GASTRIC EMPTYING AND DRUG ABSORPTION

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A thesis submitted for the
degree of Doctor of Medicine
of the University of Edinburgh

April 1982

PREFACE

The work described in this thesis was carried out in the Department of Therapeutics and Clinical Pharmacology, Royal Infirmary, Edinburgh. It has not been submitted for any other degree to any university. The thesis was composed entirely by the author. All the work described was designed and carried out by the author unless otherwise stated. Full acknowledgement has been made where the work of others has been used. Several publications are included in support of this thesis.

Walter S. Nimmo

ACKNOWLEDGEMENTS

I express my gratitude to Professor R.H. Girdwood in whose department this work was carried out and to the members of his staff who participated in the studies.

I am especially grateful to Dr. L.F. Prescott for his continuous guidance and encouragement. I acknowledge the help of Dr. R.C. Heading and Dr. P. Tothill who collaborated on the gastric emptying measurements and of Dr. J.A. Clements of Heriot Watt University who carried out the computer pharmacokinetic analysis. I am grateful for the technical assistance of Mrs. I. Darrien and Mr. I. King who carried out 20% of the paracetamol analyses.

I am indebted to the consultant obstetricians of the Simpson Memorial Maternity Pavilion, Edinburgh and to Dr. J. Wilson, consultant anaesthetist, for permission to study patients under their care.

I thank Mrs. J. Buttar who typed this thesis.

To my brother, John, for his early contribution and to my wife, Moyra, for her patience and encouragement go my deepest appreciation.

LIST OF PUBLICATIONS SUPPORTING THIS THESIS

1. Narcotic analgesics and delayed gastric emptying during labour.
Nimmo, W.S., Wilson, J., Prescott, L.F.
Lancet, 1, 890-893 (1975)

2. Inhibition of gastric emptying and drug absorption by narcotic analgesics.
Nimmo, W.S., Heading, R.C., Wilson, J., Tothill, P., Prescott, L.F.
British Journal of Clinical Pharmacology, 2, 509-513 (1975).

3. Gastric emptying following hysterectomy with extradural analgesia.
Nimmo, W.S., Littlewood, D.G., Scott, D.B., Prescott, L.F.
British Journal of Anaesthesia, 50, 559-561 (1978).

4. The influence of posture on paracetamol absorption.
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5. Kinetics of acetaminophen absorption and gastric emptying in man.
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7. Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone.
Nimmo, W.S., Heading, R.C., Wilson, J., Prescott, L.F.
British Medical Journal, 2, 1189 (1979).

ABSTRACT OF THESIS (Regulation 6.9)

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Title of Thesis GASTRIC EMPTYING AND DRUG ABSORPTION

Since drugs are not absorbed to any extent from the stomach but are absorbed from the small intestine, the rate of gastric emptying will influence the rate of absorption of most drugs given by mouth. Paracetamol has been used as a model drug in absorption studies in this thesis. It is absorbed very rapidly from the upper small bowel and its rate of absorption correlates well with the rate of gastric emptying measured simultaneously.

A variety of physiological, pharmacological and pathological factors have been shown to influence gastric emptying and in turn paracetamol absorption. In clinical situations in which direct measurement of gastric emptying was impracticable the rate of paracetamol absorption was used as an indirect measure of gastric emptying rate. In women during labour (when delayed gastric emptying results in increased risk of regurgitation of gastric contents at induction of anaesthesia) it was shown that labour itself produced only a slight delay in gastric emptying while narcotic analgesics produced a marked delay which was not influenced by metoclopramide. Extradural analgesia had little effect. Similar results were obtained in patients in the postoperative period. The narcotic induced delay in gastric emptying was partially reversed by naloxone.

A pharmacokinetic model was designed in which the gastrointestinal tract was represented by two compartments (one for the stomach and one for the small intestine). The true rate constant for transfer of paracetamol from the lumen of the small bowel to the systemic circulation was calculated.

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CHAPTER 1.

INTRODUCTION

Most drugs are administered orally and there may be great intra and inter-individual variation in the rate and completeness of absorption. This variation is rarely acknowledged and has been minimised or "swept under the carpet" by the use of pooled data in drug absorption profiles. As a result, the mechanisms of variability of absorption remain poorly understood.

However, the stomach is not an important site of drug absorption. The established belief of the pH partition theory that weak acids are significantly absorbed from the stomach has not been confirmed by more recent studies and many deviations from the predicted results of this theory have been reported. For example, phenobarbitone (pKa 7.2) and pentobarbitone (pKa 8.1) are weak acids and should be more rapidly absorbed from the stomach than from the small intestine. The reverse is true, however, and in a study in rats, more than twice as much was absorbed by the small intestine in 10 minutes than was absorbed from the stomach in 1 hour (Figure 1.1 Magnussen, 1968). This difference simply reflects the complex nature of the overall process of

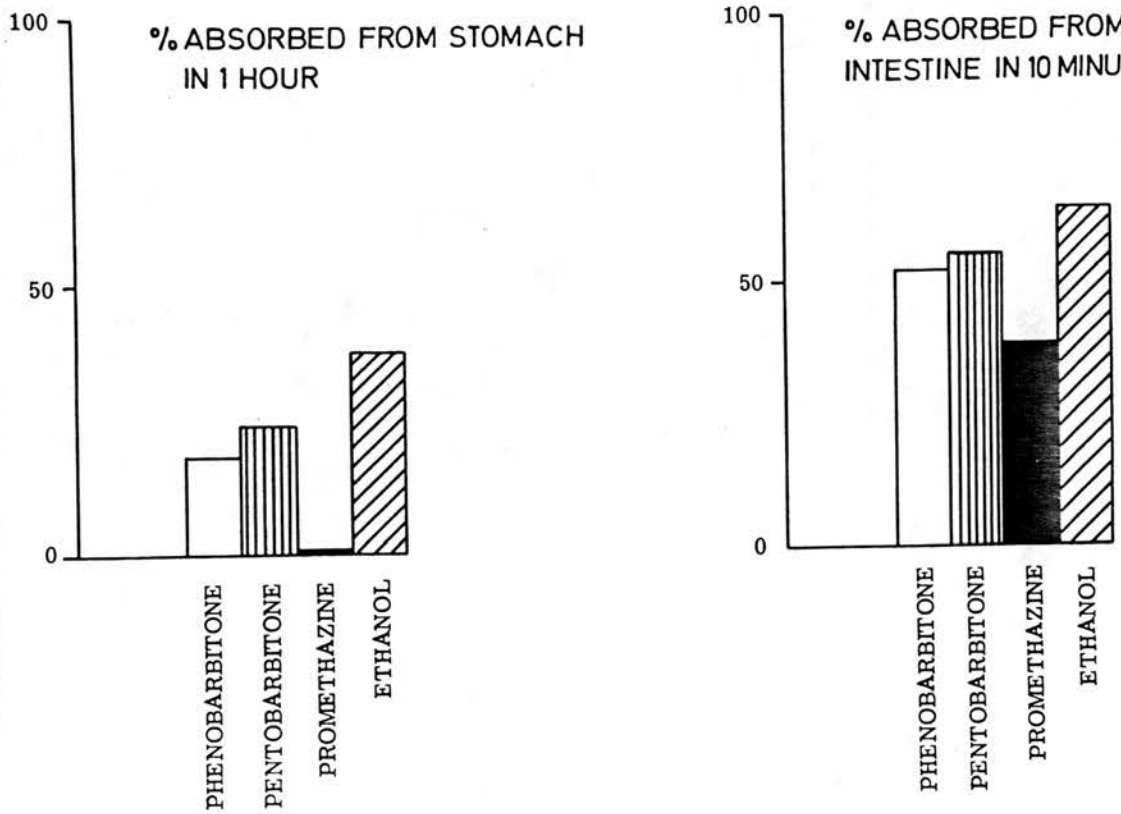


FIGURE 1.1

Comparison of absorptive capacity of stomach and small intestine in rats. Data from Magnussen 1968.

absorption and it is likely that the much greater surface area of the intestinal mucosa relative to that of the gastric mucosa more than compensates for the potentially reduced rate of absorption per unit area of intestine (Levine, 1970). The absorption of ethanol which is independent of pH, was also more rapid from the small bowel than from the stomach as predictably was promethazine, a basic drug. Similar results have been obtained in human subjects for aspirin, digitoxin and warfarin (Siurala et al, 1969; Beermann et al, 1971; Kekki et al, 1971).

Other evidence of the fallibility of the pH-partition theory as applied to gastric absorption is shown in a study of aspirin absorption in normal subjects and achlorhydric patients. An increase in the pH at the absorption site should decrease the absorption of a weak acid since the proportion of unionised drug is decreased. The reverse is true, however, and aspirin was absorbed more rapidly than normal in achlorhydric patients. The most likely explanation for this enhanced absorption is the increased solubility of aspirin in the achlorhydric stomach (Pottage et al, 1974).

Thus the rate of gastric emptying markedly influences the rate at which drugs are absorbed

irrespective of whether they are acids, bases or neutral compounds (Levine, 1970; Prescott, 1974a). It follows that any factor which influences gastric emptying rate will influence the rate of absorption and onset of action of an orally administered agent.

As a result of slowed gastric emptying, the rate of drug absorption may be reduced, or absorption may be incomplete, resulting in therapeutic failure or delayed response. On the other hand, if gastric emptying is accelerated, rapid drug absorption can theoretically increase the risk of drug toxicity but there is little, if any, data on this point. A change in the rate of absorption of long acting drugs such as warfarin or digoxin will have little or no effect whereas a change in the total amount absorbed may result in toxicity. Slow absorption of drugs with a short biological half-life such as procainamide or penicillin may result in sub-therapeutic tissue concentrations. In any situation in which drug effects are required rapidly, slow absorption will defeat the object of treatment.

There are many drugs and diseases which influence gastro-intestinal motility and affect the absorption of orally administered drugs. For example, Hercule Poirot, solving "The Mysterious Affair at Styles"

(Agatha Christie, 1920) was aware that narcotic analgesics delayed the absorption of the fatal dose of strychnine given to the victim (presumably by delaying gastric emptying) thus describing one of the earliest known drug absorption interactions. The introduction to this thesis describes some of the factors controlling the rate of gastric emptying in man, how this is influenced by drugs and disease and how this affects the absorption of orally administered drugs.

1.1 PHYSIOLOGICAL CONTROL OF GASTRIC EMPTYING

The stomach receives and stores food, mixes it with its own secretions and delivers the mixture to the duodenum at an appropriate controlled rate. The greater part of the emptying process is a simple exponential function of the volume of gastric contents (Hunt and Spurrell, 1951; Hunt and McDonald, 1954; Hopkins, 1966) but there is an initial component (during the first few minutes after a meal) when disproportionately rapid or slow emptying occurs (Colmer et al, 1973). Liquids are emptied faster than solids (James, 1957; Dozois et al, 1971 a) but the volume of the gastric contents is an important regulating factor and gastric distension is the only natural stimulus known to increase the rate of gastric emptying (Hunt and Knox, 1968 a).

Continuous electrical activity is manifest in the stomach as gastric slow waves. They represent the electrical control activity and they occur maximally at a rate of three per minute. They may be associated with intermittent secondary electrical responses which result in antral contractions (Edwards and Rowlands, 1968) and therefore they establish the frequency, velocity and direction of peristalsis (Kelly and Code, 1971).

The rate of the gastric slow waves and therefore the antral contractions is influenced by various physiological stimuli via local and distant nervous reflexes as well as by hormones but the actual mechanisms are not known. For example, the presence of acid (Hunt and Knox, 1968 a; 1969; 1972), fat (Roberts, 1931; Tidwell and Cameron, 1942; Menguy, 1960; Hunt and Knox, 1968 b), increased osmotic pressure (Hunt and Knox, 1968 a; Hunt and Pathak, 1960) and amino acids (Thomas and Crider, 1939; Cooke and Moulang, 1972) in the duodenum delay gastric emptying. It is known that there are receptors in the duodenum activated by these substances but it is unclear whether the delay is mediated by neural or hormonal mechanisms or by both. Cooke (1974) has suggested that acid in the duodenum slows gastric emptying by a neural mechanism because of the

rapidity of onset of the inhibition. The rate of gastric emptying is also influenced by the "energy density" of food (Hunt et al, 1975). People eating an energy dense mixture of food may empty their stomach more rapidly and therefore eat more than those who take their energy in more dilute form.

Gastrin (Cooke et al, 1972; Dozois and Kelly, 1971 b; Hunt and Ramsbottom, 1967), secretin (Chvasta and Cooke, 1973) and cholecystokinin (Chey et al, 1970) all delay gastric emptying and glucagon inhibits gastric motility (Necheles et al, 1966). Although gastrin delays gastric emptying, it increases antral motor activity and this apparent paradox may be due to inco-ordination of movements of the antrum and the proximal duodenum (Weisbrodt et al, 1969). However, it is doubtful if these hormones have a physiological role in the control of emptying (Cooke, 1975).

The pyloric sphincter may be of secondary importance in the normal control of gastric emptying rate (Thomas, 1957) but it relaxes with peristalsis, contracts in response to acid, fat, amino acids and glucose and it prevents duodenal reflux (Fisher and Cohen, 1973). If the distal antrum and pylorus are removed surgically, the emptying of solids is

accelerated but there is a smaller effect on emptying of liquids (Dozois et al, 1971 a).

In neonates, the stomach empties more rapidly in the prone and right lateral positions than in the supine and left lateral positions (Yu, 1975). There is no difference in the gastric emptying rate in term, preterm or small-for-dates babies and in adults there is no correlation of emptying rate with age (Halvorsen et al, 1973).

Thus, in health, the rate of gastric emptying may depend on factors such as autonomic and hormonal activity, posture, the volume, composition, tonicity and pH of the stomach contents. It is also influenced by many commonly used drugs, bile salts, surface active agents (Hunt, 1975) and by disease.

1.2 PATHOLOGICAL INFLUENCES ON GASTRIC EMPTYING RATE

Diseases which modify the rate of gastric emptying may be classified as extrinsic (extragastric) or intrinsic (intragastric).

1.2.1 Extrinsic factors

There are little data that demonstrate

conclusively the effects of extragastric disease on the rate of gastric emptying. Many reports are no more than anecdotal or merely hypothesis and in only a few situations have gastric emptying measurements been carried out. However, peritoneal irritation from any cause is usually associated with decreased peristalsis and retention of gastric contents. Thus, perforation of a peptic ulcer, appendicitis, pancreatitis, retroperitoneal haematoma, haemaperitoneum, ruptured spleen and subphrenic abscess may all be associated with gastric distension and, by inference, delayed gastric emptying (Rimmer, 1966). Gastric emptying is delayed following severe trauma (Howells et al, 1971), laparotomy (Dudley, 1975), head injury (Rimmer, 1966), myocardial infarction (Pottage et al, 1978) and in women during labour (Davison et al, 1970; Howard and Sharp, 1973) but in most of these conditions it is difficult to differentiate the effect on emptying of the disease itself and the possible effects of drugs administered to the patients. In dogs, trauma to the limbs resulted in decreased gastric motility (Zaricznyj et al, 1977). There is, however, a significant increase in the rate of gastric emptying in patients with chronic calcular cholecystitis (Van Dam, 1972) and

emptying is apparently normal three months after cholecystectomy. Various other conditions such as hepatic coma, hypercalcaemia, diabetes mellitus, myxoedema and malnutrition (Rimmer, 1966) are said to delay gastric emptying.

From a study of diazepam absorption in subjects with a high neuroticism index compared with those with a low neuroticism index, gastric emptying appears to be more rapid in the former (Nakano et al, 1980).

On the basis of aspirin absorption studies, it has been claimed that migraine produces a significant delay in gastric emptying (Volans, 1974). After 900 mg of effervescent aspirin the mean plasma salicylate at 30 minutes in 35 patients during an attack of migraine was only 4.97 $\pm$ 0.52 mg/100 ml compared with a value of 7.11 $\pm$ 0.59 mg/100 ml ($\pm$ SE) in 14 patient controls. Impairment of absorption seemed to correlate with the severity of the headache and the gastrointestinal symptoms at the time of treatment. Evidence from a radiological study also suggests that delayed gastric emptying associated with gastric contraction occurs in patients with headache (Kreel, 1973). It is likely that any severe pain (e.g. renal colic)

may retard the passage of gastric contents into the duodenum (Crohn, 1927; Eusterman and Balfour, 1935) but no convincing data are available on this point.

Delayed gastric emptying, demonstrated by radiological studies, has been associated with brain tumour with raised intracranial pressure, hypercalcaemia, hypocalcaemia, iron deficiency anaemia, pancreatitis, retroperitoneal haematoma, post operative immobilisation and gastric ulcer (Rimmer, 1966). Although only one case of each condition (except gastric ulcer) was described, many pathological factors seem to delay gastric emptying and hence have the potential to delay the absorption of orally administered drugs. However, radiological measurements of the rate of gastric emptying can only be approximate (Griffith et al, 1966) and the contrast medium itself, because of its density, might affect the emptying rate (Hunt and Knox, 1968 a).

1.2.2 Intrinsic factors

Atrophic gastritis is a common condition in which delayed gastric emptying has been reported, and marked gastric stasis was observed in patients with gastric carcinoma (Davies et al, 1971). The

well known association of atrophic gastritis and gastric carcinoma may conveniently be explained by the delayed gastric emptying in the former condition which allows prolonged contact between dietary carcinogens and the gastric mucosa. Conversely, gastric carcinoma is rare in patients with duodenal ulcer who may have a rapid rate of emptying (Griffith et al, 1968). Bromster (1969), using I^{131} and a scanning technique, demonstrated delayed gastric emptying of a solid meal in patients with pernicious anaemia (who normally have achlorhydria and atrophic gastritis) but Halvorsen et al (1973) found an increased rate in patients with achlorhydria using dilution of 750 ml of water and a nasogastric tube for the emptying measurements. One interpretation of these apparently contradictory findings is that gastric emptying of liquids is rapid in achlorhydria while emptying of solid meals is delayed. On the other hand in another study gastric emptying of liquids in achlorhydric patients did not seem to differ significantly from controls (Pottage et al, 1974).

Not surprisingly, gastric emptying is delayed in pyloric stenosis (Signer and Fridrich, 1975). Sixty-one enteric coated aspirin tablets were recovered from the stomach of a woman with rheumatoid

arthritis who had developed pyloric stenosis (Harris, 1973). Also it seems likely that emptying is delayed by any condition that produces nausea or vomiting (Kreel, 1973).

Vagotomy itself disorganises the pattern of gastric emptying (Kelly and Code, 1969) and after vagotomy and pyloroplasty, there is often a rapid "dump" of a large part of an ingested meal from the stomach into the duodenum. Thereafter, the rate becomes exponential and similar to that observed before the operation (Colmer et al, 1973). This initial "gastric incontinence" occurs after both proximal gastric and selective vagotomy, but thereafter the emptying of a liquid meal is delayed by selective vagotomy but is unaffected by proximal gastric vagotomy (Donovan et al, 1974). Diabetic autonomic neuropathy may significantly delay gastric emptying (Rimmer, 1966) as well as changing the normal pattern of emptying (Campbell et al, 1977).

1.3 DRUGS AND GASTRIC EMPTYING

Many drugs may alter the rate of gastric emptying (and in turn influence the absorption of other orally administered drugs) either by effects on the smooth muscle or by influencing the release of

intestinal hormones which modulate gastric activity. From basic pharmacology it seems likely that atropine and anticholinergics, antihistamines, tricyclic antidepressants, phenothiazines, sympathomimetics, anti-Parkinson drugs, antihypertensive agents, nitrates, anticholinesterases, prostaglandins, hypnotics, sedatives, anaesthetic agents and antacids will influence gastric motility and emptying (Prescott, 1974 a and b) but there are few studies in man to demonstrate the magnitude and significance of the effects.

In drug interaction studies in man, compounds with anticholinergic activity such as atropine (Adjepon-Yamoah et al, 1973; Wing et al, 1979), tricyclic antidepressants (Consolo et al, 1970), trihexyphenidyl (Rivera-Calimlim et al, 1973), propantheline (Nimmo et al, 1973), methyl atropine nitrate (Berkowitz et al, 1964) and ganglion blocking drugs such as hexamethonium (Ettman et al, 1957) produced effects which were attributed to reduced gastric motility and gastric relaxation. Morphine and other narcotic analgesics increase the tone of the gastro-intestinal smooth muscle and interfere with normal peristalsis (Daniel et al, 1959; Burks and Long, 1967; Cairnie, Kosterlitz and Taylor, 1961). They also delay gastric emptying

(Crone and Ardran, 1957).

Ions such as aluminium, lanthanum and potassium delay gastric emptying (Hurwitz and Sheehan, 1971; Hurwitz and Schlozman, 1974; Hunt and Pathak, 1960). The action of aluminium in rats greatly exceeds the gastric retention observed after atropine and is shared by dissociable aluminium salts but not by magnesium or calcium. The effects of other ions on gastric emptying is unclear but it is likely that ferrous, lead and barium ions also exert an influence.

Antacids influence the rate of gastric emptying as a result of changing the pH of the gastric contents as well as by the effect of the metal ions on the gastric muscle and it is difficult to separate these two actions. Magnesium hydroxide has a less pronounced and more variable effect on gastric emptying than aluminium hydroxide (Hurwitz and Schlozman, 1974) whereas solutions of sodium bicarbonate leave the stomach more rapidly than plain water (Shay and Gershon-Cohen, 1934).

Alcohol delays the gastric emptying of glucose (Tennent, 1941; Greenberg et al, 1942) fat and protein meals (Barboriak and Meade, 1969) in the rat and this delay is dose dependent. Using

chromium^{51} as a non-absorbable isotopic marker and sequential scintiscanning to measure gastric emptying, Barboriak and Meade (1970) demonstrated that 120 ml of whisky delayed the gastric emptying of a standard meal in volunteers.

