ABSORPTION OF CONTROLLED RELEASE MORPHINE SULPHATE IN THE IMMEDIATE POSTOPERATIVE PERIOD

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A controlled release formulation of morphine sulphate (MST Continus, Napp Laboratories) has been advocated as a postoperative analgesic agent (Fell, Chmielewski and Smith, 1982; Derbyshire et al., 1984) in those patients for whom an opioid agent is deemed necessary. In a previous study MST 20 mg, administered every 4 h, was shown to provide acceptable analgesia after hysterectomy or cholecystectomy (Derbyshire et al., 1985). However, the unexpectedly low serum morphine concentrations (mean 1.9 ng ml^{-1}) found 18 h after surgery led to concern that the decrease in gastric motility, which occurs commonly after anaesthesia and surgery, might have led to the accumulation of MST in the stomach. Anaesthetic techniques which use opioids are known to inhibit gastric emptying temporarily (Nimmo, 1984). Later "dumping" of any accumulated drug into the small intestine (from which it is absorbed) would then present a potential hazard.

The present study was designed to examine the absorption of MST immediately after a standard general anaesthetic technique and to compare the results with those obtained previously in healthy non-anaesthetized volunteers.

PATIENTS AND METHODS

Ten patients (mean age 72 yr (range 54–86 yr); mean weight 69 kg (range 59–84 kg)) undergoing peripheral arterial surgery for which arterial cannulation and intensive postoperative monitoring were deemed necessary were studied. Patients

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SUMMARY

The absorption of morphine sulphate, given orally as a controlled release preparation, was studied in 10 patients who had undergone peripheral vascular surgery with a standard opioid-based general anaesthetic technique. Serum morphine concentrations were measured (high pressure liquid chromatography) every 2 h for the first 16 h after surgery and the results were strongly suggestive of a decrease in the rate of absorption of morphine in this situation.

with significant preoperative pain, or who were receiving opioid therapy or who had a history of gastrointestinal pathology were excluded from the study.

All patients received a standard anaesthetic technique . Following premedication with diazepam 10 mg by mouth, sodium thiopentone 3 mg kg^{-1} was administered. Anaesthesia was maintained with 66% nitrous oxide in oxygen. Fentanyl was administered as necessary for the suppression of reflex responses, and controlled ventilation to normocapnia was facilitated by the administration of atracurium. The mean dose of fentanyl administered was 365 µg (range 300–450 µg).

After surgery the patients were prescribed MST 20 mg 4-hourly by mouth for analgesia. They were monitored (continuous ECG and direct arterial pressure recording) in the recovery suite for a period of 18–24 h.

Arterial blood was sampled every 2 h for 16 h. Time "zero" (control) was defined (for each patient) as the moment immediately before the administration of the first dose of MST. MST was administered once each patient could swallow adequately (in all patients this occurred within 30 min of the end of the operative procedure). Blood samples were allowed to clot and centrifuged

TABLE I. *Demographic details of the patients in the study*

Age (yr)	Weight (kg)	Procedure
59	60	Femoro–popliteal graft
70	59	Femoro–popliteal graft
64	84	Femoro–popliteal graft
73	80	Axillo–bifemoral graft
76	64	Femoro–popliteal graft
86	60	Femoro–femoral graft
54	68	Femoro–popliteal graft
80	74	Femoro–popliteal graft
79	70	Femoro–femoral graft
74	69	Femoro–popliteal graft

at 5000 rev min^{-1} for 15 min. The supernatant serum was extracted and frozen at $-70\ ^{\circ}C$ pending analysis for serum morphine concentration.

Serum morphine concentrations were measured by high pressure liquid chromatography (HPLC) with electrochemical detection (Aitkenhead et al., 1984). The lower limit of detection of this assay is 1 ng ml^{-1}, and the coefficient of variation is less than 5%. The assay is specific to "free" morphine and does not measure the glucuronides of morphine, which are extracted into aqueous solution before chromatography.

RESULTS

Demographic details of the patients and the procedures undertaken are shown in table I. Figure 1 represents a plot of mean serum morphine concentrations against time for the first 16 h after surgery in nine patients. No morphine was detected in the control samples. Thereafter, serum morphine concentrations increased from a mean of 1.7 ng ml^{-1} at 2 h to a mean of 12.4 ng ml^{-1} at 14 h. There is clearly a delay in the increase in serum concentrations over this period in comparison with the pattern seen from another study in volunteers (who had not undergone surgery and anaesthesia) who received MST 20 mg as a single dose (Vater et al., 1984).

Each patient was questioned hourly by the recovery suite nursing staff as to whether or not he was in pain. Although nine patients questioned thus had adequate analgesia, the respective serum morphine concentrations were considerably lower than the 50 ng ml^{-1} which has been suggested as the value providing postoperative analgesia (Berkovitz et al., 1975) in studies in which morphine was measured by radioimmunoassay techniques. However, in a study by Dahlstrom and
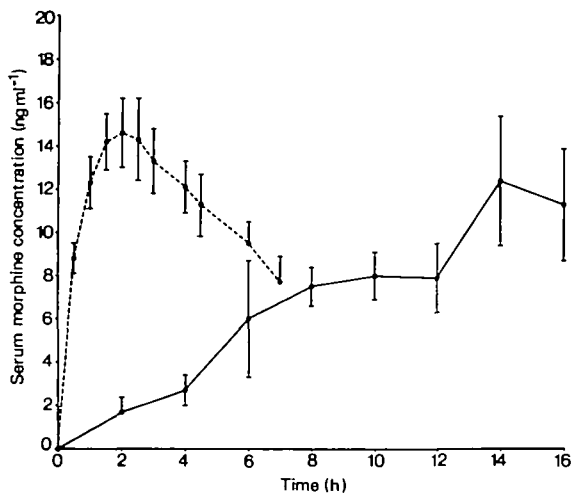

FIG. 1. Serum morphine concentrations in patients given MST 20 mg every 4 h by mouth, commencing at time 0 (o——o) following peripheral vascular surgery (mean ± SEM, n = 9). For comparison data from Vater and colleagues (1984) are also plotted (o---o), showing the profile of serum morphine concentrations in volunteers following a single dose of MST 20 mg (mean ± SEM, n = 11).

colleagues (1982) the minimum effective analgesic concentration for morphine (plasma values measured by HPLC) was 16 ng ml^{-1}.

The single patient who complained of pain had vomited after each dose of MST and the measured serum morphine concentrations in this patient were consistently less than 2 ng ml^{-1}. Analgesia was supplemented by fentanyl i.v. in this individual and the serum morphine concentrations have been omitted from the data shown in figure 1.

Although the nursing staff received instructions to omit a scheduled dose of MST if they considered the patient to be excessively sedated, this was not necessary in any patient throughout the first 24 h of the postoperative period (when strong analgesic drugs are usually required).

DISCUSSION

The pattern, displayed in figure 1, of a slow and delayed increase in serum morphine concentrations is strongly indicative of a delay in the absorption of MST—especially in the period immediately after operation.

In the study by Vater and colleagues (1984) in which starved volunteers received a single dose of 20 mg MST, the mean peak plasma morphine

concentration was 14.8 ng ml^{-1} and occurred within a mean 143 min of administration. The serum morphine concentration–time data from those volunteers have been plotted in figure 1 (dashed line) for comparison with the present data. In a more recent study of 29 volunteers given MST 30 mg the mean peak serum morphine concentration was 11.6 ng ml^{-1} and occurred at a mean time of 120 min following administration (Pinnock, Derbyshire and Aitkenhead, unpublished observations). In both these studies, morphine concentrations were measured using the same HPLC technique as in the present study (Aitkenhead et al., 1984). Thus the pattern shown for patients given MST 20 mg every 4 h contrasts sharply with the early peak and decay seen following a single dose of MST 20 mg in volunteers who had not undergone anaesthesia and surgery.

It is well documented that anaesthesia utilizing opioid drugs may cause a temporary inhibition of gastric emptying (Nimmo et al., 1975; Nimmo, 1976). In contrast, there is little effect on gastric motility, following anaesthesia for minor procedures, when opioids are not used (Reilly and Nimmo, 1984).

It seems reasonable to postulate, therefore, that intestinal motility was decreased in the patients examined in the present study following the i.v. administration of fentanyl. In addition, it should be emphasized that the majority of patients undergoing major surgery will normally receive opioids i.v. during the course of anaesthesia. Park and Weir (1984) demonstrated in healthy volunteers that MST *per se* has little effect on gastric emptying (whereas morphine i.m. may cause a considerable reduction) as assessed by the measurement of plasma paracetamol concentrations. This may be accounted for by the difference in plasma concentrations of morphine produced by the two different routes of administration. In the study of Park and Weir (1984) the oral MST administered to healthy volunteers was associated with a "normal" profile of plasma concentrations of morphine and a mean peak of around 6 ng ml^{-1}, whereas the i.m. route of administration was associated with a peak plasma concentration of approximately 30 ng ml^{-1}.

In the absence of physical obstruction to the gastric outlet (such as pyloric stenosis) opioid analgesic drugs are the major cause of delayed gastric emptying in the preoperative period (Nimmo, 1984). The results of the present study

would appear to provide evidence supplementary to that of Derbyshire and colleagues (1985) suggesting that the rate of absorption of MST in the early postoperative period is reduced following anaesthesia comprising a nitrous oxide in oxygen–neuromuscular blocker–opioid sequence.

A corollary of this statement is that, when normal gastric activity resumes, passage of accumulated MST into the small intestine may lead to excessively high blood concentrations of morphine, particularly if the period of gastric stasis is prolonged and oral administration of the drug is continued. Such a situation may be most likely to occur in a patient who has undergone intra-abdominal surgery following which the incidence of paralytic ileus is high. Whilst many factors are of importance in the aetiology of gastric stasis following surgery, the risk of accumulation of MST within the stomach followed by later absorption may be seen to be of relevance, independent of the precise mechanism underlying the inhibition of gastric transport.

The absorption of a substantial amount of morphine into the systemic circulation following regular administration of MST to a patient with gastric stasis is obviously hazardous. Estimates of the systemic bioavailability of MST have been quoted between 18 % (Vater et al., 1984) and 100 % (McQuay et al., 1983) and thus it is difficult to predict for any one individual the dose of MST which would lead to excessive blood concentrations should gastric stasis and "dumping" occur. Attention has already been drawn to the death of a patient following the use of MST for postoperative pain relief (Brahams, 1984). Thus, extreme caution must be advocated in the use of MST in the early postoperative period. However, it should be noted that, in the present study, the later postoperative course of these patients was uneventful. No patient exhibited excessive drowsiness as might have been expected if "dumping" of accumulated MST was occurring.

Although consideration of the quality of analgesia was beyond the scope of this study, it is noteworthy that in the second 24-h period after surgery only two patients required further analgesia (this was a single dose of morphine sulphate 10 mg i.m.).

The intraoperative consumption of fentanyl in all 10 patients was modest (mean 365 µg, range 300–450 µg). It is surprising, therefore, that satisfactory analgesia was achieved at low serum morphine concentrations and it is tempting to

speculate that this may be related to the biotransformation of morphine administered by mouth. All patients had evidence of partial absorption of MST as shown by detectable serum morphine concentrations from 2 h onwards. One significant breakdown pathway of morphine is by hepatic conjugation. A major metabolite from this pathway is morphine-3-glucuronide, which is not known to possess any analgesic properties. A smaller proportion of the administered dose is conjugated to morphine-6-glucuronide (M6G). M6G is thought to be three times as potent as an analgesic as free morphine and it is possible that an element of the analgesia seen in these patients is related to M6G.

(NOTE: The revised data sheet for MST Continus from Napp Laboratories does not recommend the use of MST in the early postoperative period.)

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