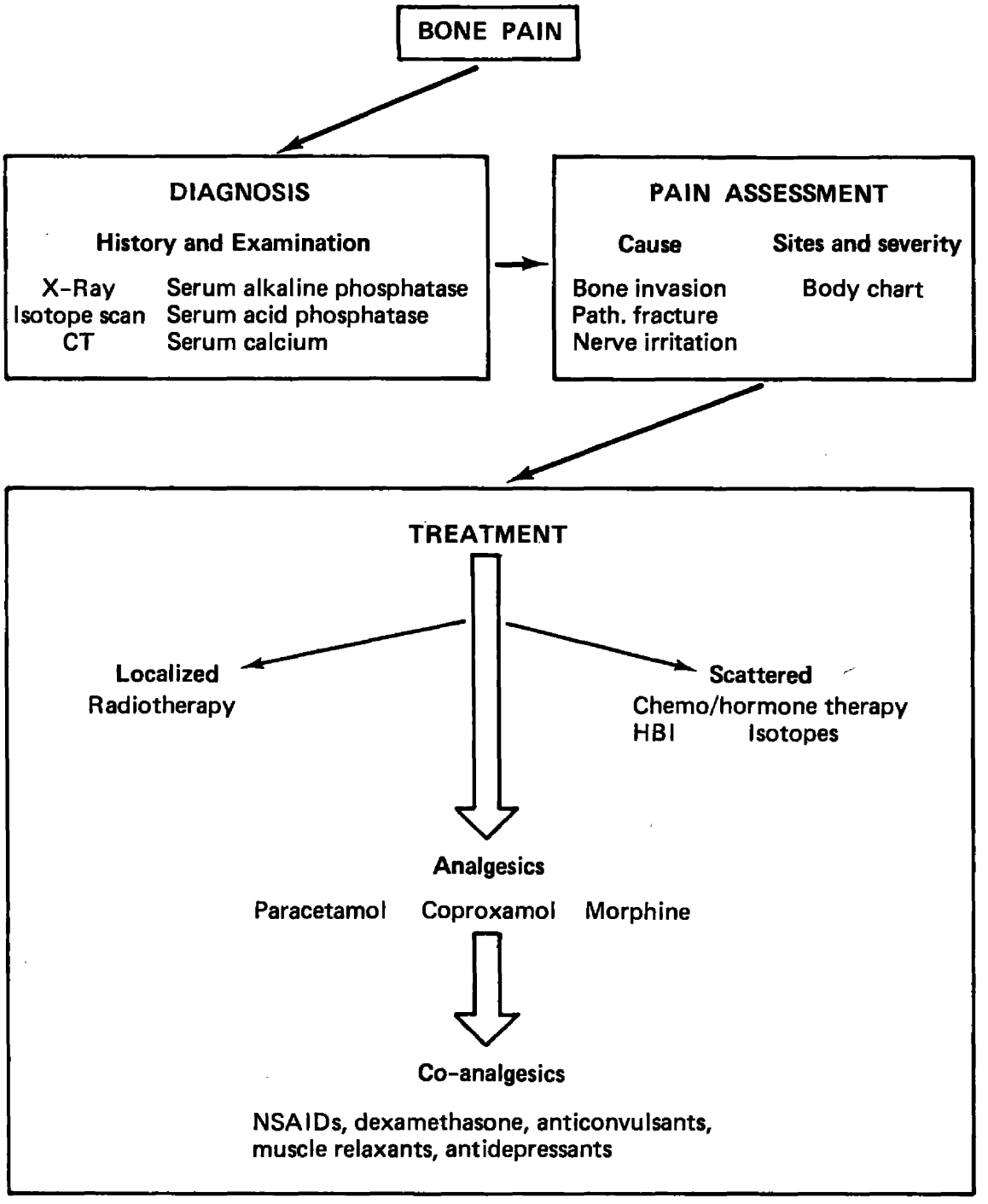

Figure 3. Summary of management of bone pain. HBI = hemi-body irradiation.

recognized to be hormone sensitive. It is unclear whether this represents a true endocrine response or is due to other sequelae of hypophysectomy such as damage to pain fibres in the vicinity, changes in endogenous endorphins, or the need for hormone supplements such as cortisone (Stoll, 1985). Such manoeuvres are, however, unlikely to form a routine part in the management of bone pain.

CONCLUSION

Bone pain from metastatic disease is a common problem in patients with advanced cancer. Effective treatment is available for the majority of patients based on careful diagnosis and assessment of the pain, and the application of a simple analgesic ladder supplemented by the use of appropriate co-analgesic drugs, radiotherapy, surgery, chemotherapy or hormone therapy, as summarized in Figure 3.

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Occasional Survey

EXPLANATION FOR POTENCY OF REPEATED ORAL DOSES OF MORPHINE?

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Summary Morphine given by injection is the standard by which all other strong analgesics are measured, but when given orally in single doses it is a poor analgesic. With repeated oral administration it becomes very effective and it may be that on repeated dosage active metabolites, particularly morphine-6-glucuronide, account for much of the analgesic activity. Enterohepatic circulation may also contribute to the maintenance of blood and tissue levels of morphine and its metabolites in chronic use.

INTRODUCTION

MORPHINE given by mouth is the strong opioid analgesic of choice for the treatment of pain in cancer. The use of oral morphine has developed empirically over the past two decades[1,2] despite scepticism from influential authorities.[3] More recently, attitudes have changed.[4] At the root of the early reluctance to prescribe oral morphine is the observation that in single doses oral morphine is not a very effective analgesic. It has been difficult to reconcile this with the established efficacy of oral morphine in repeated dosage.

ORAL MORPHINE IN ACUTE PAIN

Beecher and Houde and their colleagues' investigations of the analgesic activity of single doses of morphine and other drugs given orally to patients with acute pain indicated that the effect of morphine 10 mg was "decidedly inferior" to that of aspirin 600 mg.[5] On the basis of other single-dose studies the oral to parenteral relative potency ratio for morphine was estimated to be between 1:6 and 1:8.[6] Such ratios have been and still are widely cited both in standard texts and authoritative reviews.[7,8] The results of these single-dose studies should not be extrapolated to chronic use.

ORAL MORPHINE IN CHRONIC PAIN

There have been no reports of studies comparing repeated doses of oral against parenteral morphine for chronic pain. However, substantial well-documented clinical experience in patients with cancer pain shows that oral morphine given regularly and in adequate dosage is very effective for patients who require a strong analgesic.[1,2] This does not mean that morphine is the solution to every pain problem in cancer. It ought to be prescribed only after careful patient assessment and in the context of a systematic but simple treatment strategy which may include a variety of drugs and often other forms of palliation.[9]

Clinical experience has also shown that in repeated dosage the oral to parenteral potency ratio is in the region of 1:2 or 1:3[2]—in fact, as early as more than a century ago, shortly after the invention of the hypodermic syringe, it was observed that with morphine given by hypodermic injection "one third the quantity that would ordinarily be taken by mouth suffices, ie, the same amount exerts a triple force".[10] This is clearly different from the single dose ratios of 1:6 or 1:8. The various explanations[11] put forward for this difference fail to take into account the fact that there does appear to be a real change in analgesic activity when moving from single doses of oral morphine to repeated doses, but from recent debates about the pharmacokinetics of morphine a possible explanation for the difference has emerged.

PHARMACOKINETICS OF MORPHINE

Morphine is one of the oldest drugs in current use but there is still uncertainty about its pharmacokinetics. A major reason for this is that sensitive and specific assay methods for morphine have not been available until recently.[12]

After oral administration morphine is well absorbed, predominantly in the duodenum and upper small bowel.[13] Extensive first-pass metabolism in the gut and liver, with conjugation to morphine glucuronides, results in poor systemic availability. In healthy volunteers[14] and cancer patients[15] the average bioavailability for oral morphine is 30–40%, but there is marked variability between individuals.[14-17] The relative contributions of the gut and liver to this first-pass effect in man is not known. In rodents the gut may be responsible for up to two-thirds of the presystemic metabolism of morphine.[18]

The predominant role of the gut and liver in the metabolism of morphine has been challenged on the basis of two experimental studies and anecdotal clinical evidence of undue sensitivity to morphine in patients with renal impairment.[19] In one study the bioavailability of oral aqueous morphine was shown to be 100% and of controlled-release morphine tablets (MST) 122%. In the second study patients undergoing renal transplantation received single doses of intravenous morphine and plasma morphine concentrations were shown initially to plateau and then fall in parallel with the recovery of renal function. These data, taken together with the clinical reports of opioid toxicity in patients with renal failure, were interpreted as indicating that the kidney is the primary site of morphine metabolism and that there is no significant presystemic elimination. We have questioned these conclusions on various grounds.[20] In particular they would allow no easy explanation for the difference in pharmacodynamic effect between oral and parenteral morphine. If the bioavailability of oral morphine is 100% the oral to parenteral relative potency ratio should be 1:1. There is no clinical or experimental situation in which the ratio approaches 1:1.

The specificity of the assay used in the experimental studies was also suspect,[20] and it now seems likely that the assay cross-reacts fully with morphine-6-glucuronide,[21,22] as do other antisera raised to morphine-O-6 immunogens.[23] Several studies using specific assays have shown that morphine clearance in patients with renal impairment is normal, but there is accumulation of glucuronide metabolites.[24-26]

MORPHINE METABOLITES

Morphine-3-glucuronide, the major metabolite of morphine, has long been regarded as inactive.[27] Although it is highly polar and therefore assumed not to cross the blood-brain barrier to any great extent, it has been detected in the cerebrospinal fluid in rodents[28] and in man[29] after

systemic administration of morphine. There is no significant analgesic activity after its subcutaneous or intracerebral injection in mice,[30] and no activity in isolated tissue preparations.[31,32] One report suggests that when injected directly into the cerebral ventricles it may have some analgesic activity,[33] but this may be explained by prior deglucuronidation.[31]

Other metabolites of morphine are morphine-6-glucuronide, morphine-3,6-diglucuronide, normorphine, normorphine-6-glucuronide, codeine, and morphine ethereal sulphate.[13,34] All of these metabolites were believed to be produced in insignificant quantities and to make no contribution to the analgesic action of morphine. However, this assumption was again based on single-dose data.

Morphine-6-glucuronide, normorphine, codeine, and morphine ethereal sulphate all have analgesic activity.[30,35] Morphine-6-glucuronide is the most potent: when injected into the cerebral ventricles of rats it is 45 times as potent as morphine, and three to four times as potent by subcutaneous injection.[30] Morphine-6-glucuronide is produced in very small quantities after single doses of morphine in man,[13] but with long-term intake the average ratio of morphine-6-glucuronide to morphine in plasma is almost 4:1.[36] Morphine-6-glucuronide, like the 3-glucuronide, is highly polar but seems to cross the blood-brain barrier.[28,29] Thus this metabolite may be of considerable significance when morphine is used chronically.

WHY DOES ORAL MORPHINE WORK WELL IN REPEATED DOSAGE?

The suggestion that morphine is metabolised mainly in the kidney is almost certainly wrong but has been the impetus for focusing on the role of the metabolites of morphine. There is no doubt that some patients with renal failure are particularly sensitive to morphine and other opioids, and there is circumstantial evidence to suggest that impaired clearance of morphine-6-glucuronide may be at least partly responsible.[37]

It seems likely also that morphine-6-glucuronide contributes significantly to the overall analgesic effect of morphine given in repeated dosage by mouth, and may be the main explanation for the difference in analgesic potency between repeated and single doses. However, there is at present no direct evidence that morphine-6-glucuronide has an analgesic effect in man. The other active metabolites of morphine, notably normorphine and morphine ethereal (-6-) sulphate, have not been detected in sizeable quantities in man, even after prolonged high dosage.[36]

We have previously suggested two other mechanisms whereby the potency of oral morphine increases with repeated dosage[38]—either the presystemic metabolism of morphine is saturable, as is the case in dogs,[39] or the enterohepatic circulation contributes considerably to the maintenance of plasma and tissue levels of unconjugated morphine. The first suggestion is probably wrong—the systemic availability of oral morphine seems constant whatever the dose or duration of treatment.[36]

Enterohepatic circulation of morphine has been demonstrated in rodents,[40,41] but there is no unequivocal evidence for it in man. In healthy volunteers a secondary peak in plasma concentrations of morphine occurs 4–5 h after a dose of MST and was thought to be possibly due to enterohepatic circulation.[42] Our investigation of the relative bioavailabilities of aqueous morphine and MST with a specific radioimmunoassay[43] and high performance liquid chromatography consistently showed a secondary peak of unconjugated morphine in serum samples 2–4 h after a dose of aqueous morphine and 4–6 h after a dose of MST. There were also secondary peaks of morphine-3-glucuronide and morphine-6-glucuronide. These secondary peaks may also be due to enterohepatic circulation.

CONCLUSIONS

Oral morphine is much more effective in repeated doses than after single doses. On repeated dosage active metabolites of morphine, particularly morphine-6-glucuronide, may account for a greater proportion of the overall analgesic activity than the parent drug itself. Enterohepatic circulation may also be important in maintaining blood and tissue levels of morphine and its metabolites with chronic use.

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Child Health

ARM CIRCUMFERENCE AND OTHER FACTORS IN CHILDREN AT HIGH RISK OF DEATH IN RURAL BANGLADESH

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Summary Mid upper arm circumference (MUAC) was measured monthly for 6 months in about 5000 children aged 6–36 months from rural Bangladesh. Children who would die within 1 month of screening could be identified with 94% specificity and 56% sensitivity—almost twice the sensitivity achieved by other anthropometric screening schemes for this level of specificity. Specificity was slightly improved when the absence of breast-feeding, concurrent diarrhoea, oedema, and acute respiratory infection were taken into account. Children at high risk of death can be detected by monthly measurement of MUAC, which may be used in poor communities where interventions have to be selective.

INTRODUCTION

THE cost of comprehensive primary health care is such that the goal of "Health for all by the year 2000" set by the World Health Organisation is unattainable in many poor countries.[1] The concentration of resources on a few people at high risk of serious disease or death (the "risk approach") has been proposed as a more realistic alternative, especially for mother and child care.[2] To reduce child mortality by this means, primary health care workers must be able to accurately identify high-risk children. For the past 10 years, anthropometric measures of nutritional status to detect children at high-risk have been examined, but proved to be imprecise.[3-6] A recent report, however, suggested that nutritional screening is more accurate when the risk of death is assessed over a short time.[7] We report here the use of monthly measurements of mid upper arm circumference (MUAC) to detect children at high risk of death in a rural community in Bangladesh.

SUBJECTS AND METHODS

Since 1966, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has maintained a demographic surveillance system in the rural subdistrict of Matlab.[8] At present the scheme covers 143 villages, with a total population of about 200 000. In half of this area demographic surveillance is done by female community health workers whose only health-related skill is the recognition of severe diarrhoea and its treatment with oral rehydration solution. The only ICDDR,B health intervention is the provision of oral rehydration solution and the treatment of diarrhoea in several special centres. Diarrhoea and acute respiratory infections are the most common causes of death in young children in this community.[9]

Every month 30 community health workers, covering a population of about 100 000, measured the MUAC of children aged between 6 and 36 months and asked the mother or guardian whether the child was still breastfed or had diarrhoea (at least three liquid stools within the previous 24 h). Diarrhoea was classified as watery or bloody; non-bloody diarrhoea was termed chronic if it had started more than seven days before the interview. Health workers also checked whether the child had acute respiratory infection, defined as the simultaneous presence of cough, fever, and tachypnoea. For critically ill children, families were offered referral to Matlab diarrhoea treatment centre. Before the study, health workers were taught for 2 h in groups of 10 how to measure MUAC[10] and how to recognise oedema and the symptoms of acute respiratory infection. Three refresher courses were held during the study.

Ethical approval was granted by the ICDDR,B ethical review committee on condition that the study would last no longer than the time needed to choose criteria for screening. The study was therefore conducted for only 6 months, and seasonal variations in the relations between nutritional status, diarrhoea prevalence, and mortality could not be examined. The study period from October, 1985, to March, 1986, included part of the pre-harvest lean season.[11]

Since almost all (98·8%) breastfed children received some food in addition to breast milk, data of exclusively and partly breastfed children were combined for analysis.

MUAC was measured to the nearest 2 mm with locally manufactured insertion tapes.[12] MUAC was chosen as the indicator of nutritional status because it is easy to measure in the community and compares favourably with other anthropometric indices for the assessment of the risk of death in children.[13,14] MUAC was not corrected for age or height since this adjustment does not improve the assessment of risk of death.[7,15]

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4

Opioid therapy in malignant disease

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G. W. HANKS

The opioid analgesics have a well-established place in the management of malignant disease, but there is still a widespread reluctance to employ suitable opioid drugs in adequate doses to achieve optimum symptom control in advanced cancer. This is commonly due to fears of respiratory depression and addiction, despite good evidence that these effects are not seen in such patients. Other frequent reasons for unsuccessful pain control with opioid analgesics are: failure to anticipate and control side-effects such as constipation and nausea; the use of drugs such as the mixed agonist antagonists with their limited therapeutic range; or the inappropriate use of drugs which have cumulative effects.

Malignant disease is characterized by its ability to invade locally and metastasize. A host of symptoms may therefore be anticipated in patients with advanced cancer of which the commonest and most emotive is pain, occurring in around 60% of patients managed in a general oncology unit and up to 85% of patients referred for hospice care. Eighty per cent of patients in pain will have more than one pain, 20% will have four or more separate pains and one third of the pains identified will be unrelated to the process of tumour infiltration and spread (Twycross and Fairfield, 1982). Careful assessment and individualization of treatment is therefore vital in the management of these problems. In most patients an opioid analgesic will be an important component of their symptom control.

ROLE OF OPIOIDS IN MALIGNANT DISEASE

Analgesia. The basic principle of analgesic use in chronic pain due to progressive malignant disease is the application of a simple analgesic ladder employing regular administration of appropriate drugs. Our preferred analgesic ladder is illustrated in Table 1, in which we use a stepwise titration from a simple analgesic, paracetamol, to a weak opioid (dextropropoxyphene in the form of coproxamol), to a strong opioid (morphine).

Dyspnoea. This may result from lymphangitis carcinomatosa, progressive primary or secondary parenchymal lung tumours, progressive and recurrent

Table 1. Recommended scheme of drug use for chronic cancer pain.

	Pain		
	Mild pain	Unresponsive to simple analgesics	Unresponsive to weak opioid
Analgesic group	Simple peripherally acting analgesic	Weak opioid	Strong opioid
Drug of choice	Paracetamol 1 g 4-hourly	Dextropropoxyphene/ paracetamol 2 tablets 4-hourly	Morphine or diamorphine orally 5–200 mg 4-hourly
Alternative drugs	Soluble aspirin 600–1200 mg 4-hourly	Dihydrocodeine 30–60 mg 4-hourly	Phenazocine, Levorphanol, Oxycodone suppositories
Drugs to avoid	Compound preparations	Pentazocine	Short-acting opioids, Combinations, Opioids with cumulative toxic effects
Other measures	Co-analgesic	Co-analgesic	Co-analgesic

pleural effusions or lung collapse secondary to bronchial obstruction. Alongside specific tumoricidal treatment where appropriate, small doses of an opioid analgesic will help to alleviate symptomatic respiratory distress in these situations.

Cough. In similar situations to those above, cough may emerge as the predominant symptom. Codeine, methadone or morphine elixirs are the commonest and most effective agents for cough suppression.

Diarrhoea. This may occur in relation to malignant disease either secondary to an obstructing process or, more rarely, related to humoral agents produced by the tumour. It is also a recognized complication of radiotherapy to the pelvis or abdomen, and of certain chemotherapy agents [e.g. methotrexate or cis-platinum (cisplatin)], and is a feature of graft versus host disease following bone marrow transplantation. Where obstruction has been ruled out, symptomatic relief using codeine phosphate, diphenoxylate or loperamide is indicated.

INDIVIDUAL DRUGS

Of the many opioid drugs available a limited number will be adequate for most situations. These are dextropropoxyphene, dihydrocodeine, morphine and diamorphine for analgesia or respiratory symptoms, and codeine, diphenoxylate or loperamide for diarrhoea. The basis of this selection in the context of other available opioid drugs is discussed below.

WEAK OPIOID ANALGESICS

Our recommended scheme of opioid drugs for analgesic use is shown in

Table 1. When pain is not controlled with a peripherally acting analgesic such as paracetamol, the next step is to use a weak opioid.

Dextropropoxyphene/paracetamol

Dextropropoxyphene in combination with paracetamol (Distalgesic, Cosalgesic, coproxamol) is our drug of choice in this group.

Dextropropoxyphene

Propoxyphene is a synthetic derivative of methadone, and its dextrorotatory stereo-isomer dextropropoxyphene is responsible for the analgesic activity (Gruber et al, 1956). In animal models, dextropropoxyphene has weak opioid activity and a low affinity for μ-receptor sites, of a similar order to that of codeine (Nickander et al, 1984). The opioid effects of dextropropoxyphene (analgesia, sedation, nausea, vomiting, constipation, hypotension and respiratory depression) are reversed by naloxone.

Dextropropoxyphene is readily absorbed from the gastrointestinal tract but undergoes extensive first pass metabolism in the liver, its principal metabolite being norpropoxyphene. Norpropoxyphene has a longer half-life (about 23 hours) than dextropropoxyphene itself (15 hours) and accumulates in plasma (Inturissi et al, 1982). Both dextropropoxyphene and norpropoxyphene reach plasma concentrations in the steady state which are five to seven times greater than those found after the first dose. In elderly patients the half-life may be prolonged (Crome et al, 1984). Norpropoxyphene has analgesic activity but penetrates the brain to a much lesser extent than the parent compound with correspondingly weaker opioid effects.

Dextropropoxyphene hydrochloride is an effective analgesic in man in doses of 65 mg or more with a relative potency one-half to two-thirds that of codeine (Beaver, 1966). Dextropropoxyphene napsylate is less potent than the hydrochloride (in a ratio of 5:3).

In comparative single dose studies using acute pain models, dextropropoxyphene appears a slightly less effective analgesic than aspirin, paracetamol, and non-steroidal anti-inflammatory drugs, including ibuprofen 400 mg, mefenamic acid 250 mg and fenoprofen 50 mg (Beaver, 1984). However, the pharmacokinetic profile of dextropropoxyphene after a single dose is not comparable to that in chronic use. Presystemic metabolism of dextropropoxyphene is dose dependent so that its systemic availability increases with increasing oral dose (Perrier and Gibaldi, 1972). Thus with regular administration there is enhanced bioavailability, and some degree of accumulation because of the long elimination half-lives of the parent drug and active metabolite. Dextropropoxyphene is likely therefore to be more effective when given in repeated doses, and the results of *single dose* efficacy studies of dextropropoxyphene may be misleading. It is also important, when assessing the published studies, to be aware that the acute pain models used in these studies are in general less responsive to centrally acting drugs than peripherally acting analgesics.

Dextropropoxyphene in combination with paracetamol

The combination of dextropropoxyphene and paracetamol (coproxamol) is the usual form of administration of dextropropoxyphene in the UK, the rationale for which is that the incorporation of a peripherally acting and a centrally acting analgesic will achieve greater analgesia with less dose-related side-effects. Though there is only limited evidence from controlled studies (Huskisson, 1974; Owen and Hills, 1980) that the combination is more effective than paracetamol by itself, this lack of data may again be explained by the use of single doses in inappropriate experimental models.

The combination of dextropropoxyphene and paracetamol has also been criticized on the basis of pharmacokinetic incompatibility. Dextropropoxyphene and norpropoxyphene have long elimination half-lives whereas paracetamol does not. However, no problems attributable to persistent effects of dextropropoxyphene in the body have been reported in clinical use after chronic dosing.

In summary, dextropropoxyphene is an effective weak opioid analgesic. In combination with paracetamol it is a useful intermediate between simple peripherally acting analgesics and morphine. We would titrate the dose up to two tablets of coproxamol 4-hourly (each tablet contains dextropropoxyphene 32.5 mg and paracetamol 325 mg). At these doses serious side-effects are unusual. Constipation is common and should be anticipated and prevented. Nausea and vomiting are infrequent, but confusion, dysphoria and light-headedness may occur, particularly in the elderly. These effects are usually self-limiting.

Other weak opioid analgesics

Codeine and dihydrocodeine

Codeine (methylmorphine) is a naturally occurring alkaloid in opium, is chemically closely related to morphine (Figure 1) and has μ-receptor effects. Codeine phosphate is well absorbed from the gastrointestinal tract and is metabolized to norcodeine and morphine. Some 10% of an oral dose is converted to morphine and this may partly account for its analgesic effect (Findlay et al, 1978).

When given parenterally, codeine is less than one twelfth as potent as morphine (Lasagna and Beecher, 1954) and its oral to parenteral potency ratio is 2:3 (Beaver et al, 1978). The usual oral dose of codeine is 30–60 mg and its duration of action is four to six hours. There is disagreement about the effective dose range of codeine. Whilst it is widely believed that there is a levelling off in analgesia at doses above 60 mg by mouth, there is evidence from studies of intramuscular codeine that a progressive increase in analgesia is obtained with doses up to 360 mg (Beaver, 1966). However, in practice such doses are rarely, if ever, used.

Dihydrocodeine (DF-118) is a semi-synthetic analogue of codeine and approximately 30% more potent (Seed et al, 1958). There is a dearth of controlled clinical trial data on the use of oral dihydrocodeine. The usual

oral dose is 30–60 mg (one to two tablets) four- to six-hourly. A controlled release tablet formulation of dihydrocodeine has recently been introduced in the UK. No clinical or pharmacokinetic data are available but the formulation is an established controlled release vehicle which has previously been used with morphine (MST Continus).

Choice of weak opioid: coproxamol or codeine/dihydrocodeine

Coproxamol has less potential, theoretically, for causing opioid side-effects (particularly constipation) but some authorities prefer to use codeine or dihydrocodeine. There are no controlled clinical trial data to support a preference for either of these options.

Combination preparations of codeine and dihydrocodeine together with aspirin or paracetamol are also available. Without exception these preparations contain low doses of the opioid [e.g. Codis (cocodaprin), with 8 mg codeine and 500 mg soluble aspirin; Panadeine (cocodamol) with 8 mg codeine and 500 mg paracetamol; Paramol (codydramol) with 10 mg dihydrocodeine and 500 mg paracetamol]. These doses of the opioid, even when two tablets are given, are subtherapeutic. In contrast, two tablets of coproxamol give a therapeutic dose of dextropropoxyphene.

We use coproxamol as the weak opioid of choice and dihydrocodeine as our *alternative* if for some reason patients are unable to tolerate coproxamol.

If the pain is insufficiently controlled with a weak opioid analgesic in maximum dose (two tablets 4-hourly of coproxamol, or 60 mg 4-hourly of dihydrocodeine) oral morphine should be used, with a starting dose of 10 mg 4-hourly.

AGONIST/ANTAGONIST OPIOID ANALGESICS

This is a group of drugs which falls between the weak opioids and strong opioids in terms of their analgesic activity. They were developed in the hope of producing strong analgesics which lacked the addictive properties, respiratory depression and other major side-effects associated with the strong opioids, but this objective has never been achieved. Drugs included in this category are a heterogenous group including the partial agonist buprenorphine, the nalorphine-like agonist antagonists pentazocine, butorphanol and nalbuphine, and the more recent μ_1-selective agonist antagonist meptazinol. All of these drugs are characterized by having analgesic activity but at the same time are capable of antagonizing the effects of morphine or other opioid agonists.

Nalorphine-like agonist antagonists

Nalorphine, *N*-allylnormorphine, antagonizes the effects of morphine (Hart, 1941) but also has powerful analgesic activity (Lasagna and Beecher, 1954). In man these effects are accompanied by a high incidence of dysphoric side-effects, and for this reason a series of alternative benzomorphan derivatives were developed.

Pentazocine

Pentazocine was the first mixed agonist antagonist analgesic to be used in widespread clinical practice. Pentazocine is a weak competitive antagonist at μ-receptors and an agonist at κ and σ receptors (Martin et al, 1976).

Given parenterally, pentazocine is a powerful analgesic and estimates of its potency relative to morphine range from one-third to one-sixth. When given by mouth the analgesic action of pentazocine is much weaker. It is readily absorbed after oral administration but undergoes extensive first pass metabolism as a result of which the oral to parenteral potency ratio is one-third to one-quarter (Beaver et al, 1968). Comparative studies of its potency compared with standard analgesics have produced conflicting results. In postoperative patients pentazocine 50 mg (two tablets) appeared to be as effective as codeine 60 mg or dihydrocodeine 60 mg (Kantor et al, 1966; Daniel et al, 1971) but in patients with chronic pain due to cancer or rheumatoid arthritis pentazocine 50 mg was less effective than aspirin 650 mg, combinations of codeine 8 mg with aspirin 500 mg, or dextropropoxyphene 32.5 mg with paracetamol 325 mg (Moertel et al, 1972; Robbie and Samarasinghe, 1973; Huskisson, 1974). The duration of analgesia produced by pentazocine in these studies was about three hours. In another study of patients with rheumatoid arthritis pentazocine 25 mg four times daily could not be distinguished from placebo in terms of pain relief, but produced a higher incidence of side-effects (Nuki et al, 1973).

The other major drawback of pentazocine is that it produces a high incidence of psychotomimetic side-effects, most commonly hallucinations, euphoria and depersonalization with an incidence of between 1% and 20%, most estimates being in the region of 10% (Miller, 1975; Taylor et al, 1978). There is some evidence that the incidence is higher in chronic pain patients, and patients with cancer may be particularly at risk (Houde, 1979; Twycross and Lack, 1983).

In summary, pentazocine has weak analgesic activity when given by mouth, appears to be closer in analgesic efficacy to the peripherally acting simple analgesics than the weak opioids, and its use is associated with a high incidence of unpleasant side-effects. Pentazocine has no advantages over other weak opioid analgesics to balance these major disadvantages and has no place in our management of cancer pain.

Butorphanol

Butorphanol (Stadol) is a nalorphine-like agonist antagonist structurally related to pentazocine. It is a potent analgesic, three and a half to seven times as potent as morphine and 20 times as potent as pentazocine (Lewis, 1980). It was introduced in the UK in 1978 but was only available for parenteral administration. Butorphanol did not appear to have any particular advantages over other more established drugs and was withdrawn from the market in 1983 because of poor sales.

Nalbuphine

Nalbuphine (Nubain) is chemically closely related to naloxone, the specific

opioid antagonist, and to oxymorphone, a strong agonist. It is a weak μ antagonist and a κ agonist. Nalbuphine is approximately equipotent with morphine after intramuscular injection and its duration of action is three to six hours.

The oral potency of nalbuphine appears to be 20% of that after intramuscular injection (Beaver and Feise, 1978). No oral formulation of nalbuphine has yet been registered for general clinical use, and at present therefore it has no obvious place in the management of chronic cancer pain.

Morphine-like agonist antagonists

Buprenorphine

Buprenorphine is a semi-synthetic derivative of thebaine and chemically closely related to the potent agonist etorphine. Buprenorphine is a potent partial agonist, being around 30 times as potent as morphine (Wallenstein et al, 1982), but exhibits a ceiling or plateau effect in various animal models, and in some cases the pharmacological response actually decreases with increasing dose beyond this plateau (Rance, 1979).

Buprenorphine undergoes extensive first-pass metabolism and inactivation and is not effective by the oral route, but is readily absorbed sublingually when it is almost as effective as when given parenterally (0.3 mg intramuscularly = 0.4 mg sublingually). The duration of analgesia is six to nine hours (Bullingham et al, 1981).

The maximum effective dose has not been unequivocally demonstrated in man although there does appear to be a ceiling effect for subjective responses to buprenorphine at about 1 mg subcutaneously (and therefore probably a little higher sublingually) (Heel et al, 1979). There is however a more practical 'ceiling' effect with respect to the number of tablets a patient will tolerate, since the administration of more than three or four tablets (0.6–0.8 mg) in a single dose sublingually is impractical.

When used in chronic cancer pain, buprenorphine appears effective but poorly tolerated. In one open study 94 of 141 patients discontinued the drug within one week: 50 because of side-effects (dizziness, nausea, vomiting, drowsiness, light-headedness) though not all of these may have been directly attributable to the analgesic. The other 47 patients appeared to have satisfactory relief of their pain using doses ranging from 0.15–0.8 mg at varying dose intervals (Robbie, 1979). In another open study over half of 70 patients obtained pain relief with total daily doses of 0.4–4 mg, but 'most' patients withdrew from the study because of unwanted effects or inadequate relief (Adriaensen et al, 1985).

In two controlled studies in cancer patients, buprenorphine appeared better overall than pentazocine (Ventafridda et al, 1983; Dini et al, 1986) and others have confirmed the clinical efficacy of chronic sublingual administration (Enig, 1983; Zenz et al, 1985).

The opioid effects of buprenorphine are relatively resistant to reversal by naloxone, possibly due to the very high binding affinity of the drug to μ-receptors, and the use of the respiratory stimultant doxapram is recom-

mended in the treatment of respiratory depression resulting from overdosage of buprenorphine.

Physical dependence with an associated withdrawal syndrome on sudden discontinuation of the drug does not appear to be a problem with buprenorphine (Cowan et al, 1977; Jasinski et al, 1978). Cases of drug abuse involving buprenorphine do occur (Robertson and Bucknall, 1986) although its abuse potential is much lower than that of other strong opioid analgesics.

In summary, buprenorphine is a potent opioid analgesic which is effective when given sublingually, has a long duration of action (6–9 hours) and is less likely to cause physical dependence and abuse than other strong opioids. Against this must be weighed a number of limitations: buprenorphine has a narrow effective dose range because of its ceiling effect; it has the potential to antagonize the actions of pure opioid agonists and precipitate abstinence phenomena; and its chronic use is associated with the same range of side-effects as other strong opioids with some indications that these unwanted effects are more frequent.

In the management of cancer pain buprenorphine may be effective as an alternative to oral morphine in the lower dose range, but since dose titration is then limited by its ceiling effect, progression to morphine will invariably be required.

Patients may be converted directly from buprenorphine to a pure agonist, although there may be a delay in achieving the optimum dose level of the new drug. No problems are likely to be encountered in the transition period. The conversion ratio to oral morphine suggested by Twycross and Lack (1983) works well in practice: multiply the total daily dose of buprenorphine by 100 and convert into a convenient 4-hourly regimen.

Meptazinol

Meptazinol is a synthetic hexahydroazepine derivative with opioid agonist and antagonist properties but is unlike either the nalorphine-type agonist antagonists or buprenorphine. Meptazinol has potent analgesic effects which are almost completely reversed by naloxone, but has low dependence liability, antagonizes morphine-induced respiratory depression and precipitates abstinence phenomena in morphine-dependent rats (Goode and White, 1971). Receptor binding studies show it to be a specific μ_1-agonist (Blurton et al, 1982).

Unlike other opioids, both optical isomers possess analgesic activity and the drug has central cholinergic properties which may account at least in part for its analgesic effects (Bill et al, 1982). This differentiates meptazinol from all conventional analgesics. The effective dose range of meptazinol appears to be narrow (Staquet, 1978) and in terms of analgesic efficacy, oral meptazinol comes into the same category as the weak opioids but it does not seem to compare favourably with coproxamol either in terms of efficacy or side-effects.

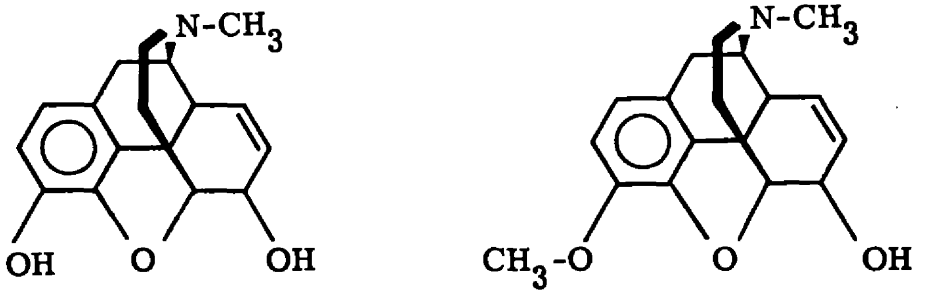
The use of meptazinol is restricted to short-term treatment of moderate pain and we do not see, therefore, any particular place for it at present in the management of cancer pain.

STRONG OPIOID ANALGESICS

Most patients with chronic cancer pain will eventually require a strong opioid analgesic to achieve pain control, and morphine given by mouth is our strong opioid agonist of choice.

Morphine

Morphine is extracted from opium and is its principal alkaloid, constituting about 10% by weight. The chemical structure of morphine base is shown in Figure 1.



MORPHINE CODEINE

Figure 1. Chemical structures of morphine and codeine.

Morphine sulphate in aqueous solution (chloroform water) or controlled release morphine tablets are the usual preparations for oral use. The limit of solubility of morphine is 400 mg in 10 ml. Morphine elixir is normally administered in a regular 4-hourly regimen: its principal disadvantage is the characteristic bitter taste which is difficult to disguise. The dose of morphine is titrated against the pain in individual patients, with no arbitrary upper limit whilst evidence of a dose–response effect is seen. Some two-thirds of patients will require doses of only 30 mg 4-hourly or less to achieve pain control, and rarely will doses in excess of 200 mg 4-hourly be required. A 50% increase or doubling of the dose at bed-time will avoid the need for patients to wake in the middle of the night.

Controlled release preparations

There are at present two slow release oral preparations of morphine available, MST-Continus and Roxanol SR, of which only MST-Continus is available in the UK. MST is designed to produce sustained plasma concentrations of morphine for 12 hours, whilst Roxanol SR has an eight hour duration of action. MST-Continus provides a useful method of delivering oral morphine in a twice daily regimen where patients have previously had their morphine dose requirements defined by titration with 4-hourly aqueous morphine (Hanks et al, 1987). Despite early suggestions that the

bioavailability of MST was greater than oral morphine elixir (McQuay et al, 1983a) two recent studies have demonstrated that there is no significant difference between the bioavailability of these preparations across a wide dose range (Sloan et al, 1986; Poulain et al, 1987). The conversion from 4-hourly morphine elixir to MST should therefore be on a dose for dose basis maintaining the same total daily dose of morphine. The need for a loading dose of morphine elixir when starting MST has yet to be defined, but clinical experience suggests that this may not be necessary when changing from an established steady state in patients stabilized on aqueous morphine.

Controlled release preparations are unsuitable where morphine treatment is to be initiated or where frequent changes in dose are anticipated because of the delay in achieving adequate plasma concentrations. In these situations the greater flexibility and shorter duration of action of aqueous morphine elixir makes this the preparation of choice.

When pain develops whilst a patient is taking a slow release preparation, top-up doses of morphine elixir can be given to redefine the daily morphine requirements before adjusting the dose of the slow release preparation. The top-up dose should be based on the 4-hourly dose equivalent to the current MST dosage, i.e. one-third of the 12-hourly dose.

Route of administration

The analgesic and other effects of opioids which are of value in symptom control are mediated through their action on central opioid receptors in both the brain and spinal cord. In order to achieve the therapeutic effect therefore a sufficient amount of morphine, or possibly its active metabolites, must be delivered to the central nervous system via the systemic circulation or directly in the case of spinal or intraventricular administration.

Oral administration is the route of choice because it is the most convenient and acceptable to the patient. Alternative routes should be considered only where this is impossible, for example because of dysphagia, nausea or vomiting. Rectal administration is probably the next best alternative. The absorption and bioavailability of morphine given rectally by suppository seems similar to that of oral morphine (Westerling et al, 1982) and a 4-hourly regimen is usually satisfactory.

Morphine suppositories are available in a wide range of doses or may be prepared in most hospital pharmacies. If rectal administration is unacceptable or impossible due to surgical removal or tumour involvement, subcutaneous infusions should be considered. Two buccal preparations of morphine are at present being evaluated and these may also have a role in such situations.

In the patient with advanced cancer intravenous infusions are probably best avoided and may, in any case, be impossible to maintain due to limited venous access. The role of patient controlled administration requires further evaluation in this setting.

Spinal and intraventricular administration of opioids have both been used for chronic cancer pain. The requirement for skilled experienced personnel and careful supervision limits the application of this technique to specialized

units and, at present, no convincing advantages have been demonstrated (Editorial, 1986).

Pharmacokinetic considerations

Both morphine and diamorphine are drugs with a high hepatic extraction ratio, the products of metabolism being principally morphine-3-glucuronide and morphine-6-glucuronide, with small amounts of normorphine, codeine and morphine-3-ethereal sulphate. Suggestions that the kidney is an important site of *metabolism* (McQuay et al, 1983b; Moore et al, 1984) are now discredited (Aitkenhead et al, 1984; Sawe et al, 1985; Woolner et al, 1986). Metabolism in the small bowel wall certainly occurs in rats (Dahlstrom and Paalzow, 1978) and possibly also in man, but no other significant extra-hepatic sites of morphine metabolism have been identified.

The influence of impaired hepatic function on morphine handling remains unclear. A recent study (Hasselstrom et al, 1986) in patients with cirrhosis has shown a significant increase in oral bioavailability and prolonged elimination half-time compared with patients having normal liver function, though an earlier study (Patwardhan et al, 1981) showed no difference in morphine handling after intravenous administration in cirrhotic and non-cirrhotic patients. A study in shocked patients with significantly reduced liver blood flow (Macnab et al, 1986) has also shown prolonged elimination half-time and reduced systemic clearance. No data are available on the influence of hepatic impairment due to metastatic cancer on morphine pharmacokinetics but a retrospective analysis of cancer patients receiving regular morphine (Regnard and Twycross, 1984) revealed no difference in median dose requirements between patients with impaired hepatic function and those with normal hepatic function.

Three independent studies (Aitkenhead et al, 1984; Sawe et al, 1985; Woolner et al, 1986) have now confirmed that morphine clearance is unaltered in renal failure but considerable accumulation of morphine glucuronides occurs. Prolonged sedation and respiratory depression have been observed in three reports of intensive care unit patients with impaired renal failure (Ball et al, 1985; Bion et al, 1986; Osborne et al, 1986) receiving morphine or other opioids. Morphine-6-glucuronide is pharmacologically active (Shimomura et al, 1971) and is in fact considerably more potent than morphine in its analgesic effect. The accumulation of this and possibly other metabolites in renal failure may well explain the clinical findings. In patients with advanced cancer, renal failure is common, particularly following ureteric obstruction by tumour, drug toxicity, septicaemia or metabolic disturbances such as hypercalcaemia. A retrospective study (Regnard and Twycross, 1984) has demonstrated that patients with serum creatinine greater than 180 mmol/l require significantly lower median doses of morphine for pain control (5–7.5 mg 4-hourly compared with 20 mg 4-hourly) than patients with normal renal function.

Management of side-effects

True intolerance to opioid drugs is rare in patients with advanced cancer.

There are, however, several side-effects which may be troublesome and if neglected result in withdrawal of a potentially useful agent.

Certain effects should be anticipated and treated appropriately. Constipation is universal in patients taking morphine or diamorphine and routine administration of a laxative is recommended. Nausea and vomiting will not occur in up to two-thirds of patients and where adequate supervision is possible, routine prescription of an antiemetic is unnecessary. Where required, haloperidol in a dose of 1.5–3 mg at night is usually effective. Drowsiness or confusion is not uncommon when a strong opioid drug is first introduced or doses are escalated. In most cases tolerance to these effects develops rapidly over only a few days and with careful explanation and reassurance, pain control with acceptable side-effects can be achieved. More serious psychotomimetic disturbances occur in only a small proportion of patients, but may require sedation, an antipsychotic agent or the use of an alternative opioid drug such as phenazocine.

The depressant effect of morphine on the respiratory centre has, in the past, been a source of concern in the light of the relatively large doses which may be required by some patients. It has been shown, however, that even in patients with longstanding chronic lung disease there is no evidence of ventilatory failure, as measured by respiratory rate, peak flow and arterial blood gases, after stabilization of morphine dosage (Walsh et al, 1984). This may reflect in part physical tolerance to the effects of morphine at the respiratory centre but also the principle that pain is the physiological antagonist of the respiratory depressant effects of opioid analgesics (Hanks and Twycross, 1984).

Addiction and tolerance

Addiction, as defined by a behavioural pattern of drug use, characterized by overwhelming compulsion to take the drug, securing its supply, and a high tendency to relapse after withdrawal (Jaffe, 1980), is not seen in asssociation with the use of regular strong opioid analgesics for cancer pain. The evidence for this comes not only from extensive clinical experience (Twycross and Lack, 1983) but also from carefully documented cases where reducing doses of morphine, and even complete withdrawal has been demonstrated following definitive treatment such as radiotherapy or a local nerve block (Sawe et al, 1983). In the wider context, a large retrospective review of medical inpatients receiving narcotic analgesics found only four out of 11 882 cases of subsequent addiction, of which only two were described as severe (Porter and Jick, 1980).

In many patients receiving regular opioids, however, some degree of tolerance and physical dependence will be seen. Dependence may be distinguished from addiction by considering it as an altered physiological and/or psychological state produced by the repeated administration of a drug, which necessitates continued administration of the drug to prevent the appearance of a withdrawal syndrome (Jaffe, 1980). Tolerance refers to the need for increasing doses of a drug to produce the same effect and may be due to changes in pharmacokinetics such as enzyme induction, increased excretion, or adaptive changes in responding tissues, possibly mediated by

reduction in receptor sensitivity. For morphine, autoinduction of hepatic enzymes does not develop with increasing doses (Sawe et al, 1983). Changes in receptor sensitivity may therefore be the most relevant mechanism. The close interaction between addiction, tolerance, dependence and habituation is shown in Figure 2.

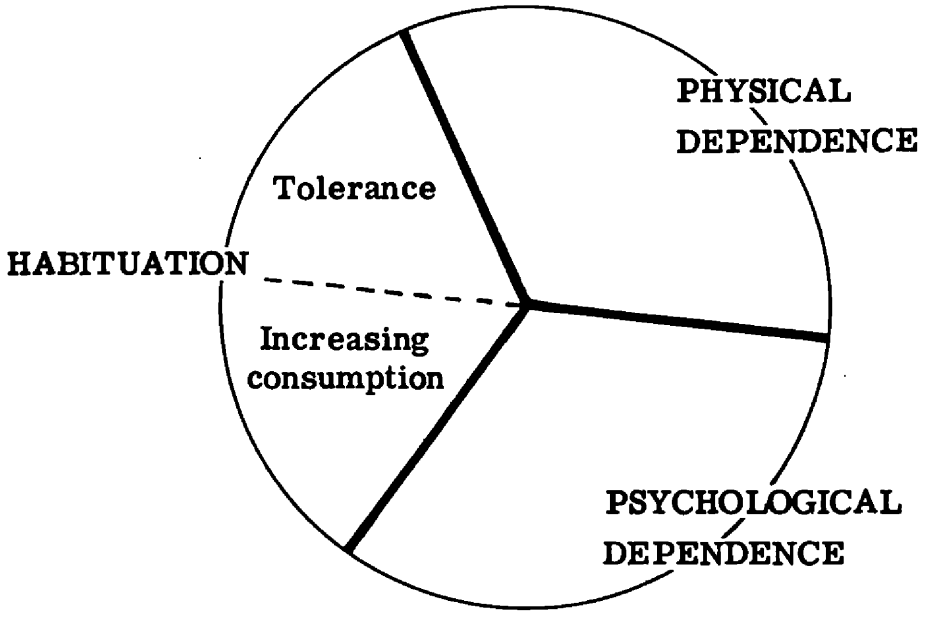


Figure 2. Components of addiction.

The precise reasons for addiction not occurring in some patients remains unclear. Risk factors such as personality type and sociological factors have been identified in occasional drug users who progress to addiction compared with those who do not (Segal, 1978), and a complex interplay of many factors is seen. The unique position in our society of the patient dying from advanced cancer and the administration of the drug under controlled medical conditions may account for otherwise susceptible individuals not becoming addicts.

Tolerance may be seen as an increase in dose requirements during the first few weeks of initiating morphine. However, as treatment proceeds and pain control is achieved a slower rate of rise in dose, with long periods of dose stability, is seen, with even dose reduction and drug withdrawal becoming possible. Tolerance does not develop equally or at the same rate to all the effects of the opioids. During dose titration, certain effects such as sedation may become prominent and then recede as tolerance develops whilst others such as constipation and analgesia persist. The increases in dose needed to maintain analgesia are usually small and in the context of advanced cancer must be distinguished from the effects of progressive disease.

Florid withdrawal symptoms are not to be expected with gradual dose reduction, but inadvertent sudden discontinuation of medication or introduction of a drug with opioid antagonist activity may provoke the typical syndrome of morphine withdrawal.

Diamorphine

Diamorphine (diacetylmorphine) is a synthetic analogue of morphine resulting from acetylation in the 3 and 6 positions, generally used in the form diamorphine hydrochloride.

Diamorphine is highly soluble in water and chloroform, the maximum solubility in both being 1 in 1.6, i.e. 1 g will dissolve in 1.6 ml of diluent. For clinical use solutions of 250 mg/ml (25% w/v) which is well below its limit of solubility have been proposed as optimum for continuous infusion (Jones et al, 1985).

It is this far greater solubility of diamorphine which makes it preferable to morphine for parenteral use, particularly in patients requiring high doses. Although diamorphine does undergo spontaneous deacetylation to monoacetyl morphine and morphine at a rate dependent upon pH and temperature (Beaumont, 1982; Poochikan et al, 1983) significant degradation does not occur if the infusion is renewed every 12–24 hours as is usually the case. Even in the setting of prolonged subcutaneous infusions which may be maintained for up to two weeks without renewal, no apparent loss of potency is seen clinically (Jones and Hanks, 1986).

When given orally, diamorphine has no advantages over morphine, and is an inefficient way of getting morphine into the systemic circulation. After oral administration, neither diamorphine nor monoacetylmorphine are detectable in plasma (Inturissi et al, 1984) due to the extensive first-pass metabolism that takes place predominantly in the liver. In contrast, when given by intravenous bolus injection, diamorphine produces more rapid analgesia than morphine and greater sedation, but a lower incidence of vomiting (Loan et al, 1969). By subcutaneous or intramuscular injection diamorphine is about twice as potent as parenteral morphine (Kaiko et al, 1981). These differences appear to be associated with significant amounts of diamorphine and monoacetylmorphine being detectable in the systemic circulation (Inturissi et al, 1984). The greater lipid solubility of these substances compared with morphine enables rapid entry into the brain where they exert their effect. The active substances at the μ opioid receptor may be monoacetylmorphine and morphine (Inturissi et al, 1983) but a direct effect of diamorphine itself cannot be excluded.

We use diamorphine by subcutaneous injection or infusion as our strong opioid of choice when parenteral administration is necessary.

Dose equivalents

The subject of equivalent doses for morphine and diamorphine and for oral compared with parenteral administration is one which can cause considerable confusion in the clinical use of these strong opioids. This may be because the recommendations for chronic use are based on empirical clinical experience rather than reliable trial data.

The relative potency, in terms of analgesic activity, of morphine and diamorphine in chronic use is unclear. On the basis of a study in which 24-hour urinary morphine excretion was measured in patients with advanced cancer after intravenous diamorphine and oral diamorphine or oral morphine, it has

been suggested that oral diamorphine is more potent than oral morphine in a ratio of 1.5:1 (Twycross et al, 1972). However, the study fails to take into account other potential sources of difference between oral and parenteral administration such as the extensive first-pass metabolism of morphine and diamorphine and the potential role of an enterohepatic circulation. A subsequent study measuring serum morphine levels after oral morphine or oral diamorphine showed no difference in 'morphine equivalents' between the two preparations, but this is based on single samples using a non-specific radioimmunoassay (Aherne et al, 1979). The most recent data using a specific high performance liquid chromatography (HPLC) assay and serial blood sampling has shown that after the same oral doses of morphine and diamorphine, the plasma morphine concentration with diamorphine is 79% of that present after morphine (Inturissi et al, 1984). Concentrations of potentially active metabolites, however, have not been taken into account in this latter study.

In practice, morphine and diamorphine appear to be equipotent in chronic oral use. It may, however, be necessary to retitrate the dose if pain breaks through.

When changing from the oral or rectal route to parenteral administration of morphine it is important to take into consideration the poor oral bioavailability of morphine and reduce the parenteral dose. There remains, however, controversy as to the appropriate dose change to be made. Conventionally, oral morphine has been considered to be one-sixth as potent as intramuscular morphine from the results of a double-blind, randomized, four-way crossover study in patients with chronic cancer pain in which single doses of 30 mg and 60 mg orally or 60 mg and 120 mg orally were compared with 8 mg and 16 mg intramuscularly. Predictably a smaller peak effect but prolonged duration of analgesia was found with the oral route compared with the intramuscular, and a ratio of 1:6 for total analgesic effect and 1:12 for peak analgesic effect was found (Houde et al, 1965). However, clinical experience in chronic dosage suggests that this ratio is not applicable and that a ratio of 1:3 or 1:2 is more appropriate, which is in keeping with pharmacokinetic data for the oral bioavailability of morphine. It has been suggested that the single dose data and clinical experience with chronic dosage is not incompatible and may merely reflect the wide confidence intervals which exist in such studies or the effect of four-hourly analgesia compared to total or peak analgesia (Kaiko, 1985). Clearly further well-designed trials addressing this problem in the setting of chronic dosage are required, but at present a ratio of 1:2 appears to work satisfactorily in most patients.

The common situations encountered clinically are a change from oral morphine to subcutaneous diamorphine or vice versa. Our usual practice is to divide the oral dose of morphine by three to give the appropriate subcutaneous dose of diamorphine.

Other strong opioid agonists

There are a number of drugs other than morphine or diamorphine which

have strong opioid agonist activity. In the treatment of pain due to advanced malignant disease these drugs do not have any particular advantages over morphine. They may, however, be indicated in the rare instance of true intolerance to morphine or where an alternative route of administration, such as with oxycodone suppositories, is more appropriate.

Oxycodone

Oxycodone is a synthetic derivative of morphine which may be given orally or by injection, and is also available as oxycodone pectinate suppositories which have an analgesic action lasting 6–8 hours.

Phenazocine

Phenazocine is a synthetic opioid structurally related to morphine. It is more potent in its analgesic action, and associated with less sedation and psychotomimetic side-effects than morphine. One 5 mg tablet is equivalent to 25 mg morphine; it may be given sublingually although administration by this route is usually avoided because of its bitter taste and variable absorption.

Nepenthe

Nepenthe was originally an alcoholic tincture of opium but is now formulated as an elixir containing anhydrous morphine 8.4 mg/ml of which only 500 μg is as opium tincture. It is therefore essentially an alternative morphine elixir with no advantages over morphine sulphate. One millilitre of undiluted Nepenthe (10 ml of 10% solution) is equivalent to 12 mg morphine sulphate by mouth.

Papaveretum

Papaveretum contains 50% morphine hydrochloride, the remainder being composed of the hydrochlorides of other opium alkaloids, predominantly noscapine with small quantities of codeine and papaverine. Of these, morphine has the strongest analgesic activity and this mixture of alkaloids has no advantages over morphine alone.

Dextromoramide

Dextromoramide is an opioid agonist with potent analgesic effects. In clinical use for chronic cancer pain it appears to have a much shorter half-life than morphine with an effective duration of action of only 1.5–2 hours. For regular analgesia, therefore, it is unsuitable, although it may be useful as a short-acting strong analgesic to cover painful manoeuvres, such as changes of dressings, between regular doses of morphine.

Dipipanone

Dipipanone is a diphenylpropylamine structurally related to both dextro-

moramide and methadone. As an analgesic it is approximately half as potent as morphine, and is only available in a combination tablet containing 10 mg dipipanone and 30 mg cyclizine. This results for many patients in excessive sedative and anticholinergic side-effects related to cyclizine when adequate analgesic doses are given.

Pethidine

Pethidine is a synthetic drug, a phenylpiperidine, structurally unrelated to morphine.

Pethidine has certain disadvantages which make it unsuitable for use in chronic pain. It has a half-life of effective analgesia of only 2–4 hours so that breakthrough pain is inevitable in most patients taking four-hourly doses. In addition, its principal route of metabolism is by hydrolysis to pethidinic acid and *N*-demethylation to norpethidine in the liver. In chronic use, norpethidine accumulates, its half-life being about 17 hours compared with only 3.5 hours for pethidine (Szeto et al, 1977). This metabolite has excitatory effects on the central nervous system, resulting in tremor, twitching, agitation and convulsions. Significant accumulation of norpethidine occurs when doses of pethidine greater than 200–300 mg three-hourly are used, except where there is impairment of renal function when effects can be seen at lower doses.

Anileridine and alphaprodine

Anileridine and alphaprodine are closely related to pethidine with similar effects and duration of action, although a longer duration of action with oral use has been claimed for anileridine.

Fentanyl and alfentanil

Fentanyl and alfentanil are both synthetic opioids structurally related to pethidine with agonist activity primarily at opioid receptors where fentanyl is approximately 80 times more potent than morphine in producing analgesic effects. Both these drugs are used primarily as anaesthetic agents because of their short duration of action.

Diphenoxylate and loperamide

Diphenoxylate and loperamide are two further piperidine derivatives with opioid agonist activity, used primarily as antidiarrhoeal agents.

Methadone

Methadone is a synthetic opioid agonist acting primarily at μ-receptors. In chronic use its half-life increases from around 15 hours after a single oral dose to around 2–3 days. It may take 2–3 weeks for plasma concentrations to reach a steady state. Methadone is also highly protein bound, both in plasma and in various tissues. The consequence of this is that accumulation of

methadone will occur to varying degrees in patients taking the drug regularly at the recommended 6–8 hourly dosage intervals, with a pool of bound drug which is slowly released maintaining plasma concentrations for some time following discontinuation of the drug. This appears to be a particular problem in the debilitated and elderly when excessive sedation, confusion and even respiratory depression are seen.

Oxymorphone and hydromorphone

Oxymorphone and hydromorphone are both semi-synthetic derivatives of morphine with similar activity, but dose for dose are more potent analgesics. They are used little in the UK but much more so in the USA.

Levorphanol

Levorphanol is structurally closely related to morphine differing only in the loss of a hydroxyl group at the 6-position. It is metabolized relatively slowly with a half-life of around 11 hours, and accumulates in body fat so that problems of cumulation and excessive sedation, particularly in the elderly, may arise.

CONCLUSION

In the management of advanced malignant disease, opioids play an important role, both as analgesics and in the control of other symptoms such as cough and dyspnoea. With the use of coproxamol (dextropropoxyphene and paracetamol), oral morphine or parenteral diamorphine and with the application of a simple three-step analgesic ladder incorporating appropriate co-analgesics, pain control will be achieved in most patients. Only rarely will alternative opioid drugs be required. Many of these, whilst effective in the setting of acute pain, are associated with important drawbacks when used in chronic dosage. True intolerance to coproxamol, morphine or diamorphine will be rare if side-effects are anticipated and prevented. Dose titration of morphine across a wide range without any arbitrary upper limit provides considerable flexibility in its use.

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Diamorphine stability and pharmacodynamics

Recent correspondence (*Anaesthesia* 1985; **40**: 1241; *Anaesthesia* 1986: **41**: 554–5, 1157) indicates that there is some confusion over the stability of diamorphine and disagreement about its properties in comparison with morphine. This has arisen to some extent because the lack of stability of diamorphine in solution has different consequences according to the route and mode of administration of the drug. It is, therefore, misleading to make blanket assertions.

Dr Reynolds suggests that diamorphine 'is simply a lipid-soluble and therefore quick-acting version of morphine'. This is an oversimplification. Diamorphine does have a quicker onset of action but also produces greater sedation and causes less vomiting when given intravenously, compared with morphine.[1] Diamorphine by subcutaneous or intramuscular injection, is about twice as potent as morphine.[2] These differences appear to be associated with significant amounts of diamorphine and monoacetylmorphine being detectable in the systemic circulation.[3] The greater lipid solubility of these substances compared to morphine enables rapid entry into the brain, where

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they exert their effect. The active substances at the μ opioid receptor may be monoacetylmorphine and morphine but it is not possible, on the basis of present knowledge, to discount a direct contribution of the parent drug to its pharmacodynamic effects.

Dr Reynolds is also concerned about the stability of diamorphine in solution but, as Drs Hain and Kirk have pointed out, this concern is misplaced. Several studies have investigated the stability of diamorphine in solution and confirm that degradation *in vitro* to monoacetylmorphine and morphine occurs at a rate dependent upon temperature and pH.[4,5] Our own studies, a preliminary report of which[6] is mentioned by Drs Hain and Kirk, were designed to investigate the stability of diamorphine when given by continuous subcutaneous infusion. We found that in an aqueous solution that contained 1 mg/ml, at 20°C, only 2.7% degradation had occurred after 14 days and in a 250 mg/ml solution, 8.5% degradation.[7] When the experiment was repeated at 37°C, the degradation of a 1 mg/ml solution at 14 days was 13%; this demonstrates a significant influence of temperature which may be of relevance where infusion pumps are worn under clothing or kept under bedclothes. However, this is of no importance for the majority of patients in whom infusions are renewed regularly, usually every 12 or 24 hours. Significant degradation does not occur in this time. Certainly, negligible degradation is likely under the conditions described by Drs Hain and Kirk.

Solutions of diamorphine are also given by mouth and, by this route, there appears to be no difference in pharmacodynamic effects between diamorphine and morphine. This is consistent with the finding that after oral administration of diamorphine, neither the parent drug nor monoacetylmorphine is detectable in plasma.[3] Extensive first-pass metabolism takes place predominantly in the liver, so that diamorphine by mouth appears to be no more than a pro-drug for morphine. Any degradation before ingestion is likely to be irrelevant.

The lack of stability of diamorphine solutions is thus of no consequence, except possibly in the specific instance of prolonged subcutaneous infusions. Our experience is that even in this setting, infusions can be maintained for 2 weeks without renewal, with no apparent loss of potency clinically.[6]

The stability of diamorphine is not an issue when the relative merits of diamorphine and morphine are considered in different indications. Diamorphine by mouth has no advantages over morphine and may, in fact, be an inefficient way to get morphine into the systemic circulation. The far greater solubility of diamorphine makes it preferable to morphine by subcutaneous or intramuscular injection in patients who require high doses (in excess of 30 mg morphine). Diamorphine by intravenous bolus injection produces more rapid analgesia than morphine and is preferable in the treatment of severe acute pain, such as follows myocardial infarction. However, the speed of onset of analgesia is not important when continuous intravenous infusions are used, as Dr Reynolds points out, and the differences between the two drugs are minimal.

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Respiratory arrest after epidural sufentanil

This is a report of two cases of respiratory arrest after epidural sufentanil.

The first patient was a 55-year-old woman with a previous history of long-standing asthma, with few symptoms, treated with betamethasone. The second patient was a 23-year-old woman with no previous respiratory problems. No narcotics were used in premedication but both patients received sufentanil during major abdominal surgery, without complications. Postoperatively, both patients received 50 μg sufentanil in 9 ml normal saline epidurally, which gave good analgesia. Both patients had respiratory arrest after the last dose of a series: four doses of sufentanil in 20 hours in the first case, and seven doses of sufentanil in 22 hours in the second. The respiratory arrest happened within 5 minutes of the last dose of

secretions. Itinerant doctors also require re-education. Despite, for instance, widespread adoption by the manufacturers of a "1-2-3" code for defibrillators, not all machines comply. Furthermore, every manufacturer's layout and every model is different and there may be several designs in one hospital.

Not all hospitals are willing to "license" their skilled nurses to perform defibrillation, even in specialist units, let alone on an unfamiliar ward. The nurses themselves may be unwilling to defibrillate because that would be to "extend" their role. Some consultants are unwilling to allow nurses to defibrillate their patients, though a doctor, when he arrives, is so allowed. The consultant may even be unwilling to train nurses.

What is to be done in order to produce a proficient technical team? Junior doctors cannot be adequately trained in sufficient numbers, and even those that are will often devolve their duties or leave the team. Nurses, however, are much more stable, and they represent a potential solution to the problem.

The technical side of managing a cardiac arrest at "advanced" level could be delegated to a small group of shift-working paramedical staff (ie, nurses and technicians) who can be adequately trained and assessed, and among whom staff turnover is slow. The doctor's role then becomes appropriate—ie, the direction of the whole event. His late arrival at an arrest (having been called from his bed) becomes less relevant, especially as the technical side and the relatively straightforward early advanced therapy have been taken over.

The treatment of ventricular fibrillation is defibrillation, not cardiac compression. Adequate management of an apnoeic patient requires skilled and rapid intubation, not expired air resuscitation, inadequate 'Ambu' bagging, or incompetent intubation. These treatments should not have to await the arrival of doctors, whose skills have been shown to be suspect.

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ENTEROHEPATIC CIRCULATION OF MORPHINE

SIR,—In their criticism of our proposed explanation for the potency of repeated oral doses of morphine (Sept 26, p 723) Dr McQuay and his colleagues (Dec 19, p 1458) dismiss "clinical experience". Their own hypothesis that morphine is metabolised in the kidney ignored the realities of clinical practice,[1] and that hypothesis has proved to be wrong. The controversy focuses attention on the possible role of active metabolites: when McQuay et al thought they were measuring unconjugated morphine they were almost certainly measuring morphine plus morphine-6-glucuronide (M6G).

McQuay et al now contend that for oral morphine "there is no convincing evidence that repeated doses are more potent than single doses". They do not dispute that repeated administration produces potent analgesia but appear to be suggesting that single oral doses are equally effective. They fly in the face of not only clinical experience but also published data.

They cite three papers. The first confirms an analgesic action of single oral doses of morphine but demonstrates that this effect is poor.[2] From that study of Houde and colleagues was derived the oral:parenteral potency ratio of 1:6. The other two studies are on experimental pain, and the relevance of such models to clinical analgesic activity has long been disputed.[3] McQuay seems to doubt their validity in other contexts,[4] but not here.

Clinical studies are more persuasive. Beecher et al[5] found 10 mg oral morphine to be less effective than 600 mg aspirin. In our trial in dental surgery only 3 of 13 patients obtained good pain relief from 20 mg aqueous morphine.[6] The poor effect of single oral doses of morphine is described in standard pharmacology texts—indeed the apparent lack of efficacy of oral formulations of morphine explains why for many years this mode of administration was not accepted in many parts of the world,[7] despite substantial British experience.

MORPHINE AND METABOLITE LEVELS IN PLASMA AND BILE

Morphine 24 h dose (mg)	Morphine and metabolite levels in plasma (P) and bile (B) (ng/ml)					
	Morphine		M3G		M6G	
	P	B	P	B	P	B
120 (oral)	51	106	1510	846	149	173
120 (oral)	..	2930	..	660	..	1920
570 (subcutaneous)	352	1730	10 200	13 800	2700	1470

None of the points raised by McQuay et al give us cause to modify our hypothesis that there is a difference between single and repeated oral doses of morphine and that the likely explanations are the analgesic contribution of M6G and the enterohepatic circulation of morphine and its metabolites.

In studies in healthy volunteers we found significant amounts of M6G after single doses of oral aqueous morphine: the mean ratio of M6G to morphine (comparing areas under the curve of plasma concentration versus time) was 11:1.[8] This is substantially higher than the ratios of 2·5:1 recorded by Sawe et al[9] and of 3:1 reported by McQuay et al. In a separate study in patients with advanced cancer on long-term oral morphine we found that the ratio of M6G to morphine was 10:1 (unpublished), a figure which is again higher than that previously reported in patients receiving repeated doses.[10] M6G seems not to accumulate in plasma but this does not invalidate our hypothesis. M6G will not cross the blood/brain barrier easily; it is likely that the pattern of distribution in the CNS of M6G and other possible active metabolites changes with repeated administration. We have obtained CSF samples at myelography from cancer patients on regular oral morphine and have found concentrations of M6G and morphine in a ratio of 2:1 (unpublished). These levels of M6G are much higher than those reported by Hand and his colleagues after single doses of morphine (Nov 21, p 1207).

McQuay et al doubt the existence of an enterohepatic circulation of morphine. In an analysis of bile samples from two patients who had been on oral morphine for several months and a third who had received repeated doses of subcutaneous diamorphine we found substantial biliary excretion of morphine, M3G, and M6G (table). This finding supports our view that there is an enterohepatic circulation of morphine in man.

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Original Article

Evaluation of WHO Analgesic Guidelines for Cancer Pain in a Hospital-Based Palliative Care Unit

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Abstract
The World Health Organization (WHO) Guidelines for the management of cancer pain were evaluated in a continuing (palliative) care unit in a specialist cancer hospital. Twenty patients completed the study and all obtained good relief of pain within the first week, which was sustained for up to 76 weeks. Where there were specific indications, tumoricidal treatments (radiotherapy, chemotherapy and endocrine therapy) were used in conjunction with the WHO guidelines to achieve optimum symptom control. Eighteen of the 20 patients were treated with strong opioid analgesics (mainly morphine) for a mean period of 25.2 weeks (range 1 to 72 weeks). No serious adverse effects were associated with long-term morphine therapy. J Pain Sympt Manag *1988;3:145-9.*

Key Words
WHO guidelines, cancer pain, morphine

Introduction

The World Health Organization (WHO) has produced guidelines for the effective use of drugs to treat cancer pain[1]. These are based on a three step analgesic ladder with additional drugs as appropriate (Figure 1). The basic drugs recommended by the WHO are aspirin or paracetamol (Step I), codeine (Step II), and morphine (Step III). The guidelines for the use of the analgesic ladder should be applicable to health care systems throughout the world. A multi-centre study was initiated in 1983 to evaluate the feasibility and efficacy of the recommendations. Preliminary results[2-3] suggest that these guidelines provide a good basis for the successful management of cancer pain.

The Continuing Care (palliative care) Unit at the Royal Marsden Hospital has participated in the study and is representative of a specialist oncological centre in which the analgesic practice is in keeping with the guidelines of the WHO. Our preferred drugs are paracetamol, dextropropoxyphene in the form of coproxamol (a combination containing 32.5mg dextropropoxyphene and 32.5mg paracetamol), and morphine[4]. A variety of adjuvant drugs and other treatment modalities are also used[5].

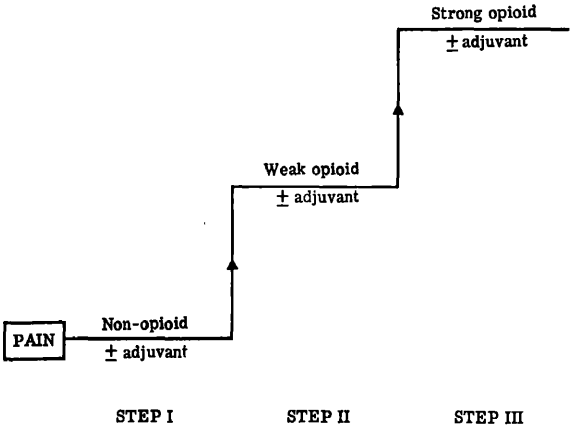

Fig 1. W.H.O. guidelines:analgesic ladder.

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Method

Patients with advanced cancer referred to the Continuing Care Unit were entered into the study if they had pain associated with their malignant disease for which analgesic therapy alone was indicated at the time of entry. All such patients were entered unless they were unable to use or understand the self-assessment rating scales.

Treatment effects were monitored by a self-assessment form completed by the patients. This included the average daily duration of pain and sleep, and a 100mm visual analogue scale (VAS) and four-point verbal rating scale (VRS) for pain intensity and pain relief. Details of the patient's general condition, their drugs and related side effects, and any other treatments were recorded at that time by an experienced research nurse. Initially, assessments were carried out at weekly intervals until pain control was achieved, and subsequently every four weeks. If pain returned and the medication was changed, weekly assessments were made until pain control was achieved once more.

Results

Between February 1985 and July 1986 20 patients entered the study, all of whom had advanced disseminated malignancy. There were six males, mean age 58.3 years (range 41-75 years) and fourteen females, mean age 62.7 years (range 38-74 years). The primary tumors were prostate (2), rectum (2), breast and myeloma in the men; and breast (9), uterus, ovary, cervix, stomach and bronchial carcinoid tumor in the women.

Pain intensity and duration

The mean duration of pain prior to study entry, as recalled by the patients, was 32.5 weeks (range 4–104 weeks). The main causes of pain were metastatic bone pain (12 patients), soft tissue infiltration (seven patients) and nerve root infiltration (one patient). The mean VAS pain score at entry was 62.5mm (range 5–97mm) and the mean daily duration of pain was 15 hours (range 1–24 hours).

Good relief from the original pain was achieved in all patients within one week of entry. In 13 patients the pain relief was attributed solely to the analgesic therapy (Figure 2), the remaining seven having received specific tumoricidal therapies in addition to analgesics. The mean pain score for these 13 patients fell from 69mm to 36mm during the first week and the daily duration of pain fell from a mean 12.3 hours to 6.7 hours. Using a paired t-test, these differences are statistically significant ($p<0.001$ and $p<0.01$ respectively).

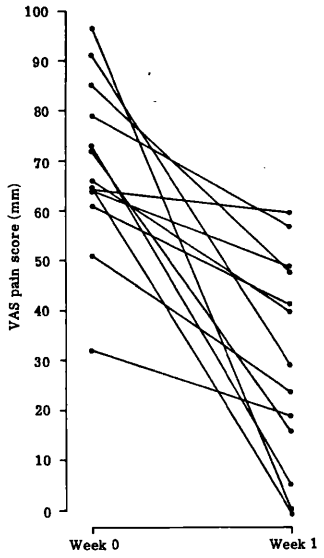

Fig 2. VAS pain scores for 1st week of the study in thirteen patients who received only symptomatic analgesic treatment.

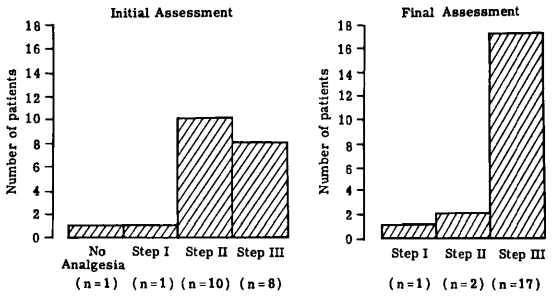

Fig 3. The change in pattern of drug use during the course of the study.

Analgesics

On entry to the study eight patients were receiving strong opioid analgesics (step III), 10 patients were taking weak opioid analgesics (step II), one patient was taking paracetamol (step I) and one patient was receiving no regular analgesic. Figure 3 shows how the pattern of drug use changed during the course of the study.

During the study period, 18 of the 20 patients were treated with strong opioid analgesics for a mean period of 25.2 weeks (range 1–72 weeks). The regular analgesic required for pain control in 16 patients was oral morphine sulphate in an aqueous or controlled-release formulation. One patient received intermittent treatment with subcutaneous diamorphine for painful episodes of intestinal obstruction and the other patient was intolerant of morphine and received phenazocine.

The main side effect of regular morphine therapy was drowsiness, experienced by 15 patients when the drug was first started or when the dose was increased. This was a transient effect and resolved in all cases without any specific remedial measures, usually over the course of a few days. Nausea was experienced by 10 patients and was controlled by regular antiemetics in all but one. Nausea in this patient had preceded the introduction of morphine elixir and remained severe until phenazocine was used instead. All patients receiving weak or strong opioids were treated with regular laxatives; as a result, constipation was not a problem. Other reported side effects included dry mouth (9), sweating (5), tremor (2), dizziness (3), disorientation (1), and jerking at rest (4). These symptoms generally subsided when the dose of morphine was stabilized.

Adjuvant drug therapies were used in accordance with the WHO guidelines and included non-steroidal anti-inflammatory drugs (14), corticosteroids (11), psychotropics (5) and anticonvulsants (1).

In nine patients with periods of stable disease, the dose of strong opioid drug required for pain control remained unchanged for a mean period of 22.6 weeks (range 4–48 weeks). An example is illustrated in Figure 4 which shows the VAS scores for pain and pain relief in a 63-year old woman with disseminated bone metastases secondary to carcinoma of the breast who received hormone therapy and step III analgesia throughout the study.

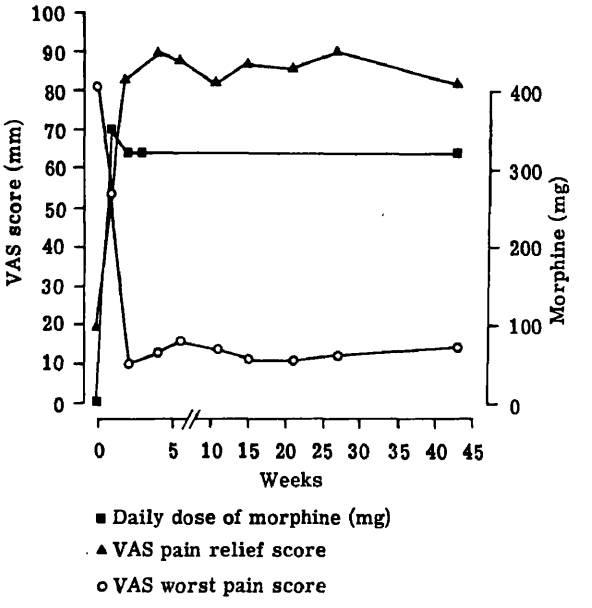

Fig 4. Long-term stable dose requirements in a patient with carcinoma of the breast and bone metastases.

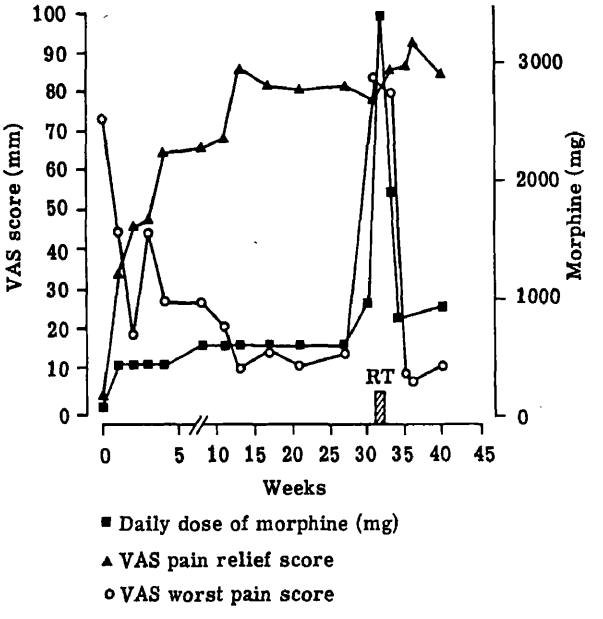

Fig 5. The value of specific therapy—in this case radiotherapy for bone pain—in controlling pain and reducing morphine requirements in a patient with carcinoma of the breastand bone metastases.

Other Treatments

During the study, 12 patients received specific anti-tumor treatment for pain relief. The treatments given included radiotherapy (6), chemotherapy (4), and hormone therapy (4). These treatments were selected for patients in whom exacerbations of pain were associated with evidence of tumor progression and where useful responses were judged likely. In this situation, morphine doses were increased until definitive treatment was given, after which doses were reduced to previous levels, or even lower if appropriate. Figure 5 illustrates the effect of radiotherapy in a 69-year old woman with breast cancer and pain associated with bone metas-

tases. This patient developed increasing bone pain requiring an increase in morphine dose to 4080 mg/day. She subsequently showed a good response to local radiotherapy, which allowed a considerable reduction in her dose of morphine.

Eight of the 12 patients receiving specific treatments had reduced pain scores following treatment. Of the other four patients, one was not assessed after she commenced chemotherapy and three had started hormone therapy prior to entry to the study so that their pain intensity before treatment was not known.

Survival

The mean survival period of the 12 patients who received these additional therapies was 45 weeks (range 22–76 weeks). In contrast, the mean survival of the 8 patients who did not receive additional therapies was 9 weeks (range 1–28 weeks). Of the 12 former patients, 7 were alive at the end of the study, with a mean follow-up of 50 weeks (range 22–76 weeks); the mean survival of the 5 patients who had died was 38 weeks (range 29–51 weeks).

Data on six of the seven long-term survivors (mean 55.5 weeks, range 24–76 weeks) were examined separately to assess the long-term efficacy of pain management using the guidelines. During the 18 months of the study these patients had been sufficiently well and pain controlled to spend a large proportion of their time at home. The mean duration of hospital admission time for pain control was 4.5 weeks compared with a mean out-patient period of 50.8 weeks. Pain intensity at the final study assessment was a mean of 39% of that on entry, and mean daily duration of pain was 28% of that on entry.

Discussion

The number of patients included in this study was small since relatively few new referrals to the Continuing Care Unit were not receiving some form of specific tumoricidal treatment. In addition, approximately 30% of new referrals to the Unit receive palliative chemotherapy, radiotherapy, hormone therapy or surgery for symptom control after referral[5].

The patients in this study all had severe pain of at least several weeks duration due to advanced cancer. Application of the WHO guidelines enabled rapid initial pain control that was well maintained.

An increased survival was seen in the group of patients who received tumoricidal therapies, though this may reflect other factors, such as stage of disease and the general condition of these patients, and may not be a direct effect of the treatment. These data do indicate, however, that specific anti-tumor treatments can be complementary to the WHO analgesic guidelines in achieving optimal symptom control.

Effective pain control should be available to patients at any stage of their disease, and this may necessitate the use of strong opioid analgesics in patients with relatively early disease. The WHO has expressed concern that fears of drug addiction and toxicity may result in delay of the administration of strong opioid drugs or the use of doses inadequate for pain control. In this study analgesic requirements were determined by the severity of pain within the WHO guidelines with no arbitrary dose limits.

We have seen no evidence of drug 'addiction' or abuse in our patients. Tolerance and physical dependence may develop in cancer patients receiving strong opioid analgesics, but rarely cause problems of any clinical consequence. Tolerance was not a problem in this group of patients, as is illustrated by the nine patients whose morphine dose requirements remained stable for several months. Withdrawal symptoms in patients who have become physically dependent can be avoided by tapering the dose of morphine, if pain is relieved by other treatments. No special maneuvers are necessary. Psychological dependence—'drug craving'—does not develop in patients receiving morphine for pain.

Morphine toxicity was not a problem in these patients and side effects were in general readily controlled with appropriate measures such as the use of laxatives and antiemetics. Our routine practice is to warn patients about the likelihood of drowsiness or sedation at the initiation of treatment with morphine or during periods of dose-titration, and to reassure them that if it occurs it will improve within a few days.

The findings of this study support the use of regular and sufficient analgesia as recommended by the WHO to control cancer pain. In addition the use of specific treatments such as radiotherapy, chemotherapy, and hormone

therapy in selected patients can greatly enhance pain control.

Acknowledgements

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The management of symptoms in advanced cancer: experience in a hospital-based continuing care unit

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Keywords: symptom control; morphine; analgesics; co-analgesics

Summary

The treatment received by 158 patients with advanced cancer admitted over one year to the Continuing Care Unit at the Royal Marsden Hospital has been reviewed. The unit is an integral part of the hospital and this is reflected in the fact that 46 patients (29%) received radiotherapy, hormone therapy, chemotherapy or surgery in addition to symptomatic treatment for palliation of troublesome symptoms.

One hundred and thirty-one patients received oral morphine in doses ranging from 2.5 mg 4-hourly to 700 mg 4-hourly. Patients with renal or hepatic impairment required lower doses of morphine and there was a highly significant inverse relationship between morphine dose and age. Eighty-five patients (54%) received parenteral diamorphine at some time due to their inability to take oral morphine.

One hundred and twenty-three patients (78%) received a co-analgesic drug and anti-emetics were required by 78 patients (49% overall; 56% of those receiving morphine). Transcutaneous electrical nerve stimulation, acupuncture and relaxation were employed in selected patients, and graduated compression sleeves were used to treat lymphoedema.

These data highlight the wide range of therapeutic options available to control the symptoms of advanced cancer and also indicate that tumoricidal treatments used in conjunction with symptomatic treatments may have a significant part to play.

Introduction

Optimal symptom control for patients with advanced cancer depends upon a detailed analysis and diagnosis of the underlying causes and careful selection of appropriate therapeutic manoeuvres individualized for each patient. Hospices and other specialized units have been established in recent years and have produced clear recommendations for the management of pain and other symptoms[1,2,3]. There is, however, little published data on the resultant patterns of drug use and the relative importance of other therapeutic options in the management of symptoms due to advanced cancer.

A retrospective review of the treatments received by patients admitted to the Continuing Care Unit of the Royal Marsden Hospital, Sutton, has been carried out. The review covers the first year of operation of the unit and provides information on the patterns of drug use and the importance of more specific therapies in these patients.

Patients and methods

Between January 1986 and January 1987 there were 233 admissions to the 13-bed Continuing Care Unit at this hospital. Patients are referred to the unit solely from within the Royal Marsden Hospital, and the emphasis is on active symptom control and rehabilitation. Admissions are both by transfer from other wards in the hospital and, following discharge or outpatient referral, from home. Of 168 patients admitted to the unit for the first time in the year of study, 97 (58%) were subsequently discharged home and 128 (76%) ultimately died as inpatients in the unit.

The case records of 158 patients admitted in this period have been reviewed, the remaining 10 records being unavailable or lost at the time of analysis. Details of the patients and the treatment they received whilst inpatients have been analysed.

Results

Clinical details of the 158 patients analysed are shown in Table 1 and the pattern of oral analgesic and co-analgesic use in Table 2. Twenty-seven patients (17%)

Table 1. Patient characteristics (n=*158)*

Mean age (range)	63.2 (19-85)
Male : female	1 : 1.32
Primary tumour:	
Breast	37 (23%)
Bronchus	36 (22%)
Prostate	11 (7%)
Colorectal	10 (6%)
Ovary	9 (5.5%)
Kidney	6 (4%)
Lymphoma	6 (4%)
Sarcoma	5 (3%)
Unknown primary	9 (5.5%)
Other	29 (20%)

Table 2. Analgesic and co-analgesic use

	No.	*(%)*
Analgesics		
Simple analgesics (paracetamol)	19	(12)
Moderate analgesics (co-proxamol or dihydrocodeine)	23	(14.5)
Strong analgesics (morphine and diamorphine)	131	(83)
Co-analgesics		
NSAID	40	(25)
Steroids	67	(42)
Antidepressant	30	(19)
Anxiolytic	61	(39)

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received no morphine during their admission, their symptoms being adequately controlled with simple (non-opioid) or moderate (mild opioid) analgesics together with appropriate co-analgesics. In 5 patients a combination of co-proxamol with additional paracetamol was given, in 6 paracetamol was used in combination with morphine and in 7 patients co-proxamol was used as breakthrough analgesia in patients on morphine.

Of the 131 patients who received morphine, 4 used suppositories and one had oxycodone suppositories substituted for oral morphine. When given orally, morphine elixir was used for most patients (aqueous morphine sulphate solution containing EDTA and sodium metabisulphite as preservatives). Thirty patients (23% of those receiving morphine) had morphine in slow release formulation (MST Continus) at some time during their admission. In 10 patients, MST was the only morphine preparation used. Four patients were taking oral diamorphine tablets at the time of referral. The only other strong opioid drug to be used regularly was dextromoramide, which 3 patients received as a short-acting top-up analgesic to cover painful dressing changes. One patient was taking pethidine and one methadone at the time of referral. The former was changed to morphine and the latter continued with methadone. All other patients who required a strong opioid analgesic and were able to take oral medication were managed with oral morphine.

Details of both the modal dose of morphine and the maximum dose received by the 131 patients requiring morphine are shown in Figure 1. In 65% of patients a modal 4-hourly dose of less than 40 mg was required and in 51% a maximum 4-hourly dose of less than 40 mg was given. Only 11% required doses greater than 120 mg 4-hourly.

Sixty-one patients who received morphine had either renal impairment (serum creatinine >120 mmol/l), hepatic impairment (alanine transaminase >30 iu/l or GGT >50 iu/l) or both. Table 3 shows that the median doses of morphine (both modal and maximum) were lower in patients with renal and hepatic impairment compared with those with normal function, though the differences did not achieve statistical significance. In contrast, a highly significant inverse relationship between morphine dose requirement and age was seen (Table 4).

Parenteral diamorphine was given to 85 patients (54%). The indication for parenteral administration in these patients was inability to take oral medication or suppositories. In 76 of the 85 patients (89%) this was due to deteriorating levels of consciousness in the final hours before death, in 8 (9%) intestinal obstruction was present, and in one case parenteral medication was used because of intolerance to high doses of oral morphine. Where patients were judged to be close to death diamorphine was administered by intermittent subcutaneous injection. In the 59 patients who received diamorphine in this way a median of one dose and mean of 2.3 doses (range 1-12) was required, median survival from the initiation of diamorphine being 12 h (range 2-48 h). To avoid multiple injections in patients with longer life expectancy a subcutaneous infusion was used in 26 patients. In two patients with sub-acute intestinal obstruction the duration of infusion was 4 weeks and 3 months, respectively. In the remaining 24 patients the median duration was 96 h, and the mean 49.8 h (range 12-192 h).

Hyoscine by injection was given with diamorphine to ameliorate respiratory symptoms from retained secretions in 54 patients (34%) and one patient received an infusion over 4 days. When given by

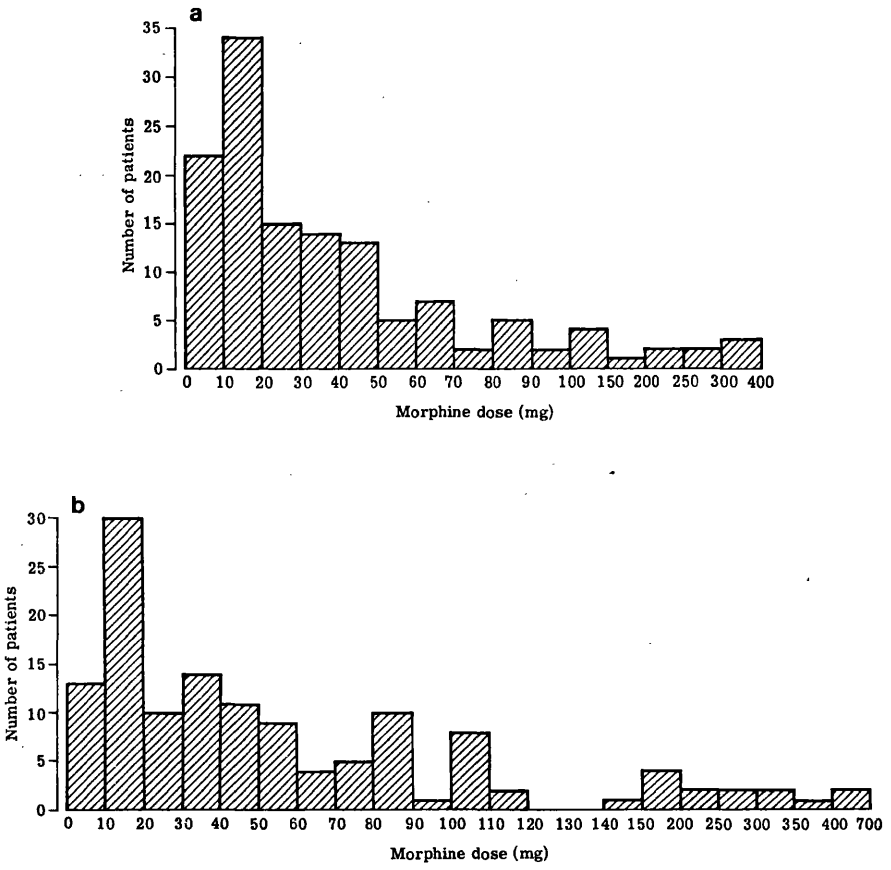

Figure 1. Distribution of (a) modal and (b) maximum 4-hourly doses of oral morphine in 131 patients

Table 3. Morphine dose in relation to renal and hepatic function

	Modal morphine dose (mg) median (range)	*Maximum morphine dose (mg) median (range)*
Normal renal and hepatic function (n=60)	30 (3-400)	45 (5-700)
Renal impairment● (n=19)	15 (3-160)	25 (3-220)
Hepatic impairment■ (n=41)	20 (3-320)	30 (3-360)
Renal and hepatic impairment (n=11)	20 (5-40)	20 (5-100)

●Serum creatinine >120 mmol/l
■Alanine transaminase >30 iu/l or Gamma glutamyl transferase >50 iu/l

Table 4. Morphine dose in relation to age

	Age group *A*	*B*	*C*
Age range (years)	19-59	60-69	70-86
Median age (years)	50.5	64.0	74.5
Number of patients	44	43	44
Maximum dose (mg) Median (range)	55 (3-700)	30 (3-100)	25 (2-200)
Modal dose (mg) Median (range)	40 (3-400)	15 (3-100)	17.5 (5-160)

The following differences are statistically significant using the Mann-Whitney test:

Maximum dose	*Modal dose*
Group *A* vs Group *B*, P=0.0001	Group *A* vs Group *B*, P=0.0023
Group *A* vs Group *C*, P=0.0007	Group *A* vs Group *C*, P=0.0012

injection the median number of injections required was one, mean 3.6 (range 1-20).

Non-steroidal anti-inflammatory drugs (NSAIDs) were selected for those patients with bone pain or other musculoskeletal pain. In the 40 patients receiving these drugs, 24 were given flurbiprofen, the drug of first choice in this unit, 7 received ibuprofen, 3 benorylate, 2 naproxen, one diclofenac and 3 patients received indomethacin by suppository. The indications for steroids in the 67 patients receiving them were spinal cord compression 4 (6%), nerve root compression 11 (16%), cerebral metastasis 10 (15%), soft tissue infiltration 20 (30%), anti-emetic 8 (12%), and for non-specific effects 14 (21%). Fifty-three patients received dexamethasone, our steroid of choice, the remaining 14 having been started on prednisolone prior to referral.

A total of 78 patients (48%) received anti-emetic drugs. Of the 131 patients receiving morphine, 74 (56%) required an anti-emetic. Thirty-nine of these patients were female and 35 male. Twelve patients required a combination of drugs, 11 receiving 2 drugs, and 1 patient receiving 3 drugs. The commonest anti-emetics to be used were haloperidol (35 patients), cyclizine (22 patients) and metoclopramide (21 patients).

Many patients also received specific tumoricidal therapy for symptom control. Twenty-one patients (13%) were treated with radiotherapy. The indications for this were bone pain 11, cerebral metastasis 3, spinal cord compression 2, pelvic mass 2, painful skin nodule 1, primary cerebral tumour 1, and base of skull infiltration 1. Twenty-three patients (14.6%) received hormone therapy. These were principally patients with breast cancer (11 patients), prostate cancer (3 patients) and renal cancer (3 patients). Tamoxifen was the most commonly used drug (11 patients), followed by medroxyprogesterone (5 patients) and aminoglutethimide (3 patients). Six patients (3.7%) received chemotherapy: 3 had 5FU for colo-rectal cancer, one had 5FU, adriamycin and mitomycin C for carcinoma of the stomach, one carboplatin for a paraganglioma, and one tumour necrosis factor for lung cancer. Five patients had surgical procedures performed: 2 had Nottingham tubes passed for obstructive dysphagia, 2 had internal fixation of a bone (in one case prophylactically and in the other after pathological fracture) and one patient had examination under anaesthetic and cystoscopy. In addition, two patients had dental procedures under general anaesthetic.

Other pain relieving measures were also employed in selected patients. Twenty-one (13%) received treatment with a graduated compression sleeve (Lymphapress) for lymphoedema. Transcutaneous nerve stimulation, acupuncture and relaxation were given to some patients but accurate figures for their use are not available. Only one patient had a specific nerve blocking procedure; a coeliac plexus block for pain and nausea resulting from a primary carcinoma of the pancreas.

Discussion

The data presented demonstrate the wide range of therapeutic options available to control the symptoms of advanced cancer. The use of a simple analgesic ladder escalating from paracetamol to co-proxamol or dihydrocodeine and then to morphine has meant in practice that only a limited number of analgesic drugs were used. Seventeen per cent of patients achieved good symptom control without the use of morphine or any other strong opioid analgesic. This may reflect in part the fact that pain was a presenting symptom on admission in only 127 patients (80%), although this is more than balanced by the finding that the prime indication for morphine in 29 patients (22%) was relief of respiratory symptoms rather than pain.

The pattern of morphine dosage is similar to that reported in other published data[4,5]. In one series, 67% of patients required a maximum 4-hourly dose of less than or equal to 30 mg in contrast to 40% in this study, and 2% required a maximum 4-hourly dose of greater than 200 mg compared to 7% in this study. Other studies have reported only maximum doses whilst the modal doses seen here demonstrate that much lower doses were required for most of the period that the patient required morphine. Approximately one-quarter of patients received slow-release morphine tablets. These were used once a patient's pain had been controlled on a stable dose of 4-hourly morphine elixir, and they provided a highly convenient means of delivering regular morphine. In patients who were starting morphine or who required frequent dose adjustments, however, this formulation was unsatisfactory and 4-hourly elixir was preferred.

The relatively small percentage of patients receiving MST was a reflection of the fact that this was an inpatient population, often with difficult pain problems or an otherwise unstable clinical state. MST may have a greater application in a stable outpatient population.

A previous report has examined the influence of renal and hepatic impairment on morphine requirements and found much lower median dose requirements (in terms of maximum doses) in patients with renal but not hepatic impairment[6]. These data were not subjected to statistical analysis. Our data show that although lower median doses were required, in this case for both renal and hepatic impairment, there was wide individual dose variation and the differences were not statistically significant. In contrast, a highly significant effect of age can be seen with much higher morphine dose requirements in younger patients. The explanation for this is not clear. It may reflect a more marked affective component to chronic cancer pain in younger patients making pain control more difficult, although a similar effect has also been observed in acute postoperative pain[7]. Pharmacokinetic data suggest that the disposition of morphine in the elderly is altered with a much smaller volume of distribution which may account to some extent for their lower dose requirements[8].

True intolerance to oral morphine is rare if side effects are anticipated and prevented. Three of our patients had particular difficulties: one was troubled by persistent nausea and vomiting, and 2 by excessive drowsiness. In these patients, conversion to a subcutaneous diamorphine infusion (one patient) or oral phenazocine (2 patients) proved effective in reducing side effects but maintaining pain control. All other patients who required a strong opioid analgesic and were able to take oral medication were managed with oral morphine.

Previous reports have indicated that 69%[1] and 51%[9] of patients have required parenteral diamorphine before death. In our series the figure was 54%.

Spinal opioid administration is not used in this unit and the evidence to date does not support any particular advantage for this route of administration[10], except in rare situations when patients are unable to tolerate any strong opioid given systemically.

Only 49% of all patients required an anti-emetic and of those receiving morphine, 56%. This proportion is lower than reported previously[11,12] and supports the policy of close surveillance of inpatients, with immediate introduction of anti-emetics where symptoms arise, rather than routine administration in all patients. The proportion of patients receiving combination anti-emetics is similar to that reported by Hanks[11] and significantly lower than the series from St Christopher's Hospice[12]. This latter report also showed that a greater proportion of females required anti-emetics though this was not apparent in the Oxford data[11], and in the present series the sex incidence was approximately equal.

Co-analgesics were used to enhance the pain control provided by conventional analgesia in 124 patients (78%). The significant affective component of chronic cancer pain is reflected in the relatively high proportion of patients receiving an antidepressant or anxiolytic drug. As far as NSAIDs are concerned, their use was reported in 14.5% of 643 patients at St Christopher's Hospice[9] compared with 25% of the 158 patients in this series.

A fundamental difference between this continuing care unit and a hospice is its place as an integral part of the hospital, benefiting from close and easy access to specialist oncological teams. This is reflected in the considerable proportion of patients who had specific tumoricidal therapy either initiated or continued whilst in the unit. In each case this was for control of specific symptoms. In total 46 patients (29%) received either radiotherapy, hormone therapy, chemotherapy or had surgery. This contrasts with data from St Christopher's Hospice reporting the use of radiotherapy in 5% of inpatients[13], hormone therapy in 6% and chemotherapy in 1.6%[14]. This finding may have implications when considering both the optimum environment for units specializing in symptom control for advanced cancer and the training of those wishing to enter this field.

This retrospective study confirms that for most patients with pain due to advanced cancer, a simple therapeutic regimen using a three step analgesic ladder and a limited number of co-analgesic drugs is appropriate. In addition, almost one-third of patients benefited from specific selected anti-tumour therapy. In particular radiotherapy or hormone therapy can be used to optimize symptom control without additional treatment-related toxicity.

Acknowledgments: We are grateful to Dr S Jackson, St Bartholomew's Hospital, for valuable statistical advice. Dr P Hoskin is supported by the Cancer Research Campaign.

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ml/hour. (Each labour room bed has a syringe pump mounted permanently on a bar bolted to the wall above the patient's head). This technique has been used in this hospital for 2 years without any problems in approximately 1000 patients.

When the epidural block was working well about 30

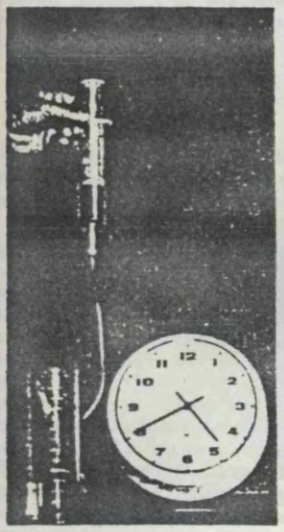

Fig. 1.

Fig. 2.

minutes later the anaesthetist left. The blood pressure decreased to 70/40 mmHg about one and a half hours later (without any signs of fetal distress). Crystalloid was infused rapidly and the syringe pump switched off. The 60-ml syringe was then discovered to contain 7 ml of bupivacaine and 32 ml of air; the plunger had moved the expected distance during the 2 hours of infusion. Analgesia reached to T_4, and she was unable to move her legs, (she was not distressed because she had been warned that her legs might become weak). The missing 32 ml of bupivacaine could not be found, so it was concluded that it had inadvertently leaked into the patient's epidural space. No further local anaesthetic was given and 4 hours later the patient, with satisfactory analgesia delivered a healthy baby. She did not have a post-delivery headache and she expressed satisfaction with the epidural, (despite knowledge of the problem which had occurred.)

The syringe was examined for faults. Compression of 30 ml of air or liquid in the syringe did not produce a leak past the plunger, neither did withdrawal of the plunger of the empty syringe (with the nozzle occluded). However, with the syringe loaded and held vertically (nozzle down) liquid readily ran out of the syringe (after an initial delay) while air leaked into the syringe past the plunger. This situation is illustrated by Figs 1 and 2.

It appears that because of a faulty seal between syringe plunger and barrel, our patient accidentally received 80 mg of bupivacaine in addition to the 77.5 mg which was intended over a 2-hour period. It is noteworthy that simple examination and testing of the syringe could not detect this fault and switching off the syringe pump did not stop the leak of bupivacaine. We have attempted to avoid further similar incidents by lowering the syringe pump mounting rail below the level of the patient, and instructing our midwives to report the presence of air inside the syringe.

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Syringe drivers

Syringe drivers are used frequently to administer continuous infusions of opioid analgesics. We wish to draw attention to a potential hazard with these devices, which may deliver much greater dosages of drugs than intended in certain circumstances. There have been several recent incidents in this hospital all of which involved the use of continuous infusions of diamorphine through central venous lines, in which an inappropriately rapid rate of drug delivery occurred despite normal function of the syringe driver. The basis of this problem is that the syringe driver is a mechanical device which advances the plunger of a syringe at a fixed rate but with no restriction on forward movement of the plunger ahead of the driver.

We have observed an increased flow rate as a result of elevation of the syringe driver above the site of infusion, as for example when placed upon a bedside locker with the patient supine in bed. This prompted the following experiment. A standard 10-ml (B-D) syringe that contained 10 ml water was suspended at various heights above the end of a selection of extension tubings connected to the syringe. The volume of water collected from the end of the extension tubing over a 5-minute period was measured and the calculated flow rates in ml/hour are shown in the table. It can be seen that significant volumes may be delivered when the syringe is connected by a standard extension set without any pressure on the syringe plunger. However, this may result in the inadvertent delivery of a significant dose of drug when connected to a central venous line. A simple device is now available from the manufacturers of the widely-used Graseby syringe driver which clamps the syringe plunger onto the actuator assembly of the driver, and thereby prevents unrestricted forward movement. This is particularly recommended where infusion through a wide bore central venous catheter is to be used and has now become an integral part of the design of other makes of syringe driver.

Table 1. Flow rate (ml/hour).

Infusion set	Height above end of extension tube (cm) 15	20	25	30
Butterfly extension set 0.5 mm internal diameter 100 cm extension tube	–	–	–	1.2
1.0 mm internal diameter 150 cm extension tube	–	< 1.2	2.4	7.2
1.5 mm internal diameter	1.2	1.8	3.6	7.2

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A simple CPAP system during one-lung anaesthesia

Continuous Positive Airway Pressure (CPAP) to the non-ventilated, nondependent lung improves oxygenation during one lung anaesthesia.[1,2] Previously described systems may be complex, or cumbersome to use.[3–5]

A system can be constructed from 15 mm paediatric components: two Y-shaped T-pieces (Portex 100/276/000)

xtraction of a ureteric calculus. She was started on 00 mg of trimethoprim twice daily in accordance with ur policy of prophylaxis against urinary infection. he soon developed a cutaneous erythematous eaction, which progressed rapidly to florid toxic pidermal necrolysis. Although she had denied any llergies at the initial clerking it subsequently emerged hat she did have a history of reaction to trimethoprim.

We have treated over 2000 patients for urinary alculi at the London Stone Clinic. Most received rimethoprim, and this was the only case of epidermal ecrolysis. In view of its widespread use doctors hould be aware that trimethoprim is capable of using toxic epidermal necrolysis.

diosyncratic reaction resembling toxic pidermal necrolysis caused by chloroquine nd Maloprim

Ir P A PHILLIPS-HOWARD (London School of Hygiene nd Tropical Medicine, London WC1E 7HT) and Dr J WARWICK BUCKLER (City Hospital, Nottingham) rite: Serious cutaneous reactions have been asso- iated with the combination of pyrimethamine and ulfadoxine (Fansidar) used for malaria chemopro- hylaxis.[1,2] We report a rare and severe idiosyncratic utaneous reaction to chloroquine and the combi- ation of pyrimethamine and dapsone (Maloprim).

A 59 year old white British man visited the Republic f South Africa in May 1986. He started a prophylactic egimen of chloroquine 300 mg (Nivaquine, May and aker Ltd) weekly and pyrimethamine 12·5 mg and apsone 100 mg (Maloprim, Wellcome Foundation td) one tablet weekly, taking both on the same day e days before he set off. Concurrent drugs were 1 g f aspirin and 40 mg of propranolol daily. He had aken these continuously for the past decade with no atoward effect.

Within 24 hours of arrival he developed bullous rythema on exposed skin areas. Symptoms resem- ling sunburn subsided over two to three days. A cond dose of the same regimen was taken one week ter the first. Within three to four hours he developed ant bullae affecting the soft palate, uvula, and iglottis. A single oral dose of 5 mg of dexamethasone as given to relieve oedematous swelling of his arynx.

Some of the lesions ulcerated and the skin exfoliated t large areas of the limbs and trunk. Nikolsky's sign as positive: superficial layers of skin could be bbed off with light pressure. There was severe situde and he felt feverish. The chemoprophylaxis as stopped after the second dose, but the skin anges took 10 days to resolve and left scars on e legs.

Inquiries to the drug companies found no similar ports, suggesting no association with batch impur- es. The clinical manifestations closely resembled xic epidermal necrolysis,[3] although it was not ssible to confirm the diagnosis by biopsy. No other ses attributed to prophylaxis with chloroquine and e combination of pyrimethamine and dapsone have en reported to the Committee on Safety of Medicines Britain (personal communication).

The temporal association strongly implicates alaria chemoprophylaxis, but the evidence about hich drug was the cause is incomplete. Patch testing as rejected because this would reflect only sensitis- ion to surface allergens, and prick testing was nsidered to be too dangerous. The patient had velled extensively and had taken the combination of rimethamine and dapsone on at least 20 previous casions without complication. This was, however, e first time he had taken chloroquine.

Serious cutaneous adverse reactions have been sociated with dapsone,[4] sulphonamides,[5] and loroquine[6] at high doses. Severe skin reactions to ophylactic doses are extremely rare. Recently, a case severe dapsone syndrome was attributed to the mbination of pyrimethamine and dapsone taken ce weekly in addition to chloroquine.[7] Toxic idermal necrolysis, with a positive Nikolsky's sign, s been reported during treatment with chloroquine ne.[8]

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Acyclovir malabsorption

Dr A MINDEL and Ms O CARNEY (Academic Department of Genitourinary Medicine, University College and Middlesex School of Medicine, London W1N 8AA) write: Little is known about the exact site of absorption of oral acyclovir, although it is presumed to be absorbed over the entire length of the small intestine. We recently saw a patient with recurrent genital herpes whose terminal ileum had been removed at surgery. She failed to respond to suppressive oral acyclovir in a dose up to 400 mg four times a day and was found to have malabsorption of the drug. Adequate therapeutic concentrations were obtained and the recurrences suppressed when the dose was increased to 800 mg four times a day.

A 22 year old woman presented in December 1986 with a history of recurrent genital herpes. Her attacks occurred every five to six weeks and each lasted five to 10 days. These had been occurring since mid-1985. In 1979 her appendix had been removed after several months of abdominal pain. In 1980 she presented with acute abdominal pain and was found to have small bowel obstruction due to adhesions. At surgery 0·6 m of terminal ileum was removed, although the ileocaecal valve was preserved. After surgery she complained of intermittent diarrhoea. In 1986 she had extensive gastrointestinal investigations. Her weight was constant and there was no evidence of malabsorption; albumin, folate, and vitamin B_{12} concentrations were normal. In February 1987 she was given suppressive oral acyclovir for recurrent genital herpes at a dose of 200 mg four times daily, but her recurrences continued with unchanged frequency and severity. In June the dose was increased to 400 mg four times daily, with little success. Her plasma acyclovir concentration was measured two hours after the last oral dose and found to be 0·32 μmol/l (normal 5·21 (SD 1·32) μmol/l—see table) (P D Whiteman *et al*, second international acyclovir symposium, 1983). We therefore increased the dose to 800 mg four times a day. At this dose the peak serum value was 3·34 μmol/l (normal 8·16 (1·98) μmol/l).[1] From August to December she had no recurrences and we reduced her dose to 800 mg twice daily; a few days later she had a breakthrough recurrence. She immediately returned to the higher dose and was subsequently free of recurrence.

Maximum plasma acyclovir values (μmol/l) taken two hours after last dose

Dose (mg)	Our patient	Experimental*
200 mg	Not measured	3·02 (0·50)
400 mg	0·32	5·21 (1·32)
800 mg	3·34	8·16 (1·98)

*Mean (SD) (P D Whiteman *et al*, second international acyclovir symposium, 1983).

Frequently occurring genital herpes may be controlled with suppressive oral acyclovir.[1-3] On 200 mg four times a day recurrences are rare and the few that occur will be minor and short lived.[1] If a patient fails to respond to treatment there are several explanations to be considered. Is the medication being taken; are the recurrences herpes or some other genital complaint—for example, candida; could the patient have a drug resistant strain (already reported in immunocompromised patients)[4]; and is the drug being absorbed? The possibility of poor absorption should be borne in mind particularly if the patient has had abdominal surgery. Our patient had no other obvious evidence of malabsorption. This suggests that acyclovir may be absorbed over only a very limited region of the bowel and that the problem may be overcome by increasing the total daily dose.

We thank Dr Lancaster-Smith from the Sloane Hospital in Kent for permission to report this case and Dr Holdich from the Wellcome Research Laboratories radioimmunoassay section, Beckenham, Kent, for measuring the serum acyclovir concentrations.

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Sterile abscess formation by continuous subcutaneous infusion of diamorphine

Drs P J HOSKIN and G W HANKS and Sister I D WHITE (Continuing Care Unit, Royal Marsden Hospital, Sutton, Surrey SM2 5PT) write: Continuous subcutaneous infusion of diamorphine and antiemetic drugs in patients with advanced cancer is generally free from complications apart from minor induration and erythema at the skin site.[1] We have observed a severe local reaction with sterile abscess formation at the site of infusion in two patients who received a subcutaneous infusion using a Graseby MS series syringe driver and a 25 gauge Vygon butterfly infusion set.

A 70 year old woman received aqueous diamorphine over 22 days in a dose increasing from 30 to 100 mg/h. Solutions of 60 to 222·5 mg/ml were infused at rates of 0·3 to 0·5 ml/h. Frequent changes of site were required (mean every 2·5 days, range 20 hours to 5 days) because of a severe reaction consisting of extensive induration and fluctuant swelling at the injection site. The site of infusion, concentration of diamorphine, and volume of infusate did not influence this reaction; nor did the addition of chlorpromazine or methotrimeprazine. Biopsy specimens taken from each of nine sites about 16 hours after death showed histological appearances typical of a sterile abscess. Swabs from fluid drained from each site grew only normal skin flora.

A 42 year old woman received aqueous diamorphine increasing from 83·3 to 200 mg/h. Solutions of 125 to 240 mg/ml were delivered at rates of 0·6 to 0·8 ml/h. Within 24 hours the infusion site became painful with erythema, induration, and a fluctuant mass. The site was changed to the opposite thigh, where a similar reaction developed. Fluid obtained from surgical drainage of the abscesses grew only normal skin flora.

The development of sterile abscesses after subcutaneous injection has been reported previously with chlorpromazine[2] (M Lacomme, May and Baker abstract No 54107, 1953). In the cases reported here simple aqueous solutions of diamorphine hydrochloride without preservative were used, and the addition of phenothiazines in the first case did not affect the reaction. The only common feature was the use of relatively high doses of diamorphine. This has previously been associated with increased local skin irritation[1,2] but not with abscess formation. The infusion system is commonly used and has not been associated with specific reactions. This idiosyncratic response to subcutaneous infusion of aqueous diamorphine is unusual. Early recognition of such complications and use, whenever possible, of the rectal route as the first alternative to oral treatment are recommended.

We thank Dr R L Carter for performing the histological examination.

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Br. J. Anaesth. (1988), **61**, 569–574

RELATIVE BIOAVAILABILITY OF CONTROLLED RELEASE MORPHINE TABLETS (MST CONTINUS) IN CANCER PATIENTS

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SUMMARY

The bioavailability of oral controlled release morphine tablets (MST, Napp Laboratories) and oral morphine sulphate in aqueous solution (MSS) was compared in 10 patients with advanced cancer. Serum samples were analysed for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) using a specific HPLC assay. The relative bioavailability of morphine with MST was significantly less than that with MSS (mean 80%, range 50–110%) although there was no difference between the formulations in the relative availability of M3G and M6G. There was no significant difference between the formulations in the serum concentration of morphine at 12 h. The mean ratios morphine:M6G:M3G (comparing areas under the serum concentration–time curves) were 1:9:56. There was a highly significant linear relationship between the dose administered and AUC for morphine, M3G and M6G after MSS; and for morphine after MST. Median t_{max} for morphine was 0.5 h with MSS and 2.5 h with MST; for M3G 1.5 h with MSS and 3.0 h with MST; and for M6G 1.5 h with MSS and 3.25 h with MST. A secondary peak of unconjugated morphine, which may represent enterohepatic circulation, was seen in several patients 2–4 h after administration of elixir and 4–6 h after administration of MST.

Controlled release morphine tablets (MST Continus, MS Contin, MOS Contin) are used widely in the treatment of cancer pain. Controlled clinical trial data are limited [1, 2] but suggest that, for the majority of patients, twice daily administration of MST is equivalent to a 4-hourly regimen of aqueous morphine. This is supported by empirical clinical experience.

Investigations of the absolute bioavailability of MST in single dose studies have produced conflicting results. In one study in healthy volunteers, the mean systemic availability of MST in the first 7 h after administration was 18.3% [3]. In contrast, in a study in patients, the bioavailability of MST was calculated to be 122% [4].

An important difference in the methodology used in the two studies is that the first utilized a high performance liquid chromatography (HPLC) assay to measure plasma concentrations of unconjugated morphine [5, 6], whereas the second used a radioimmunoassay (RIA) utilizing antibodies raised to 6-succinylmorphine BSA [7]. The HPLC assay is a specific and sensitive method enabling the quantitative measurement of morphine and its main metabolites morphine-3-glucuronide and morphine-6-glucuronide. The RIA used in the second study does not have the same specificity [8] and has been shown to cross-react with morphine-6-glucuronide [9].

An investigation of the steady state kinetics of MST in healthy volunteers (using an HPLC

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assay) indicated a bioavailability of 86% relative to morphine sulphate in aqueous solution [10]. This figure is consistent with data from our earlier study in postoperative patients [11].

There is increasing evidence to suggest that the clinical effects of morphine, in particular its analgesic action, may result from not only the action of morphine itself, but also that of active metabolites, in particular morphine-6-glucuronide (M6G) [12, 13].

We have investigated the relative bioavailability of MST in patients with advanced cancer stabilized on oral morphine sulphate in aqueous solution (MSS), using an HPLC assay to measure both morphine and its principal metabolites.

PATIENTS AND METHODS

Patients with advanced cancer who were inpatients in the Continuing Care (palliative care) Unit at the Royal Marsden Hospital and who had pain requiring oral morphine were studied if their pain was controlled on a 4-hourly regimen of oral morphine sulphate (MSS) in the same dose for at least 5 consecutive days. The MSS was morphine sulphate in chloroform water with ethylene diamine tetracetic acid and benzoic acid as preservative. The concentration of MSS varied, according to the dose being administered, between the limits of 10–60 mg in 10 ml.

Patients whose clinical condition was poor or whose pain was not stable were excluded, as were patients receiving high daily doses of morphine (> 1 g) who would require a large number of tablets. Full explanation of the aims of the study and the procedures involved was given before consent to participate was obtained from patients. The study was approved by the Ethics Committee of the Royal Marsden Hospital.

A cannula was inserted into a convenient forearm vein and the study was extended over a period of 3 days. On the first study day, patients continued their usual 4-hourly doses of MSS and blood samples were taken over a 12-h period from the 8 a.m. dose. Sampling was performed at time zero and at 30-min intervals for 5 h, and at 7, 8, 11 and 12 h. On each occasion 10 ml of venous blood was taken, rolled in glass bottles without anticoagulant for at least 20 min, centrifuged at 3500 rev min^{-1} and the serum separated and frozen immediately at −20 °C.

On the second day MSS was changed to MST, maintaining the same total daily dose in two equal parts. The final dose of MSS was given at 4 a.m. and the first dose of MST at 8 a.m. No blood samples were taken.

On the third day, blood samples were taken for a 12-h period following the 8 a.m. dose of MST, at the same times as on day 1.

On days 1 and 3, patients completed 10-cm visual analogue scales for pain intensity and pain relief at 8 a.m. and 8 p.m. and a four-point verbal rating scale for morphine-related side effects was completed each day.

Analytical method

Analysis of the samples was performed using an HPLC assay developed from the method of Svensson [5]. Extraction of serum samples was performed before analysis using multiple washings through two C18 SEP-PAK cartridges with a Vac-elute system. The chromatography used a 500-µl sample injected by autosampler. Detection of M3G was by u.v. fluorescence at 210 nm using an FS 970 LC Flurometer, and of morphine and M6G was by electrochemical detection using a two-channel detector and an additional guard cell. The intra-assay coefficient of variation using this assay was < 8% for morphine, < 6% for M3G and < 13% for M6G.

Statistical analysis

The area under the serum concentration–time curve (AUC) was calculated using STRIPE, an interactive curve stripping program [14]. Student's paired *t* test was used to compare assay techniques, AUC from the different preparations and visual analogue scale scores.

RESULTS

Ten patients were studied: six females (aged 60–79 yr, weights 35–90 kg) with cancer of the breast (three), lung (two) and colon (one); and four males (aged 44–72 yr, weights 65–102 kg) with cancer of the lung (two), kidney (one), and a soft-tissue sarcoma (one).

The dose range of morphine was 40–360 mg day^{-1} (0.7–5.5 mg kg^{-1}). All patients had normal renal and hepatic function.

The blood samples were timed to give an accurate estimate of a 4-h period of administration for morphine elixir and of a 12-h-period of administration for MST. In calculating the AUC for MST, therefore, the 12-h data were used, but for morphine elixir the AUC for only the first 4 h

TABLE I. *Twelve-hour cumulative area under the serum concentration–time curve (AUC_{12h}) for morphine. †95% Confidence interval 0.64–0.98. *Significant difference AUC MST v. AUC MSS (P = 0.05)*

Patient No.	12-h dose (mg)	AUC (ng h ml^{-1}) MSS	AUC (ng h ml^{-1}) MST	Relative Bioavailability (MST/MSS)
1	20	154	149	1.0
2	30	143	72	0.5
3	30	288	145	0.5
4	30	177	180	1.0
5	30	181	144	0.8
6	90	357	338	0.9
7	120	440	478	1.1
8	120	758	623	0.8
9	180	930	898	1.0
10	180	951	572	0.6
Mean				0.8*†

was calculated and multiplied by three for the purpose of comparison (table I).

There was a highly significant relationship between dose and AUC with both formulations: $r = 0.95$, $p < 0.001$ MSS; $r = 0.91$, $P < 0.001$ MST. However, the mean relative bioavailability of MST compared with MSS of 80% (range 50–110%) is significantly lower ($t = 2.5, P < 0.05$). There was no significant difference in serum concentrations of morphine produced by MSS and MST at 12 h.

The individual serum concentration–time curves for the 10 patients are shown in figure 1. A secondary peak in the concentration of unconjugated morphine is seen 2–4 h after administration of morphine elixir in patients Nos 1, 2, 3, 5, 6, 7 and 10. Similarly in the MST curves for patients Nos 3, 5, 8, 9 and 10 there appears to be a secondary peak 4–8 h after dosing.

Attenuation of the peak serum concentration (Cs_{max}) for morphine was seen after MST. The ratio of Cs_{max} after MST to Cs_{max} after MSS was 1.32 (SEM 0.13), while the dose ratio MST:MSS was 3. A similar effect was seen with the two metabolites, the mean ratio Cs_{max} MST:Cs_{max} MSS being 1.47 (0.26) for M3G and 1.25 (0.10) for M6G (table II).

Peak serum concentrations of morphine were achieved between 0.5 and 2 h after administration of morphine elixir (median 0.5 h) and at 0.5–4 h (median 2.5 h) after MST (table III).

For MSS there was a significant correlation between the AUC for both metabolites and dose of morphine (M3G: $r = 0.74$, $P < 0.01$; M6G: $r = 0.79$, $P < 0.001$) but this was not so for MST

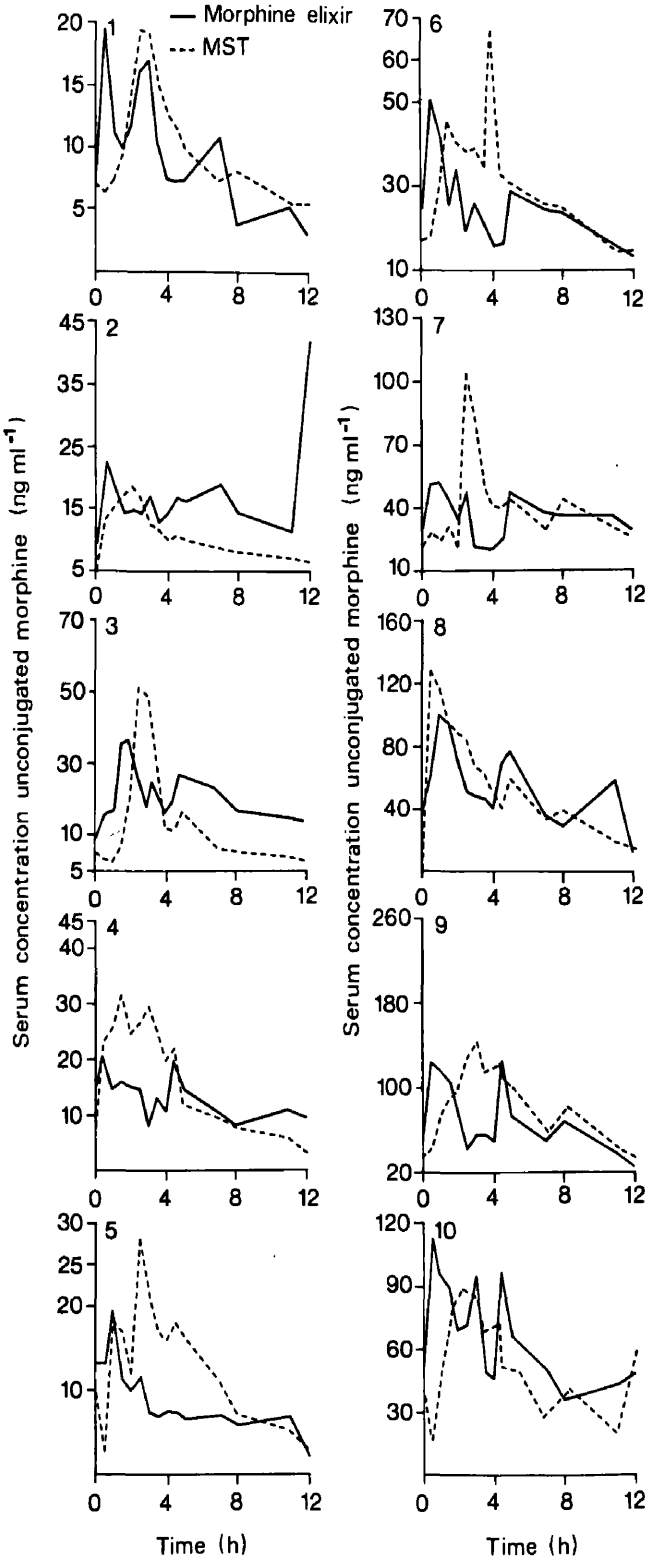

FIG. 1. Serum concentrations of unconjugated morphine in each patient. —— Morphine elixir; --- MST.

(M3G: $r = 0.32$; M6G: $r = 0.46$) (table IV). No significant difference between the formulations was seen in the relative bioavailability of either metabolite, although there was wide inter-individual variation.

TABLE II. *Peak serum concentrations (Cs_{max}) (ng ml^{-1}) for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)*

Patient No.	12-h dose (mg)	MSS			MST		
		Morphine	M3G	M6G	Morphine	M3G	M6G
1	20	19	477	72	26	855	114
2	30	19	426	59	15	1414	74
3	30	37	728	61	52	1139	77
4	30	20	1871	440	39	3395	527
5	30	26	827	145	28	782	189
6	90	50	2477	491	67	4481	718
7	120	51	2886	473	104	3300	539
8	120	97	3549	574	128	4498	907
9	180	122	3073	558	136	2080	649
10	180	115	3252	617	88	1409	336

TABLE III. *Time (h) to peak serum concentration (t_{max}) for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)*

Patient No.	MSS			MST		
	Morphine	M3G	M6G	Morphine	M3G	M6G
1	0.5	1.5	2.5	2.5	3.0	4.0
2	0.5	1.0	1.0	2.0	3.0	3.0
3	2.0	2.0	2.0	2.5	3.0	3.0
4	0.5	1.0	2.0	3.0	4.5	4.5
5	1.0	2.5	1.0	2.5	3.5	3.0
6	0.5	1.5	1.5	4.0	4.0	4.0
7	1.0	1.0	1.5	2.5	3.0	3.5
8	1.0	1.5	1.5	0.5	2.0	2.5
9	0.5	1.5	1.0	3.0	4.0	3.5
10	0.5	1.5	1.5	2.5	3.0	3.0
Median	0.5	1.5	1.5	2.5	3.0	3.25
Range	0.5–2.0	1.0–3.5	1.0–2.5	0.5–4.0	2.0–4.5	2.5–4.5

The values for the AUC corrected to a standard dose of morphine 100 mg are shown in table V. The mean ratios morphine:M6G:M3G were 1:9:56.

Analysis of the VAS ratings for pain and pain relief (table VI) showed no difference between the two study days, and there was no difference in the incidence or severity of adverse effects.

DISCUSSION

This study was primarily a pharmacokinetic investigation and was not blinded, so the ratings of pain intensity and pain relief should be interpreted in this light. However, MST appeared to provide equally good pain relief, as has been shown previously in both open and controlled

TABLE IV. *Twelve-hour cumulative area under the serum concentration–time curve (AUC_{12h}) and relative bioavailability for morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)*

Patient No.	12-h dose (mg)	AUC_{12h} (ng h ml^{-1})				Relative Bioavailability (MST/MSS)	
		MSS		MST			
		M3G	M6G	M3G	M6G	M3G	M6G
1	20	4695	701	5786	871	1.2	1.2
2	30	4041	456	9438	433	2.3	0.9
3	30	6890	546	8271	430	1.2	0.8
4	30	20784	4757	32069	4983	1.5	1.0
5	30	7503	1475	5185	1330	0.7	0.9
6	90	13589	3670	40828	6848	3.0	1.9
7	120	31963	4975	30700	4444	1.0	0.9
8	120	36771	5922	35314	6208	1.0	1.0
9	180	33181	5664	18973	5676	0.6	1.0
10	180	32791	6006	6888	1530	0.2	0.3
Mean						1.3	1.0
SEM						0.3	0.1

TABLE V. *Twelve-hour cumulative area (ng h ml^{-1}) under the serum concentration–time curve (AUC_{12h}) for morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) after dose correction to morphine 100 mg administered*

Patient No.	MSS			MST		
	Morphine	M3G	M6G	Morphine	M3G	M6G
1	770	23475	3505	745	28930	4355
2	477	13470	1520	240	31460	1433
3	960	22967	1820	483	27570	1433
4	590	69280	15857	600	106897	16610
5	603	25010	4917	480	17283	4433
6	397	15099	4078	376	45364	7609
7	367	26636	4146	398	25583	3703
8	632	30642	4935	519	29433	5174
9	517	18434	3147	499	10540	4730
10	528	18217	3337	318	3827	850
Mean	584	26323	4726	466	32689	5033
SEM	56	5064	1289	45	9026	1441

TABLE VI. *Visual analogue scales for pain (0 = no pain; 100 = worst possible pain) and pain relief (0 = no relief; 100 = complete pain relief). Mean (SEM) (mm)*

	Pain		Pain relief	
	8 a.m.	8 p.m.	8 a.m.	8 p.m.
Aqueous morphine	12.3 (3.0)	14.8 (3.7)	87.3 (4.2)	79.5 (6.5)
MST	10.3 (2.7)	14.1 (4.1)	86.8 (7.2)	81.4 (6.9)
t	1.220	0.498	0.064	1.032
P	> 0.2	> 0.5	> 0.5	> 0.2

studies [1, 2, 15, 16] in cancer patients. Similarly, there was no difference in side-effects.

The relative bioavailability of MST was measured 24 h after changing to this formulation. The time to achieve steady state is influenced by the absorption half-life, in addition to the elimination half-life, although the latter is the major determinant. We believe most patients will have achieved steady state by this time if they have already been stabilized on morphine elixir, as the elimination of morphine is not changed by this formulation.

Our pharmacokinetic data indicate that MST has a slightly lower systemic availability for morphine compared with MSS, although the relative amounts of the metabolites M6G and M3G produced by the two formulations was similar. These data, our clinical trial data [2] and those of others [1], refute the suggestion that MST may be more bioavailable [4, 17] and, therefore, relatively more potent than morphine in solution [18].

The results for M3G and M6G are of particular interest, since there are few comparable data in the literature. Sawe and her colleagues have demonstrated ratios of 1:24.4 for morphine:M3G and 1:2.5 for morphine:M6G after small single doses in cancer patients [19] and ratios of 1:34 and 1:3.9, respectively, in four patients after chronic use [20]. The corresponding ratios in this larger study were 1:56 and 1:9, which are considerably higher. We have suggested that M6G may contribute significantly to the analgesic activity of chronically administered oral morphine [12]. In our study similar amounts of M6G were produced by both MSS and MST. This may account for the equal efficacy of MST, although its bioavailability for unconjugated morphine appears to be slightly lower than that of MSS.

The median t_{max} for MST in the present study (2.5 h) is similar to figures obtained in healthy volunteers after single (2.4 h–2.7 h) [3] and repeated doses (2.3 h) [10]. Similarly, the median t_{max} for the solution of 0.5 h (range 0.5–2.0 h) is close to that found in healthy volunteers (0.8 h) [10] and in cancer patients (0.8 h) [19].

A recent investigation of the steady state pharmacokinetics of MST in healthy volunteers found a bioavailability of 86% relative to MSS [10]. The authors also found an "attenuation by 50% of the peak plasma morphine concentrations obtainable with controlled release morphine". We have shown a similar attenuation of peak serum concentrations following MST.

The secondary peak in the serum concentrations of unconjugated morphine in several patients is of considerable interest. It may represent enterohepatic circulation of morphine. This has been demonstrated clearly in rodents [21, 22] and we have recently shown high biliary concentrations of morphine, M3G and M6G in man [23]. A previous study (in healthy volunteers) showed a secondary peak in plasma concentrations of morphine 4–5 h after administration of MST [24]. In our data the secondary peak is seen most clearly in MSS curves between 2 and 4 h after dosing. We have suggested that enterohepatic circulation may be part of the explanation for the greater efficacy of repeated doses or oral morphine compared with single doses [12].

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