Other agents such as iproniazid (Leijnse and Praag, 1964) sodium nitrite (Sleeth and Van Liere, 1941) and chloroquine (Varga, 1966) delay gastric emptying by as yet undetermined mechanisms. Dioctyl sodium sulphosuccinate is a surfactant which slows emptying possibly by promoting the release of enterogastrone upon contact with the duodenal mucosa (Lish, 1961). Foodstuffs may also affect gastric motility by influencing the secretion of gastro-intestinal hormones (Cooke, 1975). Sedatives and anaesthetic agents might be expected to delay emptying and indeed phenytoin diminishes spontaneous activity in the gastro-intestinal smooth muscle in animals (Woodbury, 1969) and may delay gastric emptying in man (Ahmad, 1974). Numerous toxic substances when swallowed delay gastric emptying and produce nausea and vomiting. Thus control of emptying of the stomach would appear to be a teleological safety mechanism with a protective role to prevent absorption of an ingested undesirable chemical.

Fewer drugs are known to increase gastric emptying rate. Metoclopramide is chemically related to procainamide and increases the rate of gastric emptying and intestinal transit (Robinson, 1973). As well as gastro-intestinal actions it has a central anti-emetic effect and has now assumed the role of a gastro-intestinal panacea. It has no effect on gastric secretion and its mode of action may be to sensitise gut muscle to the action of endogenous acetylcholine (Connell and George, 1969; Eisner, 1971). The effects on gastric emptying are best seen when there is marked duodenal motor activity with weak antral contractions (Weisbrodt et al, 1969). Reserpine stimulates gastric emptying and also increases gastric acid secretion (Leibowitz and Carbone, 1957). Cigarette smoking also accelerates gastric emptying (Grimes and Goddard, 1978).

1.4 GASTRIC EMPTYING AND DRUG ABSORPTION

Drug absorption is greatly influenced by gastro-intestinal motility. Absorption from the stomach is very slow, irrespective of pH and whether the drug is acidic, basic or neutral. Therefore, unless absorption by the small bowel is normally very slow, the rate of gastric emptying

can be the rate limiting step and absorption will be influenced by all the factors described above and summarised in Table 1.1.

The clinical significance of delayed or slow absorption depends on the circumstances. It may be important if rapid onset of action is required or if elimination is so rapid that effective plasma concentrations cannot be achieved. Also, drugs such as L-dopa, methyl digoxin and penicillin are metabolised or degraded in the stomach and if emptying is delayed, the amount of active drug available for absorption is reduced (Prescott, 1974 b). L-dopa is absorbed in the small intestine by active transport and absorption is rapid when the drug is introduced directly into the duodenum or in patients following gastrectomy (Bianchine et al, 1971). A drug is usually more rapidly absorbed when given in solution rather than in tablet form. The greater the original volume of the solution distending the stomach, the more rapid is gastric emptying while, with a few exceptions, the more concentrated the solutes in the gastric contents, the slower is emptying (Hunt, 1963). Absorption of a drug is more rapid and toxicity is greatly increased in rats when a drug is given orally in the same dose but in dilute rather than concentrated solution and

TABLE 1.1 FACTORS WHICH INFLUENCE THE RATE OF GASTRIC EMPTYING

	Gastric emptying rate	
	Increased	Decreased
(a) Physiological factors		
Liquids	+	
Solids		+
Acid		+
Fat		+
Increased osmotic pressure		+
Amino acids		+
Gastric distension	+	
Physiological role uncertain: Gastrin		+
Physiological role uncertain: Secretin		+
Physiological role uncertain: Cholecystokinin		+
Physiological role uncertain: Glucagon		+
Posture (prone or R side)	+	
Energy density of food	+	
(b) Pathological factors		
Acute abdomen		+
Chronic calcular cholecystitis	+	
Laparotomy		+
Trauma and pain		+
Labour		+
Myocardial infarction		+
Gastric ulcer		+
Duodenal ulcer	+	
Hepatic coma		+
Hypercalcaemia		+
Diabetes mellitus		+

	Gastric emptying rate	
	Increased	Decreased
Myxoedema		+
Malnutrition		+
Migraine		+
Raised intracranial pressure		+
Atrophic gastritis		
- solids		+
- liquids	+	
Pyloric stenosis		+
Gastric volvulus		+
Intestinal obstruction		+
Gastroenterostomy	+	
High neuroticism	+	
(c) Pharmacological factors		
Anticholinergic drugs		
- atropine		+
- propantheline		+
- tricyclics		+
- trihexyphenidyl		+
- methylatropine nitrate		+
Ganglion blocking drugs		
- hexamethonium		+
Narcotic analgesics		+
Isoniazid		+
Sodium nitrite		+
Chloroquine		+
Alcohol		+
Dioctyl sodium sulphosuccinate		+
Phenytoin		+
Metoclopramide	+	
Reserpine	+	

	Gastric emptying rate	
	Increased	Decreased
Anticholinesterases	+	
Sodium bicarbonate	+	
Aluminium hydroxide		+
Magnesium hydroxide		+
Cigarette smoking	+	
Isoprenaline		+
Salbutamol		+
Propranolol	+	

this effect is attributable to more rapid gastric emptying (Borowitz et al, 1971). In addition, isotonic saline (Hunt, 1963), sodium bicarbonate (Shay and Gershon-Cohen, 1934) and sodium citrate solutions (Hunt and Knox, 1962) leave the stomach more rapidly than plain water while solutions of potassium salts leave the stomach slowly (Hunt and Pathak, 1960). Therefore, in drug absorption studies, the volume and composition of the ingested solution must be rigidly fixed in order to obtain meaningful results of absorption studies of a drug.

Propantheline (or atropine) and metoclopramide have been shown to retard and accelerate, respectively, the absorption of tetracycline, pivampicillin (Gothoni et al, 1972), alcohol (Finch et al, 1974; Gibbons and Lant, 1975; Bateman et al, 1978) paracetamol (Nimmo et al, 1973) and propranolol (Castleden et al, 1978). Metoclopramide was effective by the intravenous or oral route whereas propantheline was without significant effect when given orally.

Gastric emptying is delayed in women during labour (Davison et al, 1970) and in one study this delay was reduced by intramuscular metoclopramide

(Howard and Sharp, 1973). Amoxycillin absorption was delayed and therapeutic plasma or amniotic fluid concentrations were not achieved during labour (Buckingham et al, 1975). Absorption was not improved by metoclopramide. In none of these studies was information given about the administration of analgesics to the patients.

There was a striking delay in the absorption of orally administered lignocaine in patients premedicated with 0.6 mg of atropine intramuscularly prior to laparoscopy (Adjepon-Yamoah et al, 1973). The mean peak plasma concentration of lignocaine occurred at 45 minutes in healthy volunteers but was delayed until 3 hours in the patients. It is likely, however, that laparoscopy and anaesthesia also contributed to this delayed absorption. Dismethylimipramine reduced the absorption of phenylbutazone (Consolo et al, 1970) and this was attributed to delayed gastric emptying while diphenylhydramine slowed p-aminosalicylic acid absorption somewhat (Lavigne and Marchand, 1973).

Decreased gastrointestinal motility is not necessarily associated with a reduced rate of drug absorption however. In 11 patients on long term digoxin therapy, the mean plasma digoxin

concentration fell from 0.72 to 0.46 ng/ml when 10 mg of metoclopramide was taken three times daily for ten days and in another group of 13 patients, the mean digoxin concentration rose from 1.02 to 1.33 ng/ml after 15 mg of propantheline thrice daily for a similar period (Manninen et al, 1973). These effects could not be reproduced when digoxin was given in solution, and were probably due to slow dissolution of the digoxin tablets used. Rapid gastro-intestinal transit induced by the metoclopramide presumably reduced the effective time available for dissolution and absorption whereas propantheline had the reverse effect. Similar observations have been made with riboflavin (Levy et al, 1972), nitrofurantoin (Jaffe, 1975) and hydrochlorothiazide (Beermann and Groschinsky-Grind, 1978).

1.4.1 Food

Drugs are often absorbed more slowly when taken with food and the total amount absorbed is often decreased (Gower and Dash, 1969; McGilveray and Mattok, 1972; Kojima et al, 1971). This effect is attributable to the delaying effect of food on gastric emptying, dilution and probably absorption

of the drug on to food constituents (Levine, 1970; Melander, 1978). In many cases, food can seriously interfere with absorption. For example, the area under the plasma concentration time curve of pivampicillin is almost halved when the drug is taken with food (Fernandez et al, 1973) and the absorption of tetracycline taken with a typical breakfast is negligible (Kirby et al, 1961). Food may delay gastric emptying and slow down the absorption of phenobarbital in rats to such an extent that the hypnotic action is abolished (Kojima et al, 1971).

In contrast, riboflavin absorption is actually increased by food (although it may be delayed) presumably because the drug may remain longer in contact with absorbing small intestine epithelium (Levy et al, 1972) and griseofulvin absorption is greatly enhanced by a fatty meal probably for similar reasons(Crounse, 1961). Prolonged fasting reduces the rate of drug absorption in rats (Doluisio et al, 1969; Orr and Benet, 1975) but there is little information about the possibility of this occurring in humans.

1.4.2 Disease

There is surprisingly little information

available concerning the effects of gastrointestinal disease on drug absorption. In patients with achlorhydria gastric emptying and drug absorption are unpredictable. According to the pH partition hypothesis, the absorption of aspirin should be slowed in achlorhydric patients but in fact this was absorbed significantly faster and plasma salicylate concentrations were higher than in controls (Pottage et al, 1974). This effect was not due to more rapid gastric emptying. Presumably the aspirin tablets dissolved more readily at the higher pH of the gastric contents in the achlorhydrics.

Pyloric stenosis results in grossly impaired absorption of paracetamol (Prescott, 1974 b) and therapeutic failure of orally administered drugs seems inevitable in patients with gastric stasis. The absorption of effervescent aspirin is delayed in patients during an attack of migraine (Volans, 1974) and this delay correlates well with the severity of the headache and gastrointestinal symptoms. It is alleged to be due to a delay in gastric emptying during attacks of migraine. Aspirin absorption and relief of symptoms is improved by intramuscular metoclopramide (Volans, 1975).

Conflicting results have been obtained in absorption studies in patients who have undergone gastro-intestinal surgery. In one study, p-aminosalicylic acid and isoniazid absorption was unaffected by gastrectomy for peptic ulcer but in some patients there was complete failure of ethionamide absorption (Mattila et al, 1969). In another study, the absorption of sulfisoxazole, quinidine and ethambutol was unaffected by gastrectomy unless gastric emptying was slowed by vagotomy (Venho et al, 1972). Increased plasma concentrations of ampicillin were demonstrated in eight patients following partial gastrectomy and five after vagotomy (George et al 1981).

Patients on chronic anticonvulsant therapy show an "insensitivity" to frusemide in that diuresis is delayed. This may in part be due to delayed absorption of frusemide resulting from the delayed gastric emptying produced by phenytoin (Ahmad, 1974; Woodbury, 1969).

1.4.3 Antacids

Aluminium hydroxide gel delayed and depressed the gastrointestinal absorption of isoniazid in man due to delayed gastric emptying resulting from the

presence of aluminium ions in the stomach (Hurwitz and Schlozman, 1974). The effects of magnesium containing antacids were less pronounced and more variable. Therefore patients receiving antacids in addition to antituberculous therapy should be given the medications at different times. Aluminium salts and magnesium hydroxide delayed the absorption of sulphadiazine sodium (a weak acid) and quinine in rats (Hurwitz, 1971) probably by delaying gastric emptying but raising the pH precipitated the quinine (a weak base) and therefore slowed its rate of absorption. Magnesium and aluminium hydroxides both retarded gastrointestinal sodium pentobarbital absorption and delayed the onset of sleep in rats (Hurwitz, 1971). Magnesium hydroxide by raising the pH shifted the pentobarbital (a weak acid) to the ionized, non-absorbable form and aluminium hydroxide again delayed gastric emptying. Magnesium aluminium hydroxide mixture (Maalox) delays diazepam absorption in man (Greenblatt et al, 1978).

1.4.4 Metoclopramide

Intramuscular or intravenous metoclopramide increased the rate of aspirin, paracetamol, mexiletine, propranolol and alcohol absorption (Volans, 1975; Nimmo, 1973; Wing et al, 1979;

Castleden et al, 1978; Bateman et al, 1978). Oral metoclopramide increased the rate of absorption of tetracycline and alcohol (Gibbons and Lant, 1975; Nimmo, 1973). However, it had no effect on the plasma concentration curves of p-aminosalicylic acid in healthy subjects when given orally at the same time (Scalabrino and Pasquariello, 1968). Gibbons and Lant gave 20 mg of metoclopramide thirty minutes before the alcohol and Nimmo gave 20 mg fifteen minutes before the tetracycline. Therefore, if metoclopramide is to be effective when used orally to increase the rate of absorption of another orally administered drug, it must be given at least fifteen minutes beforehand.

The absorption of L-dopa from the gastro-intestinal tract is unpredictable. Peak plasma levels and the times at which they occur are variable and multiple peaks occur in some patients. In a study of 12 healthy volunteers and one patient with Parkinson's disease, metoclopramide (10 mg i.v. or 20 mg orally) increased the rate and the total absorption of L-dopa as well as eliminating the erratic absorption pattern (Mearrick et al, 1974). However, metoclopramide (40 mg orally per day) had no effect on the absorption of isoniazid in eight patients with tuberculosis. The effects of

altered gastric emptying on drug absorption are summarised in Table 1.2.

1.5 OTHER FACTORS INFLUENCING DRUG ABSORPTION IN MAN

1.5.1 Disintegration and dissolution

The majority of oral dosage forms are solids. To be absorbed from the gastro-intestinal tract, the drug must be in solution and there may be considerable variation in the disintegration of the dosage form and in the rate of release of active compound from the product and dissolution in the gastro-intestinal contents. These processes depend on the physico-chemical properties of the drug and the medium in which it is dissolving as well as the manufacturing procedures and excipients included in the formulation. Major differences have been noted, not only between products of different manufacturers, but also between lots made by the same manufacturer. Important differences have been demonstrated for a variety of drugs including digoxin (Lindenbaum et al, 1971; Shaw, 1974), warfarin (Lozinski, 1960) and phenytoin (Tyrer et al, 1970).

1.5.2 Mucosal transport

In the intestine, there is an enormous capacity

TABLE 1.2 DRUGS WHOSE ABSORPTION HAS BEEN SHOWN TO BE INFLUENCED BY ALTERED GASTRIC EMPTYING

Drug	Gastric emptying rate	Effect
L-dopa	Decreased	L-dopa metabolised in stomach
L-dopa	Increased by metoclopramide or gastrectomy	Increased rate and total absorption
Methyl digoxin	Decreased	Methyl digoxin inactivated in stomach
Penicillin	Decreased	Penicillin inactivated in stomach
Paracetamol	Increased by metoclopramide	Increased rate of absorption
Paracetamol	Decreased by propantheline	Decreased rate of absorption
Tetracycline Pivampicillin Alcohol	(Increased by (metoclopramide ((Decreased by (propantheline or (food	Increased rate of absorption Decreased rate of absorption
Lignocaine	Decreased by atropine	Decreased rate of absorption
Phenylbutazone	Decreased by desmethylimipramine	Decreased rate of absorption
P-amino-salicylic acid	Decreased by diphenhydramine	Decreased rate of absorption

Drug	Gastric emptying rate	Effect
Digoxin tablets	Increased by metoclopramide	Decreased rate of absorption
Digoxin tablets	Decreased by propantheline	Increased rate of absorption
Riboflavin	Decreased by propantheline or food	Delayed absorption but total amount absorbed is increased
Ethionamide	Increased by gastrectomy	Failure of absorption
Phenobarbital	Decreased by food	Failure of hypnotic action in rats
Griseofulvin	Decreased by fatty meal	Absorption enhanced
Amoxycillin	Decreased in women in labour	Decreased absorption
Mexiletine	Decreased by myocardial infarction and narcotic analgesics	Decreased absorption. Failure to attain therapeutic plasma concentrations
Aspirin	Decreased by migraine	Decreased absorption. Therapeutic failure.
Frusemide	Decreased by phenytoin	Patient insensitivity
Isoniazid	Decreased by aluminium salts	Delayed absorption
Pentobarbital	Decreased by aluminium containing antacids	Delayed absorption and failure of hypnotic action in rats

Drug	Gastric emptying rate	Effect
Quinine	Delayed by aluminium hydroxide	Delayed absorption
Propranolol	(Increased by (metoclopramide	Increased rate of absorption
Mexiletine	(Decreased by (propantheline or (atropine	Decreased rate of absorption
Diazepam	Decreased by atropine	Decreased rate of absorption
	Decreased by Maalox	Decreased rate of absorption
Diazepam	Increased in subjects with high neuroticism	Increased rate of absorption

for absorption because of its length and the fact that its surface area is increased by finger like villi. Each epithelial cell itself is covered with innumerable microvilli which also increases its surface area. Fusion of the outer layer of adjacent cell membranes occurs at the base of the microvilli to form a "tight junction" between the cells (Chapman, 1974), thereby producing an effective barrier between the intestinal lumen and the intercellular space.

Microvilli are covered by a filamentous surface coat (glycocalyx) which is composed of acidic mucopolysaccharides. It is firmly attached to the microvillus membrane and is an integral and dynamic part of membrane. The role of this layer in drug absorption is unknown.

In close proximity to this glycocalyx, is the acid micro-environment (figure 1.2). This "virtual pH" may be 2 pH units lower than that of the bulk of the intestinal contents (Hogben et al, 1959). This layer is 20 microns thick. If it is the unionized drug which is absorbed, the presence of this acidic layer is of great importance in determining the rate of absorption of ionizable compounds.

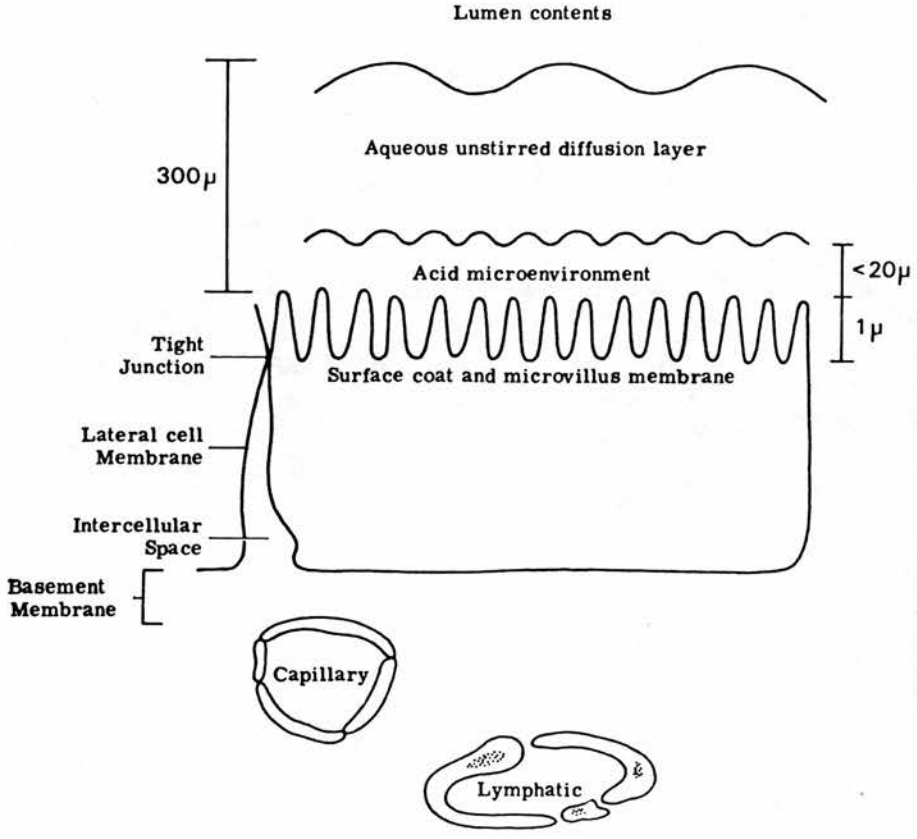


FIGURE 1.2

The nature of the intestinal mucosal barrier. Not drawn to scale. Data from Houston and Wood 1980.

The acid microclimate is in turn maintained within a much thicker (300 microns) layer of relatively unstirred fluid which is not in equilibrium with the rest of the contents of the small intestine. Thus, during absorption, drug molecules must pass through at least 2 barriers - the unstirred layer and the microvillus lipoprotein membrane. The unstirred layer is rate-limiting for the intestinal absorption of non-polar compounds and drugs in micellar solution.

In man, about 7 litres of fluid are secreted into the gastro-intestinal tract daily and an additional 1.5 litres of water are ingested. Since only 150 ml of fluid are lost in the faeces, about 8 litres of water are absorbed across the intestinal mucosa each day. Solvent drag, the phenomenon of drug molecules being carried along with the transmucosal movement of water, is probably only of importance in the small intestine. Gastric and colonic absorption of drugs is not influenced by concurrent water flux (Kitazawa et al, 1977; Wood et al, 1978). The rate of absorption of both acidic and basic drugs from the rat small intestine can be markedly enhanced by relatively small increases in water flux out of the gut lumen (Ochsenfahrt & Winne, 1974 a,b). Water flux takes

place mainly through the pores or "tight junctions" which are of limited size. However a small fraction of water also penetrates the lipid portion of the cell membrane where it interacts with the simultaneously penetrating drug molecules.

It seems likely that one compound may enhance water absorption and therefore influence the rate of absorption of another. For example, theophylline absorption is increased in the presence of alcohols which increase water flux and therefore solvent drag (Houston and Levy, 1975).

Many compounds of physiological significance, such as amino acids, sugars and bile acids, are absorbed from the small intestine by active transport mechanisms against a concentration gradient. Structurally related drugs may share these systems e.g. l-dopa, 5-fluorouracil. In addition, a few drugs not related structurally may be absorbed by active transport e.g. quaternany ammonium compounds, (Levine, 1961) and digoxin (Damm, et al, 1975). However, the absorption of most drugs from the gastro-intestinal tract takes place by passive diffusion through the mucosal membrane. Therefore, a major determinant of absorption rate is lipophilicity. Most drugs process acidic and/or basic groups whose pKa values influence absorption

rate.

1.5.3 Blood flow

The intestinal mucosa is drained by blood and lymph. Blood flow may influence intestinal absorption in three ways (Ther and Winne, 1971).

(a) Mechanical - the draining effect of the blood results in a virtual "sink" for absorbed compounds. As a result, no build up in blood concentration occurs at the site of absorption and a large concentration gradient is maintained.

(b) Biochemical - an adequate oxygen supply is maintained to allow mucosal cells to carry out active transport processes.

(c) Secondary morphological alterations - decreased blood flow results in changes in structure of the intestinal epithelium.

1.5.4 First-pass metabolism

Drugs may be metabolized by the gut bacterial flora (Goldman et al, 1974) by the mucosal tissue itself (Hartiala, 1973) or in the "first-pass" through the liver (Blaschke and Rubin, 1979) and this provides a source of variation between lumenal

disappearance of the drug and appearance in the systemic circulation.

A wide variety of drug metabolizing enzymes is present in the intestinal mucosa. The rate of oxidative metabolism is lower in the intestine than in the liver (Lake et al, 1973) but the rate of glucuronidation may be 43% higher (Chhabra et al, 1974). One important example of intestinal metabolism is the fact that orally administered isoprenaline has a potency of 1% of the same dose administered i.v. 90% of an administered oral dose is conjugated as the sulphate by the intestinal mucosa (George et al, 1974).

Other drugs extensively metabolized by the mucosa include L-dopa, terbutaline, flurazepam, salicylamide and ethinyloestradiol (Back et al, 1981). Intestinal enzymes are saturated by lower doses of drug than hepatic enzymes. Thus intestinal metabolism is particularly evident when the rate of absorption is slow. For morphine, extensive gut metabolism is linked with its low permeability (Josting et al, 1976). For lipophilic compounds such as salicylamide, factors that influence the rate of absorption could have dramatic effects on the extent of availability.

For example, delay in gastric emptying might alter the contribution of the gut wall to the overall metabolism of this drug (Houston and Levy, 1975).

Intestinal metabolism is susceptible to competitive inhibition because of its saturable nature. Salicylamide and ascorbic acid competitively inhibit the intestinal metabolism of isoprenaline and a dramatic potentiation of pharmacological activity may occur (Houston et al, 1976).

Theoretically, any drug which is metabolized by the enzyme systems of the liver undergoes "first-pass" metabolism. However the term is usually applied to those drugs which are extensively removed (e.g. $\succ$ 50%) during the first pass through the liver. These drugs include chlormethiazole, chlorpromazine, lignocaine, propoxyphene and propanolol. The net result of this phenomenon is often to seriously impair the bioavailability of a rapidly metabolized drug after oral dosing and in the case of lignocaine to prohibit administration by this route. The pharmacodynamic consequences of this phenomenon are diminished if the metabolite is pharmacologically active and this occurs for propranolol where the hydroxylated metabolite formed

during the "first-pass" has β-blocking properties.

If the high concentrations of drug reaching the liver saturate the hepatic transport and enzyme processes or if the liver is damaged by disease, a disproportionate increase in bioavailability of unchanged drug may result. The fraction of paracetamol metabolized in the liver during the "first-pass" is about 0.30 and the effect of absorption rate on the extent of first pass effect should be clinically insignificant (Clements and Prescott, 1976). However Rawlins et al (1977) demonstrated oral bioavailability of 63% after a 500 mg dose of paracetamol and 89% after a dose of 1 g or more suggesting dose-dependent "first-pass" metabolism.

1.5.5 Lymph flow and intestinal absorption

Since villous capillary blood flow is about 500 times greater than lymph flow, absorption via the lymphatics plays only a minor role in the overall absorption of most drugs. This was found to be the case for p-aminosalicylic acid and tetracycline (DeMasto and Levine, 1969). A highly lipophilic substance such as DDT is absorbed by the lymphatics, however, (Kamp and Neumann, 1975) and

other substances that meet the specific structural requirements and lipid solubility may enter the lymphatics. These substances would bypass the liver and avoid "first-pass" metabolism.

CHAPTER 2.

PARACETAMOL ABSORPTION AND GASTRIC EMPTYING

Paracetamol (acetaminophen) has been used as a model drug for drug absorption studies. It is a very weak acid (pKa 9.5) that is largely unionised in both gastric and intestinal fluids. Its rate of absorption from the gastro-intestinal tract is therefore largely independent of pH changes and is related to the rate of gastric emptying. In addition it is a widely-used drug which is safe in therapeutic doses. Variation in its rate of absorption following oral administration to healthy volunteers under standard conditions was reported by Gwilt et al, 1963. After a standard dose of 1 g with 100 ml of water, peak paracetamol concentrations were reached between 30 and 90 minutes. 24% of the subjects were "slow absorbers" of paracetamol and had blood concentrations below 10 ug/ml at 45 min.

Normal individuals had been described as consistently "rapid" or "slow" absorbers of paracetamol (Prescott and Nimmo, 1971) and in the "slow" absorbers, differences between the rates of absorption from paracetamol tablets, suspension or

effervescent preparation were more marked.

These differences in rates of absorption of paracetamol were shown to be due to variations in gastric emptying rate in a study of 14 convalescent hospital patients (Heading et al, 1973). Absorption of 1.5 g of paracetamol (as 3 Panadol tablets) with 50 ml of water and gastric emptying rate were measured on separate occasions within 6 days. Gastric emptying results were expressed as half-times and the rate of paracetamol absorption was assessed by the maximum paracetamol concentrations and the time taken to reach peak concentrations. The maximum plasma paracetamol concentrations varied from 7.4 to 37.0 ug/ml and the time taken to reach peak concentrations ranged from 30 - 180 min after ingestion. Similarly, the gastric emptying rate varied widely, and the half-time values ranged from 20 to 86 minutes. There were statistically significant correlations between the half-time of gastric emptying and both the maximum plasma paracetamol concentrations and the time taken to reach the peak (figure 2.1). Rapid gastric emptying was associated with early high peak plasma concentrations whereas peak concentrations were low and occurred late when gastric emptying was slow.

Gastric emptying was abnormally slow in 5 of the 14 patients (half-time $>$ 55 min). These patients had delayed paracetamol absorption and significant

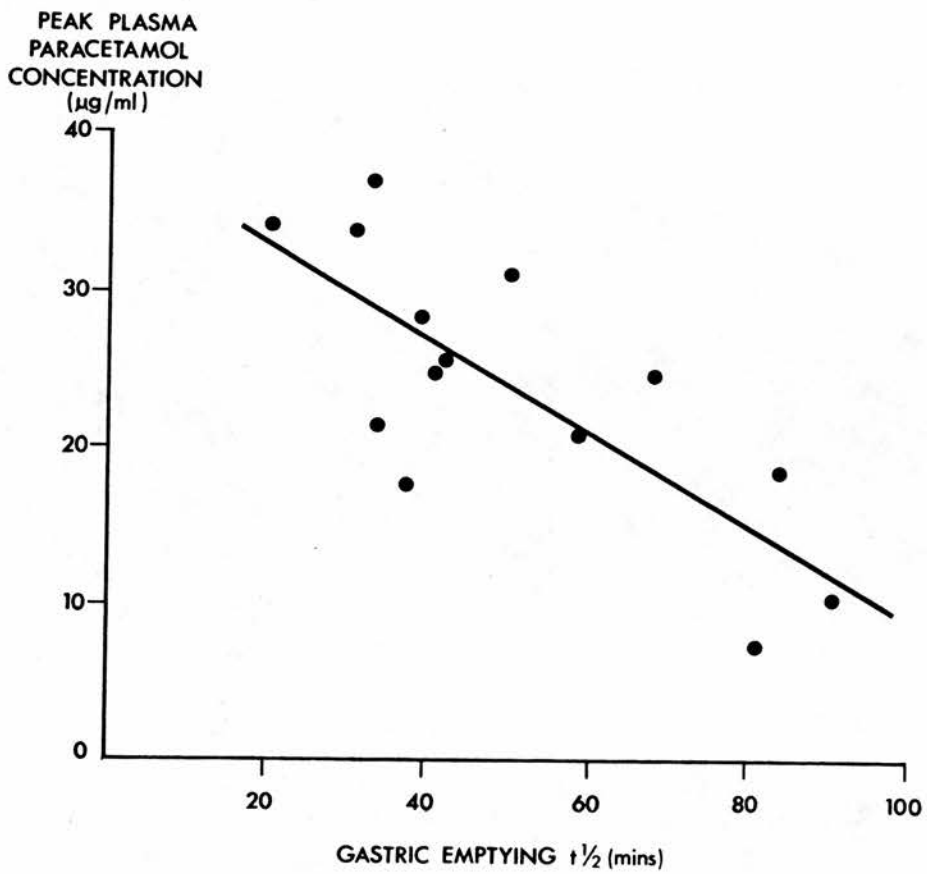


FIGURE 2.1

Relationship between gastric emptying half time ($t_{\frac{1}{2}}$) and the peak plasma paracetamol concentration ($r = 0.77$, $p < 0.005$). Data from Heading et al 1973.

reduced recovery of total unchanged and conjugated paracetamol in urine at 0 - 4 hours and at 0 - 24 hours.

Propantheline and metoclopramide delay and accelerate gastric emptying respectively and thus influence the rate of paracetamol absorption (Nimmo et al, 1973). In a study of five healthy volunteers known to be consistently slow absorbers of paracetamol, metoclopramide (10 mg intravenously) given at the same time as the paracetamol resulted in higher and earlier maximum plasma paracetamol concentrations. The mean time to reach peak paracetamol concentrations was reduced from 120 to 48 minutes while the mean maximum concentration increased from 12.5 to 20.5 ug/ml. The urinary excretion of paracetamol was not influenced.

In 6 convalescent hospital patients, propantheline (30 mg intravenously) increased the mean $t_{\frac{1}{2}}$ of gastric emptying from 25 to 152 minutes. Consequently the mean time to peak plasma paracetamol concentrations was increased from 70 to 160 minutes and the mean maximum concentration reduced from 26.3 to 17.5 ug/ml. Again total urinary excretion of paracetamol in 24 hours was not changed by this pharmacological modification of gastric emptying.

Thus paracetamol absorption is influenced directly by gastric emptying rate and modification of gastric emptying in turn changes the rate of absorption of paracetamol.

CHAPTER 3

METHODS OF MEASURING GASTRIC EMPTYING AND PARACETAMOL ABSORPTION

3.1 THE MEASUREMENT OF GASTRIC EMPTYING IN MAN

Methods for the measurement of gastric emptying may be described under four headings (Sheiner 1975).

3.1.1 Radiological methods

Some information may be obtained from conventional barium or gastrografin examination of the upper gastro-intestinal tract. However observations of rapid or delayed gastric emptying are largely qualitative and any attempt to quantitate gastric emptying is limited. In addition barium sulphate itself may influence gastric emptying rate.

3.1.2 Gastric aspiration methods

This method involves the passage of an orogastric or nasogastric tube and aspiration of gastric contents after instillation of a known volume of fluid. The difference between the instilled and aspirated volumes gives some indication of the amount emptied from the stomach

(Goldstein & Boyle 1965).

The aspiration technique may be modified by adding a non-absorbable marker such as phenol red to the instillate thus allowing correction for the volume of gastric secretions during the time period chosen for the emptying measurement. However, both these tests allow a single measurement only from each test and to define gastric emptying in detail a series of tests over several days is required.

A modification of this test allows more detailed measurements to be made (George 1968). A marker is added to the liquid meal before ingestion and small additional amounts of marker are added at intervals via the nasogastric tube. Gastric contents are mixed and then sampled after each addition so that a series of samples is obtained. Measuring the marker concentrations allows the volume remaining in the stomach at each sampling time to be calculated. No measurement of gastric secretion is obtained and the test measures emptying of gastric contents, not emptying of the test meal.

3.1.3 Duodenal aspiration methods

3.1.3 Duodenal aspiration methods

One marker is added to the ingested meal and continuous infusion of a second marker into the duodenum allows measurement of gastric emptying and secretion from samples aspirated from the stomach and duodenum (Malagelada et al, 1976). This method allows emptying measurements to be made for solids as well as liquids but the transpyloric intubation may induce motor or secretory abnormalities.

3.1.4 Scintigraphic methods

A non-absorbable gamma-emitting radioactive isotope is incorporated into a meal and the amount in the stomach is quantitated using an external gamma camera or scintiscanner on the abdomen. A series of measurements is made and the rate and pattern of emptying from the stomach are defined (Heading et al, 1971; Heading et al, 1976).

The non-invasive nature of this technique increases patient acceptability and avoids possible changes caused by the presence of a nasogastric or orogastric tube.

3.1.5 Gastric emptying measurements used in this thesis

3.1.5 Gastric emptying measurements used in this thesis

Gastric emptying measurements were carried out by me in collaboration with Dr. R.C. Heading and Dr. P. Tothill in the Department of Medical Physics, Royal Infirmary, Edinburgh. The method was described by Heading et al 1971 and 1976) and involved the use of an non-absorbable radio-active isotope in a test drink followed by external detection by a scanner. The amount of radioactively labelled liquid remaining in the stomach at intervals after its ingestion was measured. There are two problems with this technique. First, a brief early phase of rapid gastric emptying may occur after ingestion of the test solution and emptying during this early period is not easily measured by external detection methods. An estimation of this early phase may be made using a "phantom stomach" (Colmer et al 1973). Secondly, if the gastric emptying of both solid and liquid phases of a meal are to be measured, two different isotopes must be used (Heading et al 1976). In my studies, only liquid emptying was measured.

3.1.5.1 Isotope

Diethylene triamine penta acetic acid (DTPA) (Sigma, London) was labelled with ^{113m}Indium which was eluted from a generator in the Department

of Medical Physics. The Indium DTPA chelate was prepared by the method of Stern et al (1967). Indium was preferred to ^{51}chromate in these studies because of its greater gamma ray emission and its short physical half-life of 1.7 hours. This permits study of the same subject on successive days if this is required. Chromate is not suitable for successive tests on the same subject because its half-life is longer and isotope in the colon would be difficult to distinguish from that in the stomach.

3.1.5.2 Clinical studies

All studies were carried out in healthy male volunteers who were members of staff of the Departments of Therapeutics and Anaesthesia, Royal Infirmary, Edinburgh (Chapters 7, 8 and 9). After an overnight fast, each subject swallowed 350 ml of water with 50 ml orange juice concentrate ("Robinsons") containing 300 uCi of ^{113}Indium DTPA chelate which was added immediately beforehand. The subjects sat up to take the drink over a 2 minute period and then lay horizontal (with 2 pillows under the head) throughout the study (Figure 3.1). The time of ingestion was defined as the midpoint of the 2 minute period.

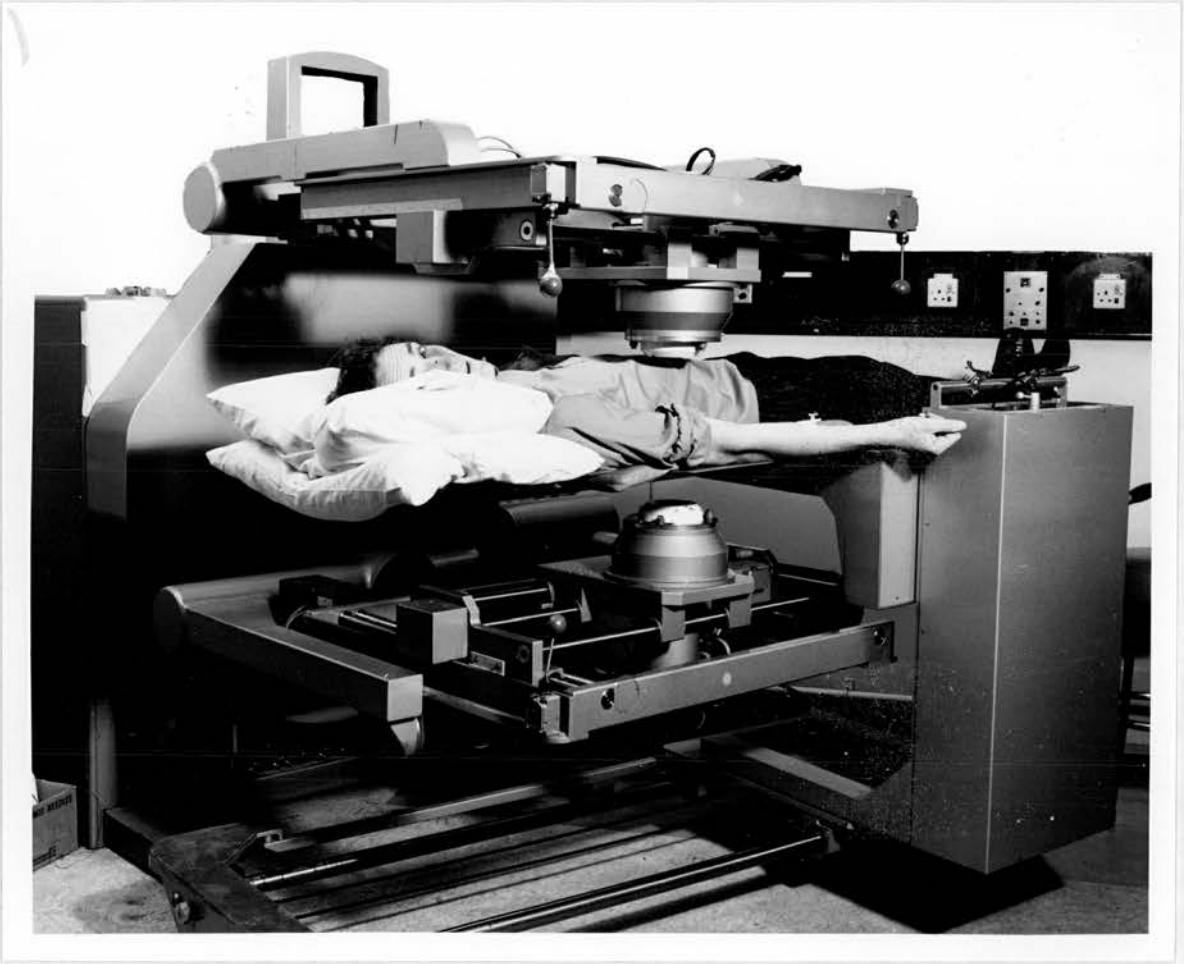


FIGURE 3.1

A healthy volunteer undergoing gastric emptying measurements by means of a double headed rectilinear scanner after ingestion of a non-absorbable radio-active isotope.

3.1.5.3 Scanning

The subject's abdomen was scanned continuously, each scan taking approximately 8 minutes. The instrument used was a double headed rectilinear scanner (J. & P. Engineering Ltd., Reading, England). The position of the xiphisternum was marked on each scan as a reference point (Figures 3.2 and 3.3).

3.1.5.4 Calculation

The scans from each subject were inspected and an area corresponding to the stomach was marked out on each. The number of dots within this area was counted and correction made for background and the physical decay of the indium. A plot of logarithm of dot counts against time was made.

An indirect quantitation of the amount of indium emptied by the time of the first scan was obtained by a technique based on that of Colmer et al (1973). The geometric mean of counts recorded in the patient's stomach area was compared with a similar scan of a dummy stomach (400 ml normal saline in a Baxter Travenol infusion bag) within a cardboard replica abdomen constructed to be equivalent in thickness to the anteroposterior

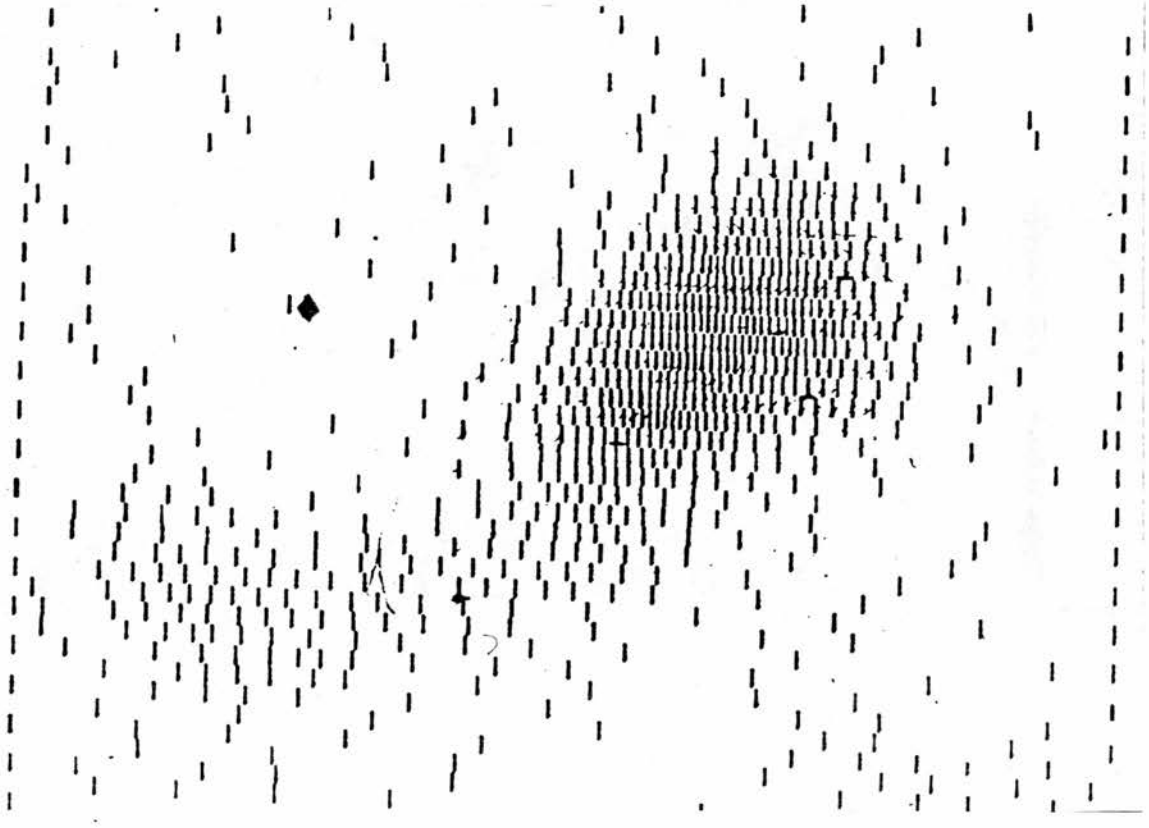


FIGURE 3.2

First scan of the subject's abdomen after ingestion of 300 uCi of ^{113m}Indium in 400 ml orange juice.

◆ = xiphisternum

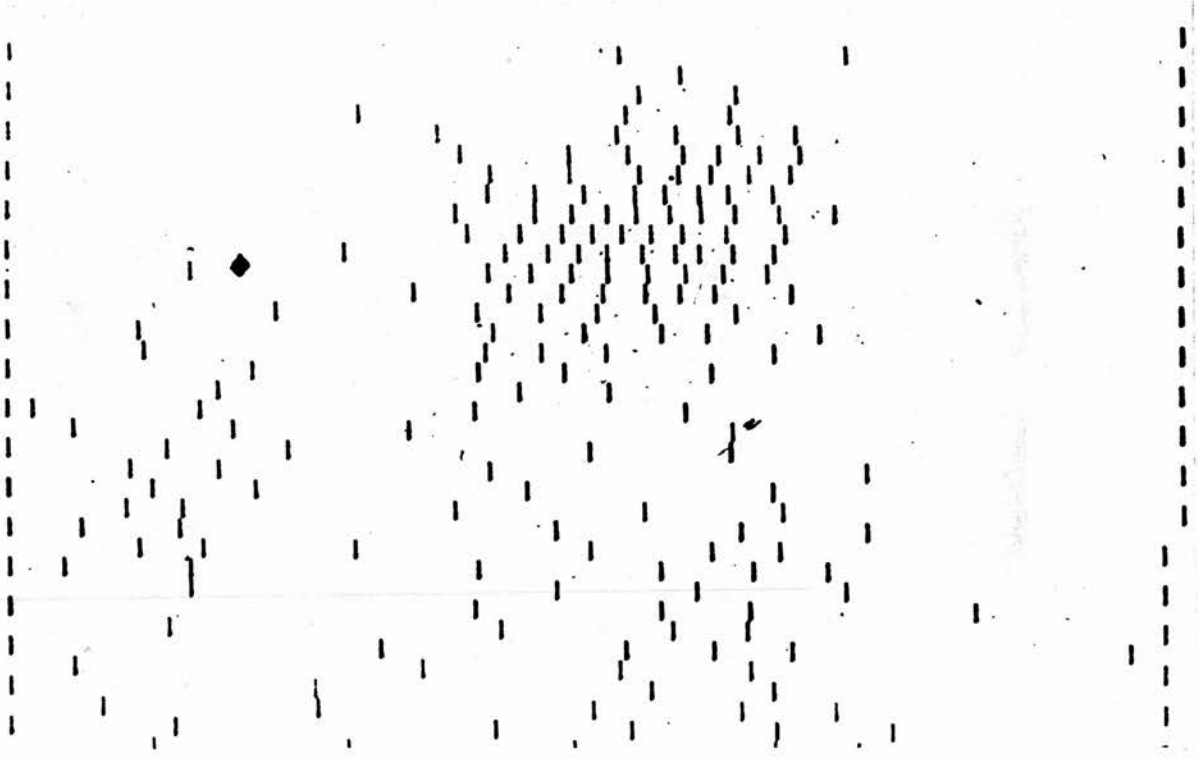


FIGURE 3.3

Late scan (after approximately 40 minutes) of the subject's abdomen after ingestion of 300 uCi of ^{113m}Indium in 400 ml of orange juice.

◆ = xiphisternum

diameter of the patient's abdomen. The absolute amount of indium corresponding to the patient count could be determined and subtraction from the amount ingested gave the amount emptied.

An example of gastric emptying measurements in one subject is shown in Figure 3.4. Full results of the studies are given in Chapters 7, 8 and 9.

3.1.5.5 Discussion

All methods of determining gastric emptying with external counters employ a gamma-emitting radio-active isotope as a marker of the ingested meal or solution. This method has been criticized as giving a falsely high value for the emptying half-life since activity which has passed beyond the pylorus may be included in the field of view. However, the use of scanning methods of detection in contrast to fixed detectors such as the gamma camera make it possible to recognise activity in the duodenum or jejunum and thus to minimise this source of error.

All external counting methods depend on the assumption that emptying of the isotope from the stomach corresponds with emptying of the test meal.

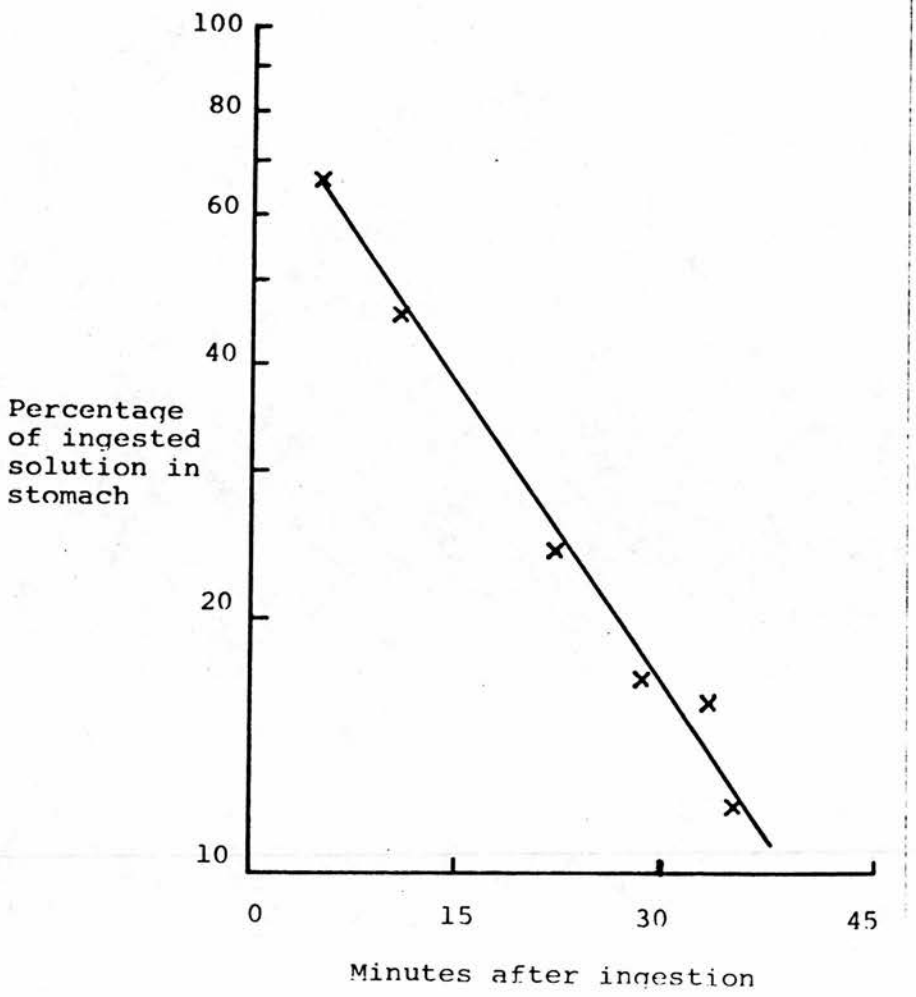


FIGURE 3.4

Example of gastric emptying in one healthy volunteer.

Initial fraction emptied from stomach = 18%

$t_{1/2}$ = 18 minutes

Throughout my studies, only liquid test meals, with the isotope in solution, were used. Problems of adsorption of the isotope to solid foodstuff in the stomach while liquid emptying occurred were thus avoided. In studies of liquid and solid emptying from the stomach, indium chelate best reflected emptying of the liquid phase of the gastric contents (Heading et al, 1976).

3.2 MEASUREMENT OF PARACETAMOL ABSORPTION

In all studies, paracetamol concentrations in plasma and urine were measured by gas liquid chromatography in the laboratories of Dr. L.F. Prescott in the Department of Therapeutics, Royal Infirmary, Edinburgh. I was personally responsible for carrying out over 80% of these estimations. For the others, I am grateful for the technical assistance of Mrs. I. Darrien or Mr. I. King.

Spectrophotometric methods for paracetamol estimation are available and are useful in drug screening and after overdosage. However after therapeutic doses they are not sensitive or specific enough for accurate measurement. At the time these studies were carried out, a high performance liquid chromatography method was not available (Howie et al

1977). Thus a specific, sensitive gas liquid chromatographic method of estimation of paracetamol concentrations was used (Prescott 1971 a and b).

3.2.1 Clinical studies

Paracetamol absorption studies were carried out in patients in the wards of the Royal Infirmary, Edinburgh and the Simpson Memorial Maternity Pavilion, Edinburgh as well as in healthy adult volunteers who were members of staff of the Departments of Therapeutics and Anaesthetics, Royal Infirmary, Edinburgh.

3.2.1.1 Patient studies

In all the patient studies, after at least a four hour fast, paracetamol was given as 3 Panadol (Winthrop) tablets (without crushing or chewing) with 200 ml of water. The brand and batch number were the same throughout all the studies to minimise the effects of differences in tablet disintegration and dissolution rate on absorption. The volume of water ingested was constant since changes in volume influence gastric emptying (Hunt and Knox 1968a).

No food, fluid or tobacco was allowed for

2 hours after drug administration and all patients remained at rest in bed to minimise the influence of changes in posture.

3.2.1.2 Blood sampling

In all cases, samples of venous blood were taken via an indwelling venous cannula (Venflon or Medicut 18g) inserted before the study into a vein in the forearm. A three way tap was attached and the cannula was kept patent by injecting 2 ml of heparinised saline (1 iu heparin/100 ml normal saline) after each sample. Ten millilitres of blood was taken into lithium heparin tubes before paracetamol administration and at intervals thereafter. This blood was centrifuged at 2000 r p m for 5 minutes, the plasma was separated using Pasteur pipettes and stored in plain glass tubes at -20^{o}C until analysis of plasma paracetamol concentrations.

3.2.1.3 Volunteer studies

In the volunteer studies, in which paracetamol absorption and gastric emptying rate were measured simultaneously, paracetamol was given in solution. Paracetamol powder was supplied by

Dr. R. Andrews, Sterling Winthrop Research and Development, Fawdon, Newcastle upon Tyne. The powder (20 mg/Kg for each volunteer) was weighed out and dissolved in 350 ml of water which was stirred by hand for 5 minutes using a glass rod until all the paracetamol dissolved. Orange juice concentrate ("Robinsons") 50 ml was added and then the Indium DTPA (2ml) for the gastric emptying measurements. The solution was stirred continuously until it was swallowed by the volunteers.

After at least a 4 hour fast, each volunteer sat upright to swallow the solution in 2 minutes. He then lay down with his head on 2 pillows for 4 hours. The time of ingestion was taken to be the mid point of the ingestion period. No food, fluid or tobacco was allowed for 4 hours.

Frequent blood samples were taken as described in section 3.2.1.2.

3.2.1.4 Urine collection

In the volunteer studies urine was collected in glass measuring cylinders at 2 hourly intervals when possible for 8 hours and at 12 and 24 hours.

The urine volume and pH at each interval was recorded and an aliquot of 20 ml placed in a glass sterile universal container which was stored at -20°C until the time of analysis.

3.2.2 Paracetamol analysis

In all cases, the plasma and urine paracetamol concentrations were analysed within one month of the study. Usually this was done within one week.

The method of paracetamol estimation was described by Prescott (1971 a and b).

3.2.2.1 Materials and methods

A Hewlett-Packard Model 402 gas chromatograph with a nitrogen-specific detector and a 4 foot long ¼" i.d. U-shaped glass tube column packed with 1% HI-EFF (cyclohexane dimethanol succinate) on 100/120 mesh Gaschrom Q (Applied Science) was used, with a column temperature 220°C. Helium was used as the carrier gas (80 ml/min).

The internal standard used in the analysis was N-butyryl-p-aminophenol (NBA) which was kindly supplied by Dr. A. Robertson, Sterling Winthrop

Research and Development, Fawdon, Newcastle upon Tyne. This was dissolved in redistilled ethyl acetate (Fisons) to form a 250 ug/ml solution. This stock solution was made each week and stored at $4^{o}C$. Each morning, a solution of 5 ug/ml was made from the stock solution and used in the extraction of paracetamol from plasma.

Paracetamol cannot be chromatographed directly in small amounts without peak tailing or absorption losses. Therefore both the paracetamol and NBA were acetylated. The derivatives are stable, sensitivity is increased and the analysis can be completed in a much shorter time (Prescott 1971 b).

Pyridine (the catalyst for the acetylation reaction) and acetic anhydride were obtained from Phase Separations Ltd. They were stored in capped vials and all transfers were made with clean dry microsyringes.

Phosphate buffer (1.0 ml, 1 M, pH 7.4) was added to plasma (2 ml) in a 15 ml glass stoppered tube. The redistilled ethyl acetate (5.0 ml) containing NBA (5 ug/ml) was added and the extraction was effected by gentle mechanical shaking for 10 minutes. The tubes were centrifuged at 2000 r p m

for 10 minutes and the upper organic phase was transferred with Pasteur pipettes to 10 ml tapered stoppered centrifuge tubes. This liquid was evaporated to dryness in a rotary vacuum evaporator with the tubes immersed in water at 26°C.

Pyridine (5 ul) and acetic anhydride (15 ul) were then added to the residue, the tubes stoppered and the contents mixed with a vortex mixer for 30 seconds. The tubes were incubated in a water bath at 45°C for 20 minutes and 1 - 3 ul aliquots were injected directly into the gas chromatograph.

The retention times of paracetamol and internal standard were 3.4 and 4.5 minutes respectively (Figure 3.5). Plasma standards of paracetamol (10 and 25 ug/ml) were run with the samples (Figure 3.6). In all cases a plasma sample from the patient taken before he received paracetamol was run with the other samples. In this one sample, the internal standard was omitted (Fig. 3.7).

3.2.2.2 Calculations

Peak heights were measured using a ruler and were assumed to reflect peak areas. The peak

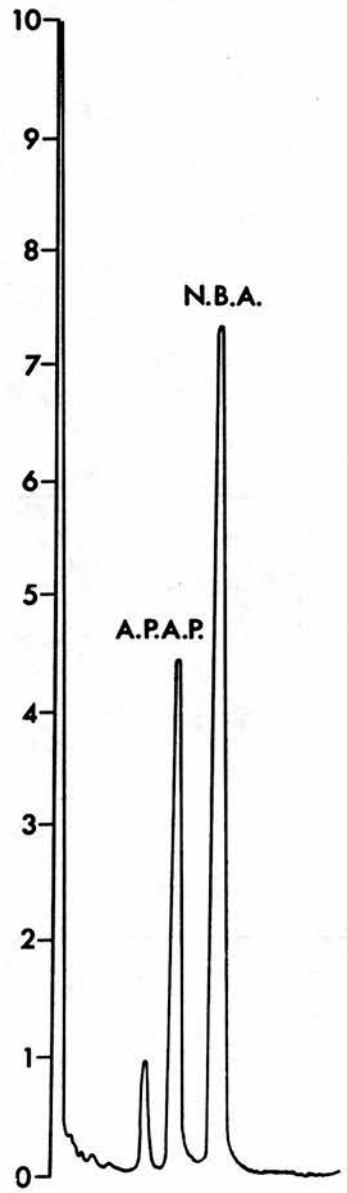


FIGURE 3.5

Chromatogram of paracetamol (APAP) and internal standard (NBA) in a patient sample.

For details, see text.

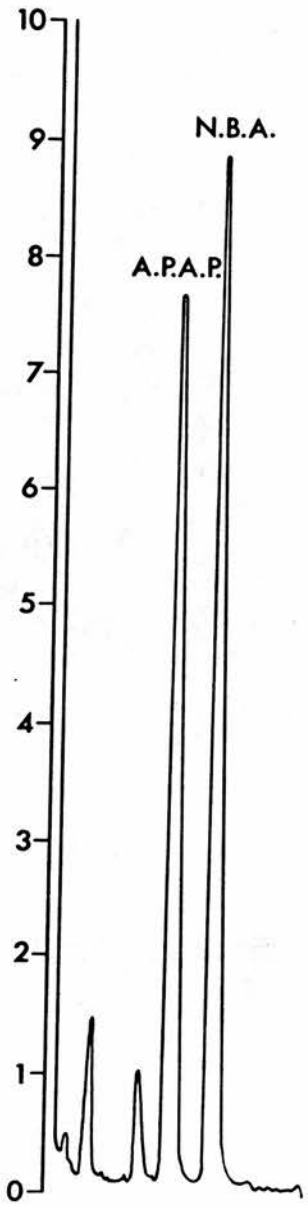


FIGURE 3.6

Chromatogram of plasma standard (25 ug/ml)

APAP = paracetamol

NBA = internal standard

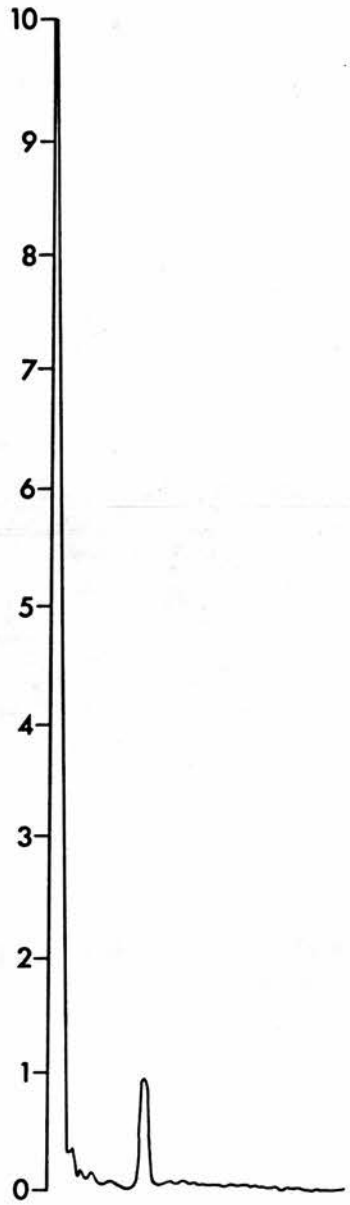


FIGURE 3.7

Chromatogram of 'blank' patient plasma

height ratio of paracetamol to internal standard (NBA) was determined for the plasma standards. From the peak height ratios of the samples, the concentration of paracetamol was calculated by simple proportion (Figures 3.5 and 3.6).

The limit of detection was 0.05 ug/ml. Within the concentration range 5 - 25 ug/ml, the standard deviation of 20 replicate analyses was 3.4%.

3.2.2.3 Urine

Free paracetamol in urine was measured as described above. However paracetamol is excreted in the urine mostly as conjugates which yield free paracetamol on acid hydrolysis (Higgins and Leach 1975). Therefore total free and conjugated paracetamol in urine was measured after incubation of a mixture of urine (0.5 ml), 0.2 M sodium acetate buffer pH 5.0 (0.5 ml) and glusulase (0.1 ml) at 37^{o}C for 16 hours. Glusulase contains 100,000 units of β glucuronidase and 50,000 units of aryl sulphatase per ml and was obtained from Endo Laboratories, Garden City, New York, U.S.A.

Aqueous standards (50 ug/ml and 500 ug/ml)

were run with the urine samples and paracetamol concentrations were measured as described above. The total paracetamol excreted at time of sampling was calculated from the volume of urine passed at these times.

The extraction of paracetamol from plasma, urine or aqueous solutions gave identical results.

3.3 EXAMPLE OF PARACETAMOL ABSORPTION

Ten healthy adult volunteers (8 male; age 28.0 $\pm$ 3.8 years; weight 69.7 $\pm$ 2.8 Kg), after at least a four hour fast, received 1.5 g paracetamol as 3 Panadol tablets with 200 ml of water. Blood samples were taken at intervals for 8 hours.

The mean peak paracetamol concentration was 17.0 $\pm$ 5.2 ug/ml and the mean time of the peak concentration was 82.5 $\pm$ 53.5 minutes after administration. Paracetamol concentrations are given in Table 3.1.

Following administration by mouth, there is an overall pattern of rising plasma concentrations (when absorption is predominating) followed by falling concentrations during the period when absorption has ceased. Following the peak

TABLE 3.1 PLASMA PARACETAMOL CONCENTRATIONS IN 10 HEALTHY ADULT VOLUNTEERS AFTER INGESTION OF 1.5 g PARACETAMOL WITH 200 ML WATER

Time / Subject	Plasma paracetamol concentration (ug/ml)						AUC 0-90' ug hr/ml
	3o'	60'	90'	3hr	5hr	8hr	
1	16.4	16.4	14.6	9.1	3.5	1.8	20.1
2	0.8	2.5	9.5	12.1	4.1	2.0	4.0
3	1.5	1.9	3.5	9.8	5.7	2.1	2.6
4	16.1	17.4	13.9	8.8	4.4	1.4	20.2
5	16.9	20.6	17.3	12.0	6.0	2.4	23.3
6	1.8	4.6	16.6	13.1	6.9	1.5	7.4
7	4.4	18.7	15.5	8.5	3.9	2.3	15.4
8	19.4	15.2	15.6	8.0	3.6	1.2	21.2
9	17.9	27.4	24.4	17.1	10.7	3.1	28.8
10	0.6	11.2	8.5	6.9	3.3	1.4	8.0
Mean	9.6	13.6	13.9	10.5	5.2	1.9	15.1
SD	8.3	8.4	5.7	3.0	2.3	0.6	9.0

concentration, the concentration declines exponentially, in the same way as following an intravenous dose (Curry 1977). However, elimination starts to occur the moment absorption starts. During the rising phase, absorption is more rapid than elimination. During the falling phase, elimination is occurring more rapidly than absorption. The peak plasma concentration represents equal absorption and elimination. This relationship is explored in Chapter 9. In the early studies it is assumed that paracetamol elimination is normal and that changes in the peak concentration and the time of the peak concentration reflect changes in the rate of paracetamol absorption.

Areas under the plasma concentration time curves were calculated using the trapezoid rule.

The amount of drug that has been absorbed at any given time after administration is determined from the integral of C_t (concentration at time t) with respect to time. This corresponds to the area under the curve in the graph of C_t against time (Bowman and Rand 1980). The area under the curve depends only on the fraction of the dose absorbed and the rate constant for elimination. In the studies reported in this thesis the area under the

plasma concentration time curve is used to compare the fractions of the dose absorbed at times after paracetamol administration.

3.4 ETHICAL CONSIDERATIONS

In all the investigations, both volunteers and patients gave informed verbal consent to participate in the study. They were free to withdraw from the investigation at any time although no one did so.

A programme of research for each study in healthy volunteers was submitted to and approved by the Ethics Advisory Committee, Royal Infirmary, Edinburgh before beginning the investigation. In the gastric emptying studies, when a radioactive isotope was used, permission was granted by the Isotope Advisory Panel of the Medical Research Council for the dose of radioactive material to be given to healthy volunteers. In the patient studies, a suggested programme of research was approved by the Ethics Advisory Committee of the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh. Permission to study each patient was sought from the consultant obstetrician responsible for the patient's care. He was free to withdraw the patient from the investigation at any time. None did so. Lastly,

the obstetric and postoperative care of the patients was not influenced by their participation in these studies.

3.5 STATISTICAL METHODS

Unless otherwise stated, data in this thesis are given as mean $\pm$ standard deviation (Swinscow 1980, Moroney 1967). Comparison of data was carried out using student's t test unless stated otherwise. In many of the studies each patient was his own control and thus statistical comparisons were made on paired observations. In other studies an unpaired t test was performed. In all cases, statistical significance was assumed when p was less than 5%.

When a normal distribution of data could not be assumed, the Mann Whitney U test was used. When comparisons of discrete variables were made, a chi square test was used.

CHAPTER 4.

NARCOTIC ANALGESICS AND DELAYED GASTRIC EMPTYING DURING LABOUR

4.1 INTRODUCTION

Unexpected vomiting or regurgitation with aspiration of gastric contents during induction of anaesthesia in labour remains an important cause of maternal death. Despite a significant decrease in the total numbers of maternal deaths reported each year, the number of fatalities related to anaesthesia has not decreased (DHSS, 1972). At least half these deaths are caused by inhalation of gastric contents. The tendency to vomit or regurgitate has been attributed at least in part to the delayed gastric emptying which is known to occur during labour (Davison et al, 1970; Howard and Sharp, 1973; McGarry, 1971). The mechanism of this delay is uncertain. In the present studies, gastric emptying rate in women during labour was investigated using the kinetics of absorption of orally administered paracetamol as an indirect measure of gastric emptying rate (page 44 Heading et al, 1973).

4.2/

4.2 PATIENTS AND METHODS

Paracetamol absorption studies were carried out during labour or in the post-partum period in 56 patients in the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh. Approval for the study had been obtained from the Hospital Ethics Advisory Committee and all patients gave verbal informed consent. None had clinical evidence of gastro-intestinal, hepatic, renal or cardiovascular disease. Their ages ranged from 17 to 34 years (mean 23).

Patients were selected for participation to include only those without obstetric complications e.g. no patient had a twin pregnancy, a breech presentation, signs of pre-eclampsia or previous delivery by Caesarean section. The onset of labour was recorded by the obstetrician managing the patient on the basis of pain and dilatation of the cervix. Many of the patients had induction of labour and were receiving oxytocin. The studies were carried out at varying times during labour and the obstetric management of the patients was not influenced by their participation in the study; e.g. analgesic drugs with or without an antiemetic were given by i.m. injection in the thigh and

oxytocin was given by i.v. infusion as prescribed by the obstetrician; sips of water were allowed if requested by the patient two hours after the test dose of paracetamol. At the time of the study, it was not common practice to prescribe alkalis such as magnesium trisilicate orally throughout labour. None of my patients received these drugs.

4.2.1 Control studies

Twelve patients in labour were studied before they had received any analgesia and these patients formed a control group (table 4.1). Their mean age was 25 $\pm$ 3 years; mean weight 72.2 $\pm$ 6.5 Kg and mean duration of labour at the time of study was 1.7 $\pm$ 1.2 hours. Ten of the 12 patients were receiving oxytocin by i.v. infusion at the time of the study. All received a narcotic analgesic later in labour, on average 3.3 $\pm$ 0.98 hours after the test dose of paracetamol. Eight received diamorphine 10 mg and cyclizine 50 mg i.m. and four had pethidine 150 mg and cyclizine 50 mg i.m. Delivery occurred 10.6 $\pm$ 6.7 hours after the study and in all patients except number 5 delivery was per vaginum. Patient number 5 had a Caesarean section because of failure to progress.

TABLE 4.1 PATIENT DATA

	Patient	Age years	Weight Kg	Parity	Oxytocin	Time from onset of labour (hours)	Time of analgesia (hours)	Time to delivery (hours)
CONTROL	1	25	71.8	1	-	2.5	4.5*	6
	2	30	75.7	1	+	4	2	6
	3	26	65.7	2	+	0.5	4.25	7
	4	26	71.4	2	-	3.25	2.5	6.5
	5	23	78.6	0	+	0.75	3.3	24
	6	25	65.9	0	+	1.5	3.5	24
	7	25	70	0	+	1.75	3.5	7
	8	28	75.5	3	+	1	3	9
	9	31	73.2	1	+	0.25	2	5.25
	10	22	86.8	0	+	0.75	2.5	12
	11	19	62.7	0	+	2.75	5	13
	12	25	70.1	2	+	1	4	7
	Mean	$\pm$ 25.4 / 3.3	$\pm$ 72.2 / 6.5		10/12	$\pm$ 1.7 / 1.2	$\pm$ 3.3 / 0.98	$\pm$ 10.6 / 6.7
POST-PARTUM	13	28	53.7	1				
	14	25	68.4	2				
	15	24	76.1	1				
	16	24	63.6	4				
	17	22	64.5	1				
	18	22	68.3	2				
	19	24	71.4	2				
	20	23	59.0	4				
	21	28	67.7	1				
	22	34	70.9	3				
	Mean	$\pm$ 25.4 / 3.7	$\pm$ 66.4 / 6.5					
PETHIDINE	23	25	80.9	0	+	0.5	0.75	1.5
	24	19	69.5	1	+	2	0.3	2.5
	25	28	53.6	1	+	6	2.25	0.75
	26	22	80	1	-	1.75	1	5.5**
	27	28	83.6	1	+	4.25	2.25	4.5
	28	19	60.9	1	-	4	1.5	1.2**
	29	18	65.5	0	+	1.5	0.5	1.3
	30	25	61.8	1	+	3	0	3.5
	Mean	$\pm$ 23.0 / 4.1	$\pm$ 69.5 / 11.8		6/8	$\pm$ 2.9 / 1.8	$\pm$ 1.1 / 0.9	$\pm$ 2.6 / 1.6
DIAMORPHINE	31	21	63.6	0	-	8.5	1	2.5
	32	17	69.5	0	-	6.5	1.3	2.5**
	33	20	60.9	0	-	9	0.25	1.5
	34	22	63.2	0	-	7.5	3	7.5
	35	17	70.9	0	-	8	1.75	2.0
	36	19	62.2	0	+	3	0.3	4.75
	37	17	67.6	0	+	2.25	1.45	4.75**
	38	20	83.2	0	+	4	0.75	8
	Mean	$\pm$ 19.1 / 2.0	$\pm$ 67.6 / 7.2		3/8	$\pm$ 6.1 / 2.6	$\pm$ 0.8 / 1.3	$\pm$ 4.2 / 2.5

TABLE 4.1 PATIENT DATA

	Patient	Age years	Weight Kg	Parity	Oxytocin	Time from onset of labour (hours)	Time of analgesia (hours)	Time to delivery (hours)
PENTAZOCINE	39	26	64.4	0	-	6.5	0.5	6.0
	40	24	71.8	0	-	1.0	0.5	3.5
	41	22	64.7	0	-	3.5	0.5	1.5
	42	22	64.3	0	-	6.0	0.5	3.5
	43	24	70.3	0	-	2.5	0.5	10.0
	44	26	69.4	1	-	6.5	0.5	1.75
	45	26	69.8	1	+	4.5	0.5	9.0
	46	23	91.5	1	+	4	0.5	2.5
	Mean	$\pm$ 24.1 / 1.7	$\pm$ 70.7 / 8.9		2/8	$\pm$ 4.3 / 2.0	0.5	$\pm$ 4.7 / 3.3
DIAMORPH/ METOCLO.	47	21	60.9	0	+	4.0	0.5	2.2
	48	26	68.8	0	+	3.5	0.5	12.1
	49	28	65.4	0	+	4.0	0.5	6.3
	50	23	80.2	0	+	3.0	0.5	3.2
	51	26	68.4	0	+	6.0	0.5	10
	Mean	$\pm$ 24.8 / 2.8	$\pm$ 68.7 / 7.1		5/5	$\pm$ 4.1 / 1.0	0.5	$\pm$ 6.7 / 4.3
PETHIDINE/ METOCLO.	52	24	64.3	1	+	5.5	0.5	2.5
	53	26	78.2	2	+	2	0.5	1.5
	54	28	61.1	1	+	5.75	0.5	0.5
	55	29	62.7	1	+	2	0.5	1
	56	25	74.6	0	+	2	0.5	2
	Mean	$\pm$ 26.4 / 2.1	$\pm$ 68.2 / 7.7		5/5	$\pm$ 3.5 / 2.0	0.5	$\pm$ 1.5 / 0.79

* In all patients in the control group, the analgesia was given after the start of the study.

** Did not receive cyclizine.

In addition to this control study, paracetamol absorption was studied in 10 women (age 25.4 ± 4 years; weight 66.4 ± 7.3 Kg) 2 to 5 days after normal vaginal delivery (table 4.1). They had all received a narcotic analgesic during labour - 6 had pethidine, 1 pethidine and diamorphine and 3 had diamorphine alone. Although Distalgesic (dextropropoxyphene and paracetamol) had been given orally as requested for any post-partum pain, none of these patients had received any type of analgesic drug for 16 hours before the test dose of paracetamol was given.

4.2.2 Pethidine

Eight patients in labour (age 23 ± 4 years; weight 69.5 ± 11.8 Kg) were studied 1.1 ± 0.9 hours after pethidine 150 mg i.m. (table 4.1). Six of these patients received cyclizine 50 mg i.m. with the pethidine. The patients were on average 2.9 ± 1.8 hours since onset of labour and 2.6 ± 1.6 hours before delivery. All patients had a vaginal delivery.

4.2.3 Diamorphine

Eight women in labour (age 19 ± 2 years; weight 67.6 ± 7.8 Kg) were studied 0.8 ± 1.3 hours after they had received diamorphine 10 mg i.m.

(table 4.1). Six had received cyclizine at the same time. The patients were on average 6.1 ± 2.6 hours since onset of labour and 4.2 ± 2.5 hours before delivery which in all cases was per vagina.

4.2.4 Pentazocine

Similar studies were carried out in 8 patients (age 24 ± 2 years; weight 70.8 ± 9.1 Kg) who had received pentazocine 60 mg and cyclizine 50 mg i.m. 30 minutes before the administration of paracetamol (table 4.1). These patients were on average 4.3 ± 2.0 hours after onset of labour and 4.7 ± 3.3 hours before delivery which in all cases was per vagina.

4.2.5 Metoclopramide

Additional studies were performed to assess the possible influence of metoclopramide (Maxolon) on the effects of narcotic analgesics on paracetamol absorption. The dose selected was 10 mg i.m. since this had been used previously during labour (Howard and Sharp, 1973) without apparent toxicity in the mother or neonate.

Five women (age 25 ± 3 years; weight 68.6 ± 7.1 Kg) were studied 30 minutes after diamorphine

10 mg and metoclopramide 10 mg i.m. These patients were on average 4.1 $\pm$ 1.1 hours after onset of labour and 6.7 $\pm$ 4.3 hours before delivery.

A further 5 patients in labour (age 26 $\pm$ 2 years; weight 68.2 $\pm$ 7.7 Kg) were studied 30 minutes after pethidine 150 mg and metoclopramide 10 mg i.m. At the time of the study, these patients were 3.5 $\pm$ 2.0 hours after onset of labour and 1.5 $\pm$ 0.79 hours before delivery.

4.2.6 Paracetamol absorption

In all patients, paracetamol absorption was studied as described in page 60.

4.3 RESULTS

Patient data are summarised in Table 4.2. The women who received pethidine were statistically significantly younger than those in all the other groups ($p < 0.05$) but this difference is likely to be of little clinical significance. There were no differences in the weights of patients between the groups although, not surprisingly there was a trend for the women studied in the post-partum period to be lighter than the other groups. In the group of women who received

TABLE 4.2 SUMMARY OF PATIENT DATA (Mean $\pm$ SD)

Patients number	Study	Age years	Weight Kg	Parity 0 1 2 3	Syntocinon	Time from onset of labour hours	Time of analgesia hours	Time to delivery hours
1 - 12	Control	25.4 ± 3.3	72.2 ± 6.5	5 3 3 1	10/12	1.7 ± 1.2	3.3 ± 0.98 (after study)	10.6 ± 6.7
13 - 22	Post partum	25.4 ± 3.7	66.4 ± 7.3	0 4 3 3	-	-	16hrs	-
23 - 30	Pethidine	23.0 ± 4.1	69.5 ± 11.8	1 7	6/8	2.9 ± 1.8	1.1 ± 0.9	2.6 ± 1.6 *
31 - 38	Diamorphine	19.1 ± 2.0 *	67.6 ± 7.8	8	3/8	6.1 ± 2.6 *	0.8 ± 1.3	4.2 ± 2.5 *
39 - 46	Pentazocine	24.1 ± 1.7	70.8 ± 9.1	5 3	2/8 *	4.3 ± 2.0 *	0.5	4.7 ± 3.3 *
47 - 51	Diamorph/ Metoclo	24.8 ± 2.8	68.3 ± 7.1	5	5/5	4.1 ± 1.1 *	0.5	6.7 ± 4.3
51 - 56	Pethidine/ Metoclo	26.4 ± 2.1	68.2 ± 7.7	1 3 1	5/5	3.5 ± 2.0 *	0.5	1.5 ± 0.79 *

* = Significantly different from control group data ($p < 0.05$)

pentazocine, significantly fewer were receiving oxytocin infusion at the time of study ($p < 0.05$ X^2 test). The parity of the patients varied considerably between groups and women receiving diamorphine were all primiparous. It is likely that this reflects the prescribing habits of the obstetricians who tend to give this drug more frequently to primipara when a longer labour is anticipated.

All the groups except the one which received pethidine alone had been in labour significantly longer than the control group ($p < 0.05$) and all the groups except the diamorphine/metoclopramide group were closer to delivery than the control group ($p < 0.05$).

In the control studies, analgesia was given on average 3.3 hours after the test dose of paracetamol. In the other groups, analgesia had been given before the study and there were no significant differences between the groups in the interval between administration of the analgesia and the test dose of paracetamol.

4.3.1 Control studies

In the 12 patients in labour who had not

received a narcotic analgesic, paracetamol absorption was rapid (figure 4.1 ; table 4.3). The mean peak paracetamol concentration was 26.0 $\pm$ 12.2 ug/ml and the mean time of the peak concentration was 57.5 $\pm$ 46.9 minutes. The corresponding values in non-pregnant volunteers were 17.0 $\pm$ 5.2 and 82.5 $\pm$ 53.5 minutes (page 70). The peak concentrations in these women in labour were significantly higher than in non-pregnant volunteers ($p < 0.05$). The times of peak concentrations did not differ. Plasma concentrations at each of the sampling times did not differ significantly between the two groups. Neither did the areas under the plasma concentration time curves (AUC) from 0 to 90 minutes differ significantly (table 4.9).

The 10 women studied in the post-partum period comprised an additional control group, although blood samples were taken for only 2 hours. Paracetamol absorption was again rapid (table 4.4 ; figure 4.1). Concentrations at each time and the AUC from 0 to 90 minutes did not differ significantly from the non-pregnant volunteers nor from the control women during labour.

4.3.2 Pethidine

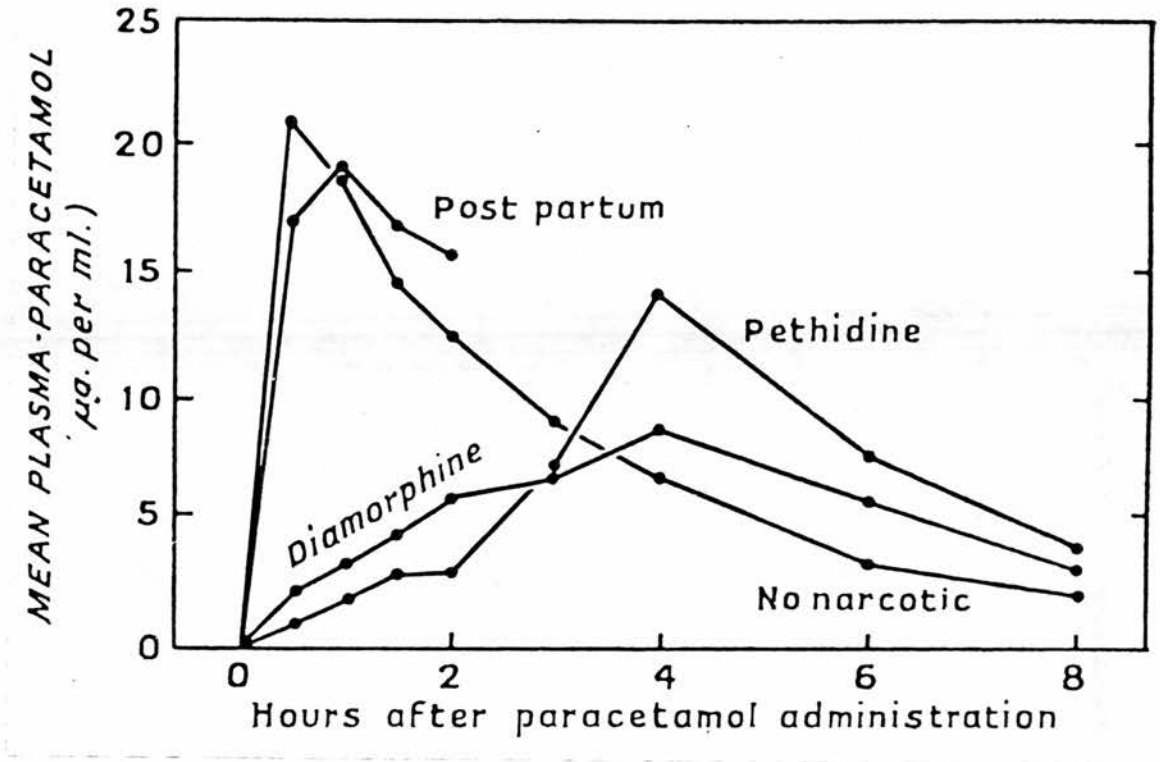


FIGURE 4.1

Mean plasma paracetamol concentrations in 38 women during labour after 1.5 g orally with 200 ml water.

No narcotic controls	(n = 12)	
Post partum	(n = 10)	
Pethidine	(n = 8)	1.1 hours after pethidine 150 mg i.m.
Diamorphine	(n = 8)	0.8 hours after diamorhpine 10mg i.m.

TABLE 4.3 PARACETAMOL ABSORPTION IN WOMEN DURING LABOUR BEFORE ADMINISTRATION OF A NARCOTIC ANALGESIC

Time / Patient	Plasma Paracetamol Concentration (ug/ml) 30'	60'	90'	120'	3 hrs	4 hrs	6 hrs	8 hrs	A.U.C.(ug hr/ml) 0-90min	0-6hrs
1	21.2	23.2	19.5	17.3	13.4	9.0	3.2	1.2	27.1	65.4
2	8.0	21.1	12.9	11.6	7.3	5.4	1.9	0.7	17.8	47.0
3	1.9	28.4	27.8	23.8	15.2	11.6	4.8	2.1	22.1	83.9
4	21.4	19.6	14.6	10.3	7.4	5.1	2.1	-	24.2	52.7
5	2.7	13.0	12.7	13.4	9.3	8.4	5.0	2.7	11.2	41.4
6	37.3	23.0	18.1	13.1	9.2	8.9	4.2	-	34.7	75.8
7	1.0	1.0	1.9	3.7	8.0	7.3	5.5	4.2	1.5	29.2
8	19.7	18.6	13.5	10.1	9.3	5.7	2.8	-	22.5	54.1
9	38.7	18.4	12.9	9.5	6.3	4.2	2.1	-	31.8	56.8
10	18.5	11.9	8.6	7.3	4.3	2.8	1.0	-	17.4	34.5
11	29.4	19.7	14.7	14.2	9.4	5.8	3.1	1.9	28.2	63.8
12	52.5	26.9	17.0	14.3	8.7	6.6	2.4	1.2	43.9	79.9
Mean	21.0	18.7	14.5	12.4	9.0	6.7	3.2	2.0	23.5	57.0
SD	16.29	7.4	6.2	5.07	2.92	2.42	1.23	1.18	11.1	17.5

TABLE 4.4 PARACETAMOL ABSORPTION IN PATIENTS 2 TO 5 DAYS AFTER CHILDBIRTH

Patient \ Time	Plasma Paracetamol Concentration(ug/ml) 30'	60'	90'	120'	AUC (ug hr/ml) 0-90'
13	35.8	26.8	20.5	16.9	27.4
14	23.4	21.1	16.3	12.6	26.3
15	8.3	13.3	16.7	14.7	15.0
16	5.8	22.4	22.6	19.2	19.8
17	35.0	26.3	21.6	17.4	36.1
18	22.6	14.7	11.8	-	21.6
19	15.8	20	14.6	11.3	21.6
20	1.8	7.7	9.5	11.7	7.1
21	1.8	17	13.6	18.8	12.8
22	19.7	21.2	20.9	17.5	25.7
Mean	17.0	19.0	16.8	15.6	21.3
SD	12.6	5.9	4.5	3.1	8.3

4.3.2 Pethidine

In all the patients given pethidine, paracetamol absorption was delayed (table 4.5, figure 4.1). The mean peak plasma paracetamol concentration was 15.4 $\pm$ 10.2 ug/ml and the mean time to peak concentration was 240.0 $\pm$ 55.5 minutes (control 26.0 $\pm$ 12.2 ug/ml (NS) and 57.5 $\pm$ 46.9 min ($p < 0.001$) respectively). Plasma concentrations at 30, 60, 90 and 120 minutes were highly significantly lower than those in the control group ($p < 0.001$). The AUC from 0 to 90 minutes was also significantly lower after pethidine ($p < 0.01$) but the AUC from 0 to 6 hours did not differ significantly in the 2 groups.

4.3.3 Diamorphine

Paracetamol absorption was also delayed in all 8 patients who had received diamorphine before the study (table 4.6, figure 4.1). The mean peak paracetamol concentration was 10.5 $\pm$ 5.4 ug/ml and the mean time of peak concentration was 225 $\pm$ 147 minutes ($p < 0.05$ and $p < 0.005$ respectively compared with control values). Plasma paracetamol concentrations at 30, 60, 90 and 120 minutes were significantly lower than in the control study ($p < 0.01$). The AUC from 0 to 90 minutes and from 0 to 6 hours were significantly smaller than in the control studies ($p < 0.01$ and $p < 0.05$ respectively).

TABLE 4.5 PARACETAMOL ABSORPTION AFTER PETHIDINE 150 mg INTRAMUSCULARLY

Patient \ Time	30'	60'	90'	120'	3 hrs	4 hrs	6 hrs	8 hrs	AUC ug hr/ml 0-90'	AUC ug hr/ml 0-6h
23	0.7	2.2	3.6	4.5	3.9	3.4	6.0	-	2.4	21.6
24	2.4	2.7	3.2	3.2	5.9	19.0	-	-	3.4	-
25	0.8	1.0	1.6	2.3	18.7	12.5	14.0	-	1.3	54.9
26 *	2.4	4.7	4.7	5.3	5.3	6.8	5.9	3.5	4.7	31.3
27	0	0	1.6	2.1	2.4	19.9	4.1	-	0.4	38.7
28 *	0.3	1.2	1.3	1.4	2.0	10.6	9.1	4.3	1.1	29.5
29	0	3.0	5.4	4.1	7.8	4.2	2.6	-	2.9	24.0
30	0	0.6	0.9	1.3	11.3	35.6	11.5	-	0.5	78
Mean	0.8	1.9	2.8	3.0	7.2	14.0	7.6	3.9	2.1	39.7
SD	1.0	1.5	1.7	1.5	5.6	10.7	4.1	0.6	1.5	20.2

* did not receive cyclizine

TABLE 4.6 PARACETAMOL ABSORPTION AFTER DIAMORPHINE 10 mg INTRAMUSCULARLY

Time / Patient	30'	60'	90'	120'	3 hrs	4 hrs	6 hrs	8 hrs	AUC ug hr/ml 0-90'	AUC ug hr/ml 0-6h
31	1.6	1.6	2.6	-	-	9.3	-	13.3	2.3	-
32 *	0.5	1.2	1.4	1.9	2.4	2.8	-	-	1.2	-
33	0	1.8	2.4	6.6	13.2	21.2	8.8	-	1.5	60.9
34	0	1.0	1.4	2.6	4.4	7.2	5.2	3.5	1.3	23.6
35	4	7.1	13.1	11.9	11.0	12.3	5.9	-	8.8	56.4
36	1.9	4.2	5.4	4.8	4.8	4.7	8.7	-	4.4	30.0
37 *	0.6	3.8	4.1	8.8	7.4	7.9	3.8	-	3.2	33.9
38	9.2	5.6	5.9	4.7	4.2	3.5	2.6	2.3	8.9	25.9
Mean	2.2	3.3	4.5	5.9	6.8	8.6	5.8	2.9	3.9	38.5
SD	3.1	2.3	3.9	3.5	4.0	6.0	2.5	6.0	3.2	16.1

* did not receive cyclizine

Of the patients given narcotics, 6 in each group were also given cyclizine. Paracetamol absorption in these patients was similar to that in the women receiving diamorphine or pethidine alone (Tables 4.5 and 4.6).

4.3.4 Pentazocine

Thirty minutes after pentazocine 60 mg and cyclizine 50 mg i.m., paracetamol absorption was markedly delayed in all 8 patients, at least for the 90 minutes during which blood samples were taken (Table 4.7, Figure 4.2). The mean plasma paracetamol concentration at 90 minutes was only 2.5 ± 1.8 ug/ml and the concentrations were still rising at this time. Concentrations at 30, 60, and 90 minutes were significantly lower than those observed in the control group ($p < 0.01$). The AUC from 0 to 90 minutes was significantly lower than in the control study ($p < 0.01$).

4.3.5 Metoclopramide

Paracetamol absorption was abnormally slow in all the women who received metoclopramide at the same time as pethidine or diamorphine (Table 4.8, Figures 4.3 and 4.4). The mean concentrations at 90 minutes were only 5.3 ± 6.1 and 3.3 ± 1.6 ug/ml respectively and at this time the concentrations were still rising.

TABLE 4.7 PARACETAMOL ABSORPTION AFTER PENTAZOCINE 60 mg AND CYCLIZINE 50 mg INTRAMUSCULARLY

Patient \ Time	15'	30'	45'	60'	75'	90'	AUC ug hr/ml 0-90'
39	0	0	0	0	0.2	0.7	0.2
40	0	0	0	0	0	0	0
41	0	1.5	3.0	4.8	4.4	4.3	4.2
42	0.7	3.3	4.9	5.4	4.9	4.9	5.6
43	0	1.4	1.9	1.9	1.9	1.9	2.1
44	0	0	0.9	2.4	2.8	3.3	2.0
45	0	0.3	0.5	0.8	1.0	1.6	0.95
46	0.3	0.5	0.3	0.5	1.5	3.6	1.4
Mean	0.125	0.87	1.43	1.97	2.1	2.5	2.1
SD	0.25	1.15	1.74	2.11	1.8	1.8	1.9

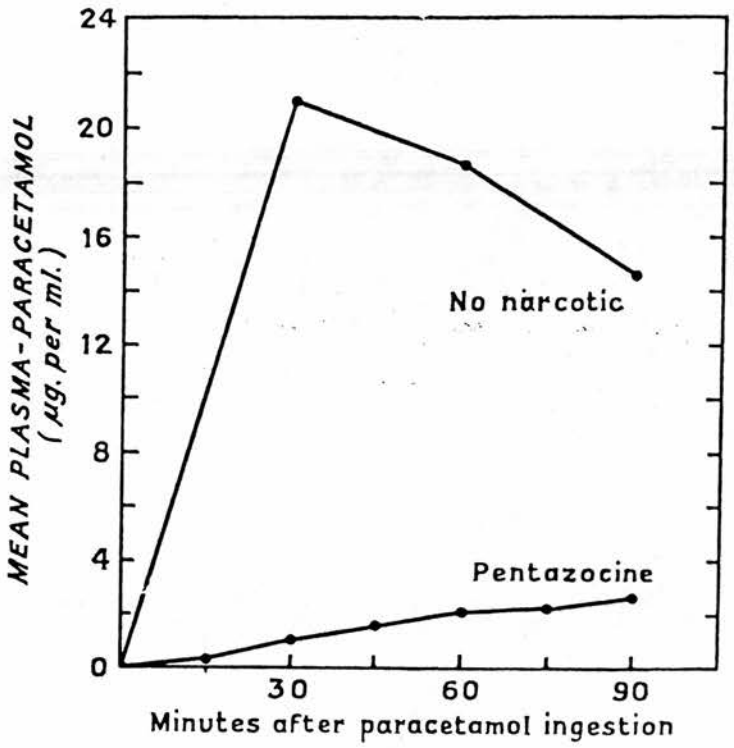


FIGURE 4.2

Mean plasma paracetamol concentrations in 20 women during labour after 1.5 g orally with 200 ml water.

No narcotic controls (n = 12)

Pentazocine (n = 8) 30 minutes after pentazocine 60 mg and cyclizine 50 mg i.m.

TABLE 4.8 THE EFFECT OF METOCLOPRAMIDE ON NARCOTIC INDUCED DELAY IN PARACETAMOL ABSORPTION

Patient \ Time	Plasma paracetamol concentrations ug/ml 15'	30'	45'	60'	75'	90'	AUC ug hr/ml 0-90'
Diamorphine/Metoclopramide							
47	0.3	0.6	0.9	1.3	3.1	3.5	1.8
48	0	0.6	0.7	4.7	7.8	5.9	4.1
49	0	0	0	0	0	0	0
50	0.5	0.8	1.1	2.4	2.4	2.4	2.2
51	0	3.2	4.9	4.2	4.9	4.6	4.9
Mean	0.16	1.04	1.52	2.52	3.64	3.28	2.6
SD	0.16	1.24	1.9	2.0	2.9	1.57	1.9
Pethidine/Metoclopramide							
52	0.6	0.6	0.6	0.6	1.0	1.6	1.0
53	0	0.3	1.3	5.2	3.9	5.5	4.1
54	0	0	1.0	2.0	1.7	4.1	2.0
55	4.6	10.9	12.0	15.1	15.1	15.5	16.9
56	0.6	0.6	0	0.6	0	0	0.6
Mean	1.2	2.5	3.0	4.7	4.3	5.3	4.9
SD	1.9	4.7	5.0	6.1	6.2	6.1	6.8

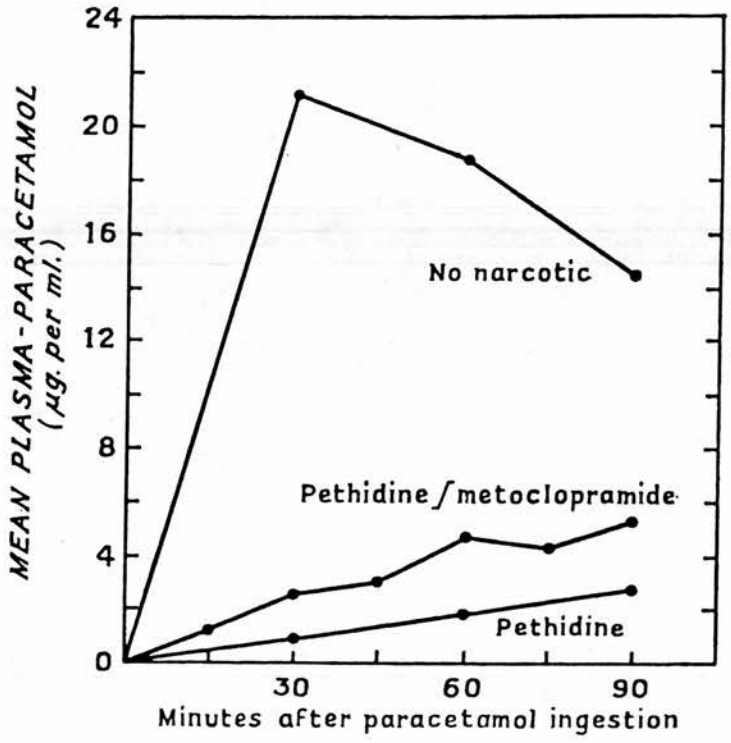


FIGURE 4.3

Mean plasma paracetamol concentrations in 25 women during labour after 1.5 g orally with 200 ml water.

No narcotic controls	(n = 12)	
Pethidine	(n = 8)	
Pethidine/Metoclopramide	(n = 5)	30 minutes after pethidine 150 mg and metoclopramide 10 mg i.m.

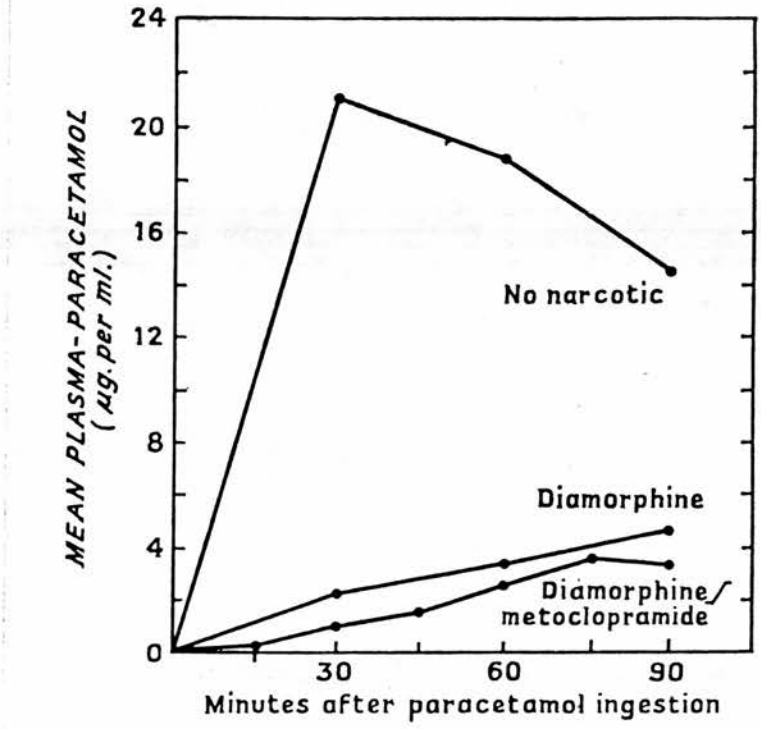


FIGURE 4.4

Mean plasma paracetamol concentrations in 25 women during labour after 1.5g orally with 200 ml water.

No narcotic controls	(n = 12)	
Diamorphine	(n = 8)	
Diamorphine/metoclopramide	(n = 5)	30 minutes after diamorphine 10 mg and metoclopramide 10 mg i.m.

Plasma paracetamol concentrations at 30, 60 and 90 minutes after pethidine and metoclopramide did not differ significantly from those in the women who received pethidine alone or with cyclizine ($p < 0.05$) but were significantly lower than those observed in the control study ($p < 0.01$). Similarly the AUC after pethidine and metoclopramide did not differ from that after pethidine alone but was significantly lower than that in the control study ($p < 0.01$).

Metoclopramide obviously did not enhance significantly the rate of paracetamol absorption after diamorphine and statistical analysis is unnecessary. A summary of the results is given in table 4.9.

4.4 DISCUSSION

In 12 women in labour before narcotic administration and in 10 post partum patients, paracetamol absorption was rapid. The time to achieve peak plasma paracetamol concentrations did not differ significantly from that observed in healthy non-pregnant volunteers. Peak concentrations were significantly higher in the women during labour but the area under the plasma

TABLE 4.9 SUMMARY OF PARACETAMOL ABSORPTION STUDIES

Group	Mean peak concentr. ug/ml	p	Mean time to peak minutes	p	AUC 0-90' ug hr/ml	p	AUC 0-6 h ug hr/ml	p
Non-pregnant volunteers n = 10	17.0 ± 5.2		82.5 ± 53.5		15.1 ± 9.0		-	
Controls n = 12	26.0 ± 12.2	0.05 *	57.5 ± 46.9	NS *	23.5 ± 11.1	NS *	57.0 ± 17.5	
Pethidine n = 8	15.4 ± 10.2	NS **	240 ± 55.5	0.001 **	2.1 ± 1.5	0.01 **	39.7 ± 20.2	NS **
Diamorphine n = 8	10.5 ± 5.4	0.001 **	225 ± 147	0.005 **	3.9 ± 3.2	0.01 **	38.5 ± 16.1	0.05 **
Pentazocine n = 8	-		-		2.1 ± 1.9	0.01 **	-	
Diamorphine + Metoclopramide	-		-		2.6 ± 1.9	0.01 **	-	
Pethidine + Metoclopramide	-		-		4.9 ± 6.8	0.01 **	-	

* Compared with non-pregnant volunteers

** Compared with controls

concentration time curve from 0 to 90 minutes did not differ in the groups.

In this study, the obstetric management of the patients was not influenced by their participation and 10 of the 12 controls received an i.v. oxytocin infusion. This infusion was constantly varying as it was titrated to the patients' needs - the rate was varied by the nursing staff to produce uterine contractions at regular intervals. Thus it was not possible from these data to determine any effect of oxytocin on paracetamol absorption. Since oxytocin produces smooth muscle contractions it is possible that it increases gastric emptying and gastrointestinal motility but there is no published information on this possibility. In the 2 controls who did not receive oxytocin, plasma paracetamol concentrations appear similar to the 10 who did not but the number is too small for statistical analysis. It is possible that the oxytocin contributed to the significantly higher peak paracetamol concentrations in the control group compared with those in the non-pregnant volunteers.

When paracetamol absorption was studied during labour 30 to 60 minutes after an intramuscular injection of pethidine or diamorphine, paracetamol

absorption was markedly and significantly delayed as shown by comparison of mean peak paracetamol concentrations, time to achieve the peak concentrations, plasma concentrations at 30, 60, 90 and 120 minutes and the AUC from 0 to 90 minutes. In the pethidine study the mean peak plasma paracetamol concentrations were not significantly lower than in the control group but the time of the peak concentration was delayed. In addition, the AUC from 0 to 6 hours was significantly less in the diamorphine group when compared with controls but not in the pethidine group. This may reflect the shorter duration of action of pethidine.

Narcotic analgesics are known to produce analgesia, sedation, respiratory and cough suppression, nausea, vomiting and contractions of smooth muscle which results in constipation, urinary retention, miosis, constriction of the sphincter of Oddi and the ureter (Jaffe 1970). In addition they increase the tone of gastro-intestinal smooth muscle and interfere with normal peristalsis (Daniel et al, 1959; Burks and Long 1967; Cairnie, Korterlitz and Taylor 1961). In an X-ray study in healthy volunteers, morphine was shown to delay gastric emptying after an initial transient acceleration

(Crone and Ardran 1957). In the present study it seems likely that diamorphine and pethidine contributed to the delayed paracetamol absorption by delaying gastric emptying.

Six of the 8 patients in each group who received pethidine or diamorphine also received cyclizine 50 mg i.m. (tables 4.4 and 4.5). The paracetamol concentrations appear similar in those who received cyclizine and those who did not but the numbers are too small for statistical analysis. Cyclizine is known to have very weak peripheral anticholinergic effects in addition to its antihistamine and anti-emetic effects (Turner and Richens 1978). Theoretically cyclizine may have contributed to the delay in paracetamol absorption by delaying gastric emptying. However, the magnitude of the delay is much greater after pethidine or diamorphine than it was after atropine or propantheline which have marked peripheral anticholinergic effects (Adjepon-Yamoah et al 1973; Nimmo et al 1973).

The use of cyclizine was standardised or it was omitted in all the following studies.

Pentazocine is a partial agonist-antagonist

narcotic analgesic. Its main advantage is in chronic use when it does not result in addiction. In human subjects, it produced a delay in gastric emptying and small intestinal propulsive motility, prolonging stomach to rectum transit time of an oxygen bolus (Danhof 1967). In the present study, pentazocine 60 mg i.m. and cyclizine 50 mg i.m. markedly delayed paracetamol absorption at least for the 90 minutes that blood samples were taken. The magnitude of this delay was similar to that observed after diamorphine. This is compatible with delayed gastric emptying and the relationship is explored further in Chapters 7, 8 and 9.

In this study, the controls were not ideal since they had been in labour for a shorter period and were further from delivery than the groups who received narcotic analgesics. Thus it is not possible to determine the effect of labour itself on paracetamol absorption. All patients in the hospital in Edinburgh received some form of analgesia in late labour. However, all patients who received diamorphine, pethidine or pentazocine had delayed paracetamol absorption.

Tomson et al (1979) confirmed these findings. In 12 women in labour, oxazepam was rapidly absorbed

after oral administration. Plasma oxazepam concentrations were similar to those seen in healthy non-pregnant volunteers unless pethidine was given one hour before when oxazepam absorption was delayed without a change in bioavailability. The times of peak concentrations were 1 to 3 hours and 6.5 to 8 hours without and after pethidine respectively.

In a study of 257 patients undergoing Caesarean section under general anaesthesia, Holdsworth (1978) found that patients who had received pethidine had significantly larger volumes of stomach contents than those who had received no analgesia or extradural analgesia during labour. In addition, he found no correlation between the length of labour and the volume of gastric contents at induction of anaesthesia.

Davison et al (1970) studied gastric emptying in eight women during labour using a nasogastric tube and a double sampling aspiration technique (George 1968). They measured the disappearance from the stomach of 750 ml of water containing 30 ug/ml of phenol red as a marker. Only one patient had a normal exponential emptying pattern. Thirty minutes after swallowing the test solution a mean of 393 ml remained in the stomach (non-pregnant

control - 275 ml). Each patient had an initial rapid emptying in the first 10 minutes, the volume in the stomach falling by almost one third. Thereafter the ability of the stomach to empty the water test meal was impaired. The authors do not record the state of labour or the possibility of analgesia administration although they state that their patients were not given sedatives. Therefore it is difficult to compare their results with others. However, it is possible that the rapid paracetamol absorption observed in my controls in labour reflects the initial rapid gastric emptying seen by Davison et al.

Howard and Sharp (1973) studied gastric emptying in 30 patients in labour using the same method as described by Davison et al. Their patients had been in labour for at least 4 hours and all were receiving intravenous oxytocin. Pethidine 150 mg i.m. was given as required to provide "adequate analgesia" but no data were given on the time of injection with respect to the gastric emptying measurements. Five patients were unable to tolerate the nasogastric tube or vomited after the test solution and were withdrawn from the study. Thirteen of the remaining 25 patients received metoclopramide 10 mg i.m. and 12 received

placebo. Thirty minutes after the metoclopramide a mean of 363 ml remained in the stomach (placebo = 567 ml $p < 0.0005$). The half-life of gastric emptying was 141 minutes in the control group and 51 minutes after metoclopramide (value for non-pregnant controls = 11.2 minutes). Howard and Sharp concluded that metoclopramide was of value in accelerating gastric emptying during labour.

Metoclopramide is a chlorbenzamide derivative which is anti-emetic and which accelerates gastric emptying perhaps by sensitizing gastric smooth muscle fibres to the effect of acetylcholine (Pinder et al 1976). It has been shown to accelerate gastric emptying and paracetamol absorption in healthy volunteers (Nimmo et al 1973, page 44).

However, in the present studies in women during labour, metoclopramide 10 mg i.m. given simultaneously with diamorphine 10 mg i.m. or pethidine 150 mg i.m. did not increase significantly the rate of paracetamol absorption as judged by the plasma concentrations at 30, 60 and 90 minutes and the AUC from 0 to 90 minutes. It seems likely that these results differ from those of Howard and Sharp because of the timing of the pethidine administration and that the two results

are compatible. Metoclopramide 10 mg i.m. may accelerate gastric emptying during labour if given at a different time from a narcotic analgesic. It is not known whether a larger dose of metoclopramide would overcome the effect of the narcotic.

The rate of paracetamol absorption depends on the rate of gastric emptying (p 44) and factors which influence gastric emptying will in turn influence the rate of paracetamol absorption. In the present studies, paracetamol absorption was rapid in women in early labour who had not received narcotic analgesics and in women 2 to 5 days post partum. It seems inevitable that gastric emptying was rapid in these patients. After pethidine, diamorphine or pentazocine paracetamol absorption was markedly delayed presumably due to delayed gastric emptying. It seems likely that the narcotic analgesics contributed to this delay but it is not possible to exclude the effect of labour itself and the pain which was the indication for the narcotic administration. Metoclopramide 10 mg i.m. did not affect significantly the delay in paracetamol absorption seen after the narcotic administration.

Delayed gastric emptying during labour is at least partly responsible for maternal death related

to anaesthesia, and the number of deaths has not decreased over a period of two decades (DHSS 1972). The use of narcotic analgesics for the relief of pain in labour may be a major factor in producing the delay in gastric emptying.

CHAPTER 5

FURTHER STUDIES OF GASTRIC EMPTYING IN WOMEN DURING LABOUR

5.1 INTRODUCTION

It was not possible to demonstrate conclusively that labour itself had no effect on paracetamol absorption since the control patients in the previous chapter were studied in early labour while the patients receiving analgesics were in late labour and approaching delivery. At the University Hospital, Nijmegen, Holland, almost all women experience labour and childbirth without receiving any analgesia. The patients are told they should expect pain and are taught deep-breathing exercises to perform during each uterine contraction. In general, the husband is present throughout labour and delivery to provide support for his wife. In a publication from Amsterdam describing pain relief during labour, the first paragraph is as follows.

" It is written in the Bible (Genesis 3.16) that a woman shall bear children with suffering. An emotionally well-balanced woman, or a woman who has received psychological guidance during pregnancy

(with or without special exercises during pregnancy), is usually able to tolerate labour pain without resort to medication." (Kronig 1967).

In the present study, I visited the Department of Obstetrics in the University of Nijmegen for 3 weeks and estimated gastric emptying rate from the absorption of orally administered paracetamol in women in labour approximately 2 - 4 hours before delivery to determine if the pain of labour itself with approaching delivery might contribute to the observed delay in emptying of the stomach.

5.2 PATIENTS AND METHODS

Fifteen patients (age 26.9 $\pm$ 4.8 years; weight 67.6 $\pm$ 7.7 Kg) without evidence of cardiac, respiratory, gastrointestinal or hepatic disease were studied (Table 5.1). After at least a 4 hour fast, each was given 1.5 g of paracetamol as 3 Panadol tablets with 200 ml of water at a time when delivery would be expected within 2 - 4 hours as determined by the obstetrician. All patients were experiencing severe pain during the uterine contractions throughout the study. None had received any drugs in the previous 24 hours and no other drugs were administered throughout except for patients 10 and 13 who were receiving an intravenous

TABLE 5.1 PATIENT DATA

Patient	Age years	Weight Kg	Parity	Oxytocin	Time from onset of labour hours	Time to delivery hours
1	27	69	0	-	3	2
2 *	28	61	1	-	4	1.5
3	28	64	0	-	1.5	3.3
4 *	27	62	0	-	4	3.3
5	28	69	0	-	3.25	8
6	21	71	0	-	2	8.3
7	34	84	1	-	2.5	2.13
8	38	63	1	-	1	11
9	30	65	0	-	5.5	3.3
10	24	77	0	+	1	3
11	24	65	0	-	10	1.5
12	28	58	1	-	12	3.5
13	22	56	0	+	12	5
14	24	77	0	-	6	2
15	20	73	0	-	12	3
Mean	26.9	67.6	11 x 0	2/15	5.3	4.1
SD	4.8	7.7	4 x 1		4.1	2.8

* Patients had Caesarean section.

oxytocin infusion which was titrated by the obstetrician to maintain frequent uterine contractions. No patient took anything by mouth after the test does of paracetamol.

Blood samples were taken at intervals for 90 minutes and unchanged paracetamol in plasma was measured as before by gas liquid chromatography in the same laboratory in Edinburgh as in previous studies.

No patient delivered a child during the study and the time from the start of the study to delivery ranged from 90 minutes to 11 hours (mean 4.1 $\pm$ 2.8 hours). All patients had vaginal deliveries except patients 2 and 4 who were delivered by Caesarean section under general anaesthesia because of foetal distress. The mean time from the onset of labour to test dose of paracetamol was 5.3 $\pm$ 4.1 hours.

5.3 RESULTS

The results obtained in this study were compared with those obtained from the women in labour studied in Edinburgh and described in the previous chapter. There were no significant differences between the Holland group and any of the groups in Edinburgh with respect to age, weight, parity or administration

of oxytocin (Table 4.1 and Table 5.1). There was a significant difference between the times that the women had been in labour before the study in the Holland group and the control group in Edinburgh ($p < 0.05$) but not between the Holland group and any of the groups who had received any form of analgesia in Edinburgh. In addition the Holland group were significantly closer to delivery than the control group in Edinburgh ($p < 0.01$) but were very similar to all the groups who received analgesia in this respect.

Thus the group of 15 women studied in Holland were similar in all respects to the patients studied in Edinburgh except that they were studied late in the first stage of labour at a time when they were experiencing severe pain and patients in Edinburgh would have received some form of analgesia.

Plasma paracetamol concentrations are shown in Table 5.2 and Figure 5.1. In 9 patients (Nos. 1, 2, 3, 4, 8, 10, 11, 13, 15) paracetamol absorption was rapid while, in the others, absorption was slow. A mean peak plasma concentration of 12.8 $\pm$ 10.1 ug/ml was achieved 60 minutes after ingestion. Corresponding values for the women studied in Edinburgh were 21.0 $\pm$

TABLE 5.2 PLASMA PARACETAMOL CONCENTRATIONS IN WOMEN DURING LATE LABOUR WHO HAVE RECEIVED NO ANALGESIA

Time / Patient	Plasma paracetamol concentrations (ug/ml)						AUC 0 - 90 min (ug hr/ml)
	15 min	30 min	45 min	60 min	75 min	90 min	
1	6.8	14.4	11.0	9.2	7.3	6.5	13.4
2	0	0.5	5.1	13.8	15.7	20.0	12.2
3	41.2	31.9	26.1	22.9	20.0	17.8	31.9
4	7.5	18.7	24.9	19.8	17.4	16.3	23.3
5	0	0	1.0	6.6	6.5	9.0	5.6
6	0	0	0	0.9	1.0	0.7	0.63
7	1.9	2.8	3.7	4.3	4.7	5.5	4.9
8	2.3	11.6	28.0	30.8	24.3	21.9	26.7
9	0.7	3.1	4.4	4.5	6.7	10.9	6.5
10	9.8	21.7	20.8	22.3	17.6	14.3	25.6
11	1.4	13.6	34.4	27.3	22.7	19.9	25.4
12	0	0	0.3	0.9	4.3	6.2	2.0
13	0	4.7	7.6	17.8	13.9	13.7	14.7
14	0	0.5	0.7	0.9	1.3	1.8	1.2
15	9.4	10.2	9.4	9.6	11.7	10.3	12.5
Mean	5.4	8.9	11.8	12.8	11.7	11.6	13.8
SD	10.5	9.7	11.7	10.1	7.7	6.7	10.5

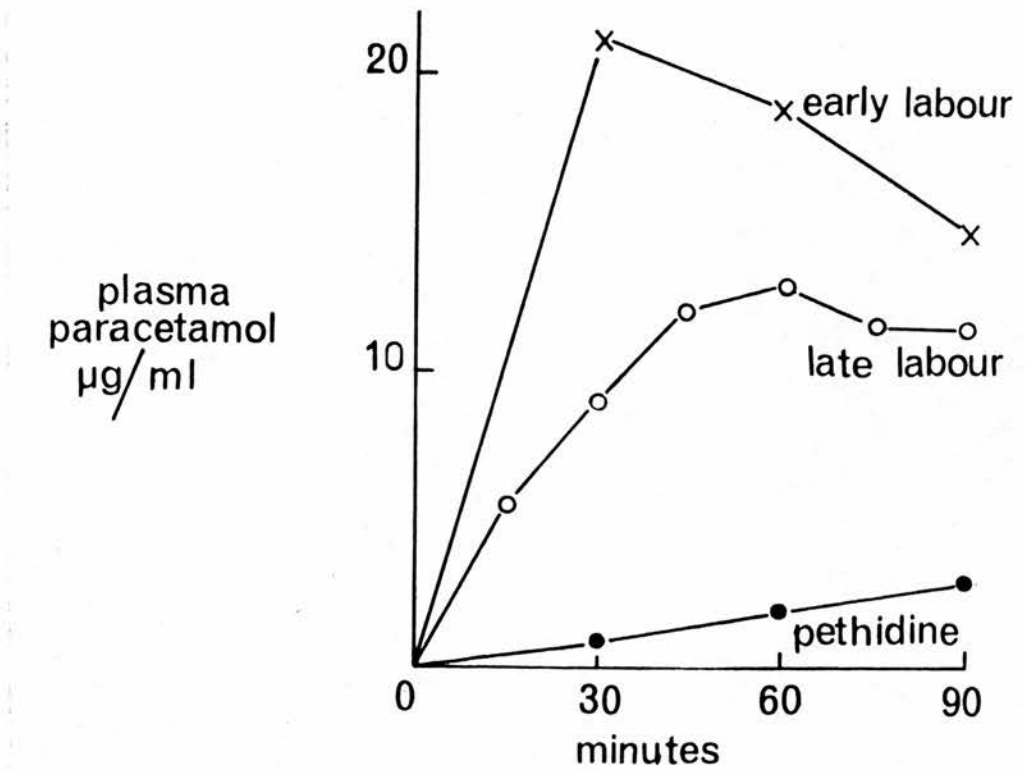


FIGURE 5.1

PARACETAMOL ABSORPTION IN WOMEN DURING EARLY OR LATE LABOUR. ON EACH OCCASION AFTER A 4 HOUR FAST, EACH PATIENT RECEIVED PARACETAMOL 1.5 g WITH 200 ML WATER

x——x	early labour -	no analgesia	(n = 12)
o——o	late labour -	no analgesia	(n = 15)
●——●	late labour -	pethidine 150 mg i.m.	(n = 8)

16.3 ug/ml at 30 minutes (controls) and 8.6 $\pm$ 6.0 ug/ml at 4 hours (diamorphine). Only the plasma concentrations at 30 minutes were significantly lower than those in the Edinburgh control group ($p < 0.05$). Concentrations at 30, 60 and 90 minutes were significantly greater than those after pethidine, diamorphine or pentazocine ($p < 0.02$).

The area under the concentration time curve from 0 to 90 minutes was significantly lower in the Holland group than in the Edinburgh controls ($p < 0.05$) but was significantly greater than after pethidine ($p < 0.005$), diamorphine ($p < 0.02$) or pentazocine ($p < 0.005$).

5.4 DISCUSSION

Paracetamol absorption was delayed in some patients late in the first stage of labour when no analgesic drug had been administered. The plasma paracetamol concentrations at 30 minutes were significantly lower than those observed in women in early labour and the area under the plasma concentration time curve from 0 to 90 minutes was significantly lower. However the magnitude of the delay was much less than that observed in patients in late labour after the administration

of pethidine, diamorphine or pentazocine. Plasma concentrations at all times and the area under the curve from 0 to 90 minutes were significantly greater in the Holland group compared with those who had received pethidine, diamorphine or pentazocine.

The patients studied in Holland appeared to fall into 2 groups. The majority of patients had rapid paracetamol absorption and the others had very slow absorption. There was no obvious association of slow absorption with duration of labour, proximity of delivery, oxytocin administration or delivery by Casaerean section. It is an important observation that 2 of the patients (Nos. 6 and 14) had paracetamol absorption which was just as poor as was observed after administration of a narcotic analgesic. It is likely that the observed changes in paracetamol absorption are due to changes in gastric emptying rate and if so then some patients in late labour will be at risk from a full stomach due to delayed gastric emptying even in the absence of narcotic administration.

5.5 INTRODUCTION TO EXTRADURAL ANALGESIA

Extradural analgesia is used increasingly both during labour and in the postoperative period to

replace more conventional methods of analgesia (Scott 1977; Taylor et al 1977). Access to the extradural space is usually gained via the lumbar route and a needle is inserted between the lumbar spinous processes at L2/3 or L3/4. A flexible plastic catheter is inserted through the needle and the needle is removed. A bacterial filter is attached to the catheter and injections of local anaesthetic drug may be given as required to maintain analgesia. This technique of analgesia is by far the most effective form of obstetric analgesia (Scott 1977).

The pain of uterine contractions is mediated through the sympathetic afferent nerves which enter the spinal cord with the spinal nerves T10, 11, 12 and L1 and L2. It is these nerves which are blocked to provide analgesia during the first stage of labour. The local anaesthetic drug used is bupivacaine 0.5% which has a longer duration of action than lignocaine. A dose of 8 - 10 ml (40 - 50 mg) is given as required (usually every 1.5 - 2 hours) to maintain analgesia. This results in a maximum plasma bupivacaine concentration of approximately 0.75 ug/ml (Reynolds and Taylor 1971).

The side effects of extradural blockade include vasodilatation of the lower limbs with a tendency for hypotension, some motor weakness of the legs and perineal muscles. However the avoidance of respiratory depression, sedation and nausea and vomiting which accompanies the administration of narcotic analgesics has meant that extradural analgesia is preferred by patients, anaesthetists and obstetricians.

In the present study, paracetamol absorption was measured as an index of gastric emptying in women undergoing extradural analgesia during the first stage of labour in the Simpson Memorial Maternity Pavilion, Edinburgh.

5.6 PATIENTS AND METHODS

Eight women (age 24.4 $\pm$ 2.3 years, weight 71.6 $\pm$ 10.3 Kg) without evidence of gastrointestinal or hepatic disease were studied (Table 5.3). These patients had been in labour for a mean of 5.4 $\pm$ 3.8 hours and had extradural analgesia established for 30 - 60 minutes before the administration of paracetamol. All were pain free at the time of the study but none had had a significant fall in arterial pressure. After at least a 4 hour fast, all

TABLE 5.3 PATIENT DATA

Patient	Age years	Weight Kg	Parity	Oxytocin	Time from onset of labour hours	Time to delivery hours
1	27	71	0	+	0.75	9.25
2	24	54	1	+	3.5	4.5
3	21	74	0	+	12	3.0
4	24	92	0	+	9.5	1.5
5	25	70	0	+	3	4.0
6	28	70	0	+	5.5	3.0
7	22	72	0	+	6.25	16
8	24	70	0	+	2.5	4.0
Mean SD	24.4 2.3	71.6 10.3	1x1 7x0	8/8	5.4 3.8	5.7 4.8

received 1.5 g paracetamol as 3 Panadol tablets with 200 ml of water. Blood samples were taken at intervals for 90 minutes for measurement of plasma paracetamol concentrations. All the patients were receiving an intravenous infusion of oxytocin which was titrated by the obstetricians and the midwives to maintain frequent uterine contractions. All patients had a vaginal delivery of the child, at a mean time after the study of 5.7 $\pm$ 4.8 hours.

5.7 RESULTS

This group did not differ significantly from the group studied in Holland with respect to age, weight, duration of labour and proximity to delivery (Table 5.1 and 5.3). In addition, there were no significant differences between this group and any of the groups in Chapter 4 with respect to age, weight, parity and administration of oxytocin (Table 4.1 and Table 5.3). This extradural group had been in labour significantly longer than the control group in Chapter 4 ($p < 0.005$). The interval between the study and delivery did not differ from any group in Chapter 4. Thus the extradural group was similar to the various groups studied in Edinburgh in late labour and in Holland.

Plasma paracetamol concentrations are shown in Table 5.4 and Figure 5.2. The absorption of paracetamol was very similar to that seen in the Holland group. The mean peak plasma paracetamol concentration was 12.9 $\pm$ 5.5 ug/ml at 75 minutes compared with 12.8 $\pm$ 10.1 ug/ml at 60 minutes and at no time were the plasma concentrations significantly different. The areas under the plasma concentration time curve did not differ significantly.

Concentrations at 30 minutes were significantly lower than those observed in the control group in Chapter 4 ($p < 0.05$) but at other times they did not differ significantly. The area under the concentration time curve from 0 to 90 minutes was significantly lower than in the control patients ($p < 0.02$).

When compared with patients who had received pethidine, diamorphine or pentazocine, plasma paracetamol concentrations were significantly greater at 30, 60 and 90 minutes ($p < 0.02$). The area under the concentration time curve was significantly greater than that observed after pethidine ($p < 0.005$), diamorphine ($p < 0.02$) or pentazocine ($p < 0.005$).

TABLE 5.4 PLASMA PARACETAMOL CONCENTRATIONS IN WOMEN DURING LATE LABOUR UNDERGOING EXTRADURAL ANALGESIA

Time / Patient	Plasma paracetamol concentration (ug/ml)						AUC 0 - 90min ug hr/ml
	15min	30min	45min	60min	75min	90min	
1	-	0.3	-	1.0	-	1.0	0.9
2	1.8	2.1	7.9	10.9	16.2	17.6	11.9
3	0	1.0	7.4	18.3	17.0	13.1	12.5
4	0	1.9	5.8	8.1	6.8	6.1	6.4
5	0.3	0.3	0.6	1.8	3.7	4.6	2.3
6	6.4	11.0	8.8	12.2	12.5	14.9	14.6
7	2.8	8.3	16.0	20.6	16.3	14.7	17.8
8	-	28.8	21.4	22.2	17.5	16.3	28.3
Mean	1.9	6.7	9.7	11.9	12.9	11.0	11.8
SD	2.5	9.8	6.9	8.1	5.5	6.3	8.9

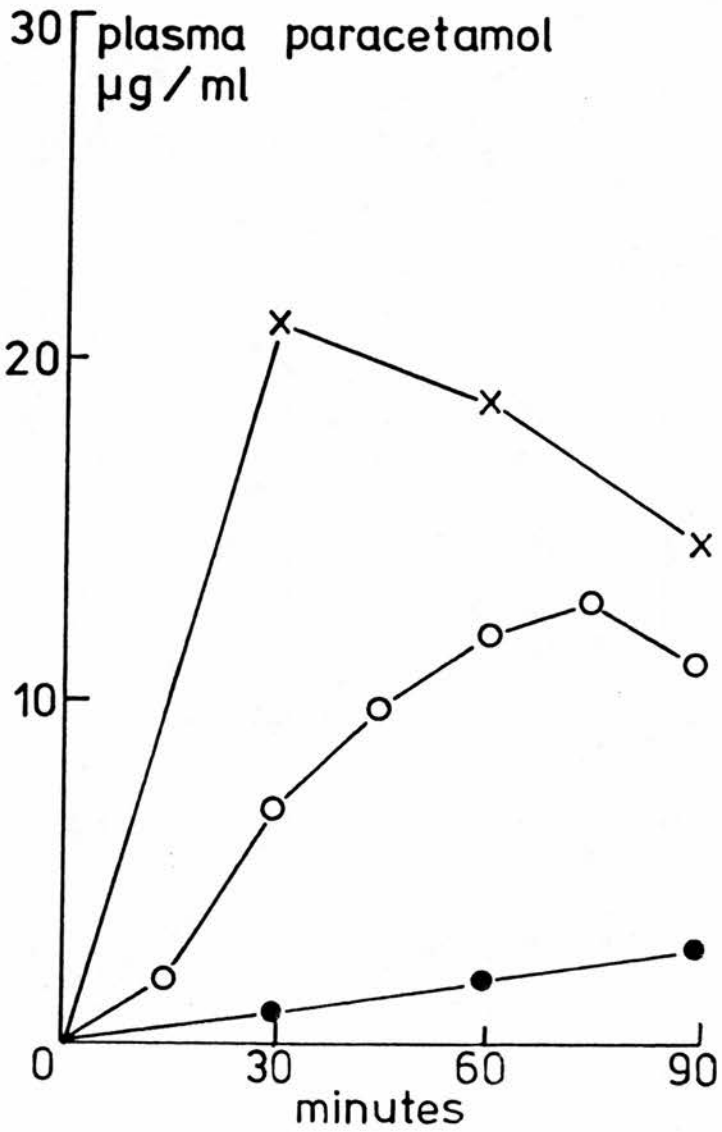


FIGURE 5.2

PARACETAMOL ABSORPTION IN WOMEN DURING EARLY OR LATE LABOUR. ON EACH OCCASION, AFTER A 4 HOUR FAST, EACH PATIENT RECEIVED PARACETAMOL 1.5 g WITH 200 ML WATER

x——x	early labour	-	no analgesia	(n = 12)
o——o	late labour	-	extradural analgesia	(n = 8)
●——●	late labour	-	pethidine 150 mg i.m.	(n = 8)

5.8 DISCUSSION

Paracetamol absorption was slightly delayed in patients late in the first stage of labour who were undergoing continuous lumbar extradural analgesia when compared with patients in early labour. The plasma paracetamol concentrations at 30 mintues were significantly lower than those observed in women in early labour and the area under the plasma concentration time curve from 0 to 90 minutes was significantly lower. However the magnitude of the delay was much less than that observed in patients in late labour after administration of pethidine, diamorphine or pentazocine.

Of particular interest is the observation that the results in the extradural group and Holland group are very similar. The patients were at the same stage of labour and the only difference between the groups was the presence of pain in the Holland group and the extradural analgesia resulting in complete absence of pain in the other group.

Little is known of the influence of extradural analgesia or the drug bupivacaine on gastro-intestinal motility or drug absorption. The abolition of sympathetic supply to the gastro-intestinal tract

may itself accelerate gastric emptying. Clark et al (1980) and Rees et al (1980) demonstrated that the sympathomimetic drugs isoprenaline and salbutamol significantly delayed gastric emptying and paracetamol absorption in patients and volunteers. Propranolol, a β-sympathetic antagonist, accelerated gastric emptying and paracetamol absorption. Extradural analgesia resulted in an increased electrical activity in the stomach in 80% of patients undergoing cholecystectomy (Gelman et al 1977) although it is likely that these patients had a higher sympathetic block than had my patients in labour.

There is little evidence that, in the absence of hypotension, splanchnic blood flow is influenced by extradural analgesia but this must be a possibility which might influence the rate of paracetamol absorption.

However, it seems inevitable from the results of these studies that extradural analgesia does not produce the marked delay in gastric emptying and paracetamol absorption that occurs after narcotic analgesia. The results of the two studies suggest that gastric emptying is delayed slightly by advancing labour and that this is not significantly

affected by extradural analgesia. Patients in late labour who have received no analgesia or are undergoing extradural analgesia are less likely to have delayed gastric emptying with a resulting full stomach than patients receiving narcotic analgesics.

CHAPTER 6

GASTRIC EMPTYING FOLLOWING HYSTERECTOMY WITH EXTRADURAL ANALGESIA

6.1 INTRODUCTION

In the first few days after abdominal surgery, gastro-intestinal motility is commonly decreased and this may be accompanied by anorexia, nausea, vomiting, diminished bowel sounds and, occasionally, paralytic ileus (Donovan and Alexander-Williams 1976; Gelman et al 1977). Conventional analgesia with narcotic analgesic drugs may contribute to this state because of their action on smooth muscle which delays gastro-intestinal transit (Daniel et al 1959; Burks and Long 1967; Cairnie et al 1961). Extradural analgesia (by means of an indwelling catheter introduced before operation) is an increasingly popular alternative to narcotic analgesia (Spence and Smith 1971) but little is known of the effect on gastro-intestinal motility. From studies in women during labour it appeared to have little effect on gastric emptying and thus it seemed worthy of study in the postoperative period.

The rate of paracetamol absorption was measured as an index of gastric emptying in patients after

hysterectomy who were receiving either narcotic or extradural analgesia in the gynaecology wards of the Royal Infirmary, Edinburgh.

6.2 PATIENTS AND METHODS

Twenty-one patients undergoing hysterectomy through a lower abdominal incision because of menorrhagia or fibroids of the uterus gave informed consent for the study. None had clinical evidence of gastro-intestinal, hepatic, cardiac or renal disease and none received any other medication during the study. The patients were randomly allocated into 3 groups to receive different regimes of postoperative analgesia (Table 6.1). One group (6 patients) age 48.7 $\pm$ 12.4 years, weight 65.0 $\pm$ 10.8 Kg was allocated extradural analgesia alone in the postoperative period. Another group (7 patients) age 36.4 $\pm$ 13.8 years, weight 61.7 $\pm$ 13.7 Kg, received diamorphine 5 mg intramuscularly as required 6 hourly. A third group (8 patients) age 46.1 $\pm$ 7.6 years, weight 52.4 $\pm$ 7.3 Kg had extradural analgesia by day when medical staff were available to give the 'top-up injections' as required and diamorphine 5 mg intramuscularly 6 hourly overnight.

After premedication with diamorphine 5 mg

TABLE 6.1 DETAILS OF PATIENTS

Group	Mean age (± SD) years	Mean weight (± SD) Kg	Anaesthesia	Analgesia after operation
Extradural (n = 6	48.7 ± 12.4	65.0 ± 10.8	Thiopentone, nitrous oxide, oxygen, halothane; lumbar extradural	Extradural analgesia alone 8-10 ml bupivacaine 0.5% as required
Diamorphine (n = 7)	36.4 ± 13.8	61.7 ± 13.7	Thiopentone, tubocurarine, nitrous oxide, oxygen, Halothane; IPVV	Diamorphine 5 mg i.m. 6 - hourly
Combined extradural plus diamorphine (n = 8)	46.1 ± 7.6	52.4 ± 7.3	Thiopentone, nitrous oxide, oxygen, halothane; lumbar extradural	Extradural analgesia by day, diamorphine by night

intramuscularly, anaesthesia was induced in all patients with thiopentone 500 mg intravenously. For maintenance of anaesthesia, the 14 patients who were to receive extradural analgesia in the post-operative period had an extradural catheter inserted at the level of L3/4 and lignocaine 2% 15-20 ml administered via the catheter. This regional analgesia was combined with general anaesthesia consisting of halothane 1% and nitrous oxide 66% in oxygen (Scott 1975). Respiration was spontaneous via a face mask. After operation, the extradural catheter was left in situ for 24 hours for administration of bupivacaine 0.5% 8 - 10 ml (a longer acting local anaesthetic drug than lignocaine used to provide postoperative analgesia). In the other 7 patients, anaesthesia was maintained by halothane 1%, nitrous oxide 66% in oxygen and the lungs were ventilated with intermittent positive pressure ventilation following the injection of tubocurarine.

After operation, 6 of the 14 patients with an extradural catheter in situ received extradural analgesia alone with 8 - 10 ml of bupivacaine 0.5% as required, usually every 2 - 3 hours. The other 8 patients had the same mode of analgesia by day and had diamorphine 5 mg intramuscularly 6 hourly

overnight. None of this group had been given diamorphine for at least 6 hours before the paracetamol absorption study.

The 7 patients who did not receive extradural analgesia during surgery received only diamorphine 5 mg intramuscularly 6 hourly and the last administration of diamorphine ranged from 1.5 to 4 hours before the study (mean 3.1 $\pm$ 1.0 hours).

Each patient was studied on 2 occasions - once at 11 a.m. on the day after operation and again one week later, so that each patient served as her own control. After a fast of at least 4 hours, each patient was given paracetamol 1.5 g (3 Panadol tablets) with 200 ml of water. The patients remained at rest in bed and no food, fluid or tobacco was allowed throughout the study. Venous blood samples were taken at intervals for 120 minutes and plasma paracetamol concentrations were measured by gas liquid chromatography.

6.3 RESULTS

There were no significant differences between the groups with respect to age and weight. One week after operation, all patients were pain free,

ambulant, on a normal ward diet and ready for discharge from hospital.

6.3.1 Control measurements (during convalescence)

One week after hysterectomy, paracetamol absorption was rapid in all but one patient (patient No.7) (Table 6.2). This one patient had no apparent reason for delayed absorption. Her general condition was similar to the other 20 patients and she was taking no other drugs.

The mean peak plasma paracetamol concentration of 25.8 $\pm$ 9.5 ug/ml occurred 45 minutes after ingestion (Table 6.2, Figure 6.1) and plasma concentrations at all time points did not differ from those observed in health volunteers (Heading et al 1973; Nimmo et al 1973, Chapter 3) (mean peak concentration 13.9 $\pm$ 5.7 ug/ml at 90 minutes).

One week after hysterectomy there were no significant differences in plasma paracetamol concentrations between the diamorphine, extradural or mixed groups (Tables 6.3; 6.4 and 6.5). In the diamorphine group the mean peak concentration was 26.7 $\pm$ 3.7 ug/ml at 60 minutes. Corresponding values were 26.2 $\pm$ 7.6 ug/ml at 45 minutes in the

TABLE 6.2 PLASMA PARACETAMOL CONCENTRATIONS IN CONTROL STUDY AFTER 1.5 g PARACETAMOL (ug/ml)

Patient \ Time	15'	30'	45'	60'	90'	120'
1	13.8	39.1	31.9	30.3	24.0	17.2
2	5.6	43.4	36.4	28.0	19.1	15.1
3	31.7	31.7	27.5	24.8	20.3	18.1
4	0	29.7	32.9	31.8	28.8	23.6
5	0	0.8	35.0	31.1	27.4	19.1
6	6.0	49.5	34.6	30.8	24.6	22.0
7	0	0	1.3	1.4	1.9	5.0
8	25.4	32.8	25.7	23.5	21.8	19.7
9	37.4	33.9	31.6	28.2	22.5	18.4
10	14.4	27.8	26.9	30.1	28.2	22.6
11	37.5	27.6	24.6	21.6	18.1	16.3
12	0	14.4	24.3	27.2	16.8	13.4
13	3.0	10.1	21.3	23.6	26.4	21.6
14	17.6	11.4	13.6	16.8	15.3	13.5
15	0	1.6	3.8	21.5	23.7	22.5
16	15.3	28.1	33.7	29.4	21.4	17.6
17	6.4	33.5	34.4	30.6	30.6	25.1
18	12.5	27.2	26.9	19.5	19.5	17.6
19	0	2.9	24.0	20.4	20.4	19.7
20	10.0	21.4	24.9	25.3	20.8	18.0
21	13.8	25.4	26.7	25.7	22.4	18.6
Mean	11.9	23.4	25.8	24.8	21.6	18.3
SD	12.2	14.4	9.5	6.9	6.1	4.4

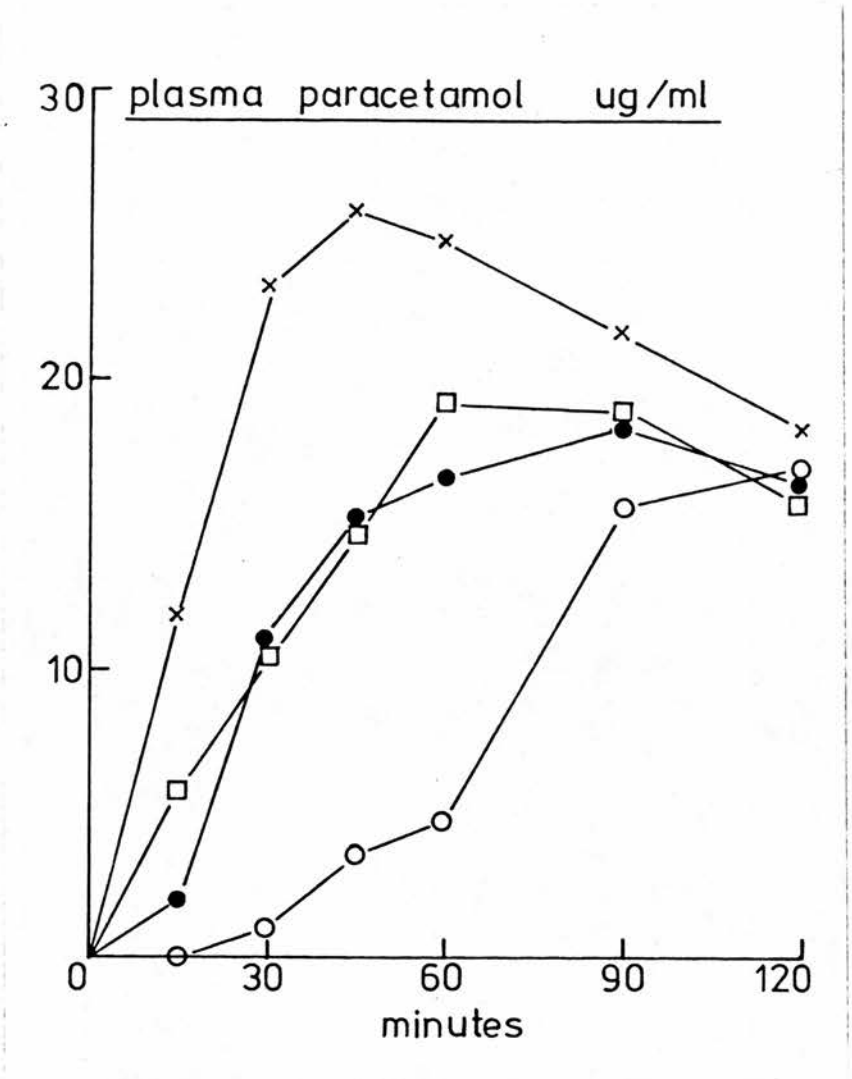


FIGURE 6.1

MEAN PLASMA PARACETAMOL CONCENTRATIONS FOLLOWING AN ORAL DOSE OF 1.5 g IN PATIENTS AFTER HYSTERECTOMY

x - x = 1 week after operation (n = 21)

o - o = Narcotic analgesia 1 day after operation (n = 8)

□ - □ = Extradural analgesia 1 day after operation (n = 6)

● - ● = Combined extradural and narcotic analgesia 1 day after operation (n = 7)

TABLE 6.3 PLASMA PARACETAMOL CONCENTRATIONS IN PATIENTS RECEIVING DIAMORPHINE FOR POSTOPERATIVE ANALGESIA (ug/ml)

Time / Patient	15'	30'	45'	60'	90'	120'
1	0	2.9	6.9	8.0	37.5	24.7
2	0	0	0	0	4.5	21.3
3	0	0.5	7.5	12.4	31.4	17.9
4	0	0	0	1.4	10.9	25.7
12	0	0	0	0	0	0
13	0	0	1.2	3.5	10.4	12.0
15	0	2.9	8.9	7.4	8.8	15.8
Mean	0	0.9	3.5	4.7	14.8	16.8
SD		1.4	4.0	4.7	14.1	8.8
Controls						
1	13.8	39.1	31.9	30.3	24.0	17.2
2	5.6	43.4	36.4	28.0	19.1	15.1
3	31.7	31.7	27.5	24.8	20.3	18.1
4	0	29.7	32.9	31.8	28.8	23.6
12	0	14.4	24.3	27.2	16.8	13.4
13	3.0	10.1	21.3	23.6	26.4	21.6
15	0	1.6	3.8	21.5	23.7	22.5
Mean	7.7	24.3	25.4	26.7	22.7	18.8
SD	11.7	15.7	10.9	3.7	4.2	3.9

TABLE 6.4 PLASMA PARACETAMOL CONCENTRATIONS IN PATIENTS UNDERGOING EXTRADURAL ANALGESIA ALONE FOR POSTOPERATIVE ANALGESIA (ug/ml)

Time / Patient	15'	30'	45'	60'	90'	120'
17	0.4	2.9	3.1	8.2	16.6	15.7
11	21.6	27.0	24.7	21.8	17.1	13.1
19	0	4.1	11.5	12.8	15.2	20.6
14	6.2	16.3	17.8	19.5	15.7	14.4
18	0.6	12.2	21.7	18.4	21.2	16.1
16	0	0.9	9.3	34.7	27.5	15.8
Mean	4.8	10.6	14.7	19.2	18.9	16.0
SD	8.6	10.0	8.2	9.0	4.7	2.8
Controls						
17	6.4	33.5	34.4	33.5	30.6	25.1
11	37.5	27.6	24.6	21.6	18.1	16.3
19	0	2.9	24.0	26.8	20.4	19.7
14	17.6	11.4	13.6	16.8	15.3	13.5
18	12.5	27.2	26.9	23.9	19.5	17.6
16	15.3	28.1	33.7	29.4	21.4	17.6
Mean	14.9	21.8	26.2	25.3	20.9	18.3
SD	12.8	11.9	7.6	5.9	5.2	3.9

TABLE 6.5 PLASMA PARACETAMOL CONCENTRATIONS FOLLOWING MIXED NARCOTIC AND EXTRADURAL ANALGESIA (ug/ml)

Patient \ Time	15'	30'	45'	60'	90'	120'
5	0	0	0	0	0	0
6	6.4	13.6	17.3	19.8	22.6	20.0
7	0	0	0	0	0	0
8	9.6	33.9	33.0	27.2	18.4	16.6
9	0	8.7	24.0	21.2	26.7	27.3
10	0	7.4	8.2	15.6	23.8	27.3
20	0	0	1.9	16.2	29.8	20.2
21	0	23.9	38.1	31.7	25.1	21.6
Mean	2.0	10.9	15.3	16.5	18.3	16.6
SD	3.8	12.4	15.2	11.5	11.8	10.9
Controls						
5	0	0.8	36.0	31.1	27.4	19.1
6	6.0	49.5	34.6	30.8	24.6	22.0
7	0	0	1.3	1.4	1.9	5.0
8	25.4	32.8	25.7	23.5	21.8	19.7
9	37.4	33.9	31.6	28.2	22.5	18.4
10	14.4	27.8	26.9	30.1	28.2	22.6
20	10.0	21.4	24.9	25.3	20.8	18.0
21	13.8	25.4	26.7	25.7	22.4	18.6
Mean	13.4	24.0	25.8	24.5	21.2	17.9
SD	12.8	16.7	10.7	9.7	8.2	5.5

extradural group and 25.8 $\pm$ 10.7 ug/ml at 45 minutes in the mixed group.

6.3.2 Diamorphine group

There was a striking inhibition of paracetamol absorption on the day after surgery in patients who received diamorphine for analgesia (Table 6.3). The mean plasma paracetamol concentration at 45 minutes was only 3.5 $\pm$ 4.0 ug/ml and plasma concentrations were still increasing 90 - 120 minutes after ingestion (Figure 6.1). The concentrations at 30, 45 and 60 minutes were significantly less than those in the control study ($p < 0.01$).

6.3.3 Extradural group

In the patients who received extradural analgesia alone, there was a moderate delay in the rate of paracetamol absorption (Table 6.4). The mean peak plasma concentration of 19.2 $\pm$ 9.0 ug/ml occurred 60 minutes after ingestion. Only the values at 15 minutes were significantly less than those in the control study ($p < 0.05$). The concentrations at 30, 45 and 60 minutes were greater than those in the narcotic study ($p < 0.05$).

6.3.4/

6.3.4 Combined extradural and diamorphine group

Paracetamol absorption in these patients, who had not received a narcotic for 6 hours, was almost identical to that in the patients receiving extradural analgesia alone (Table 6.5). A mean peak concentration of 18.3 $\pm$ 11.8 ug/ml occurred 90 minutes after ingestion. Only the values at 15 minutes were significantly smaller than those in the control study ($p < 0.05$). The plasma concentrations at 30, 45 and 60 minutes were greater than those in patients who had received diamorphine within the previous 6 hours.

The areas under the plasma concentration time curve (AUC) from 0 to 45 minutes and from 0 to 120 minutes are shown in Table 6.6. Up to 45 minutes all three groups had significantly lower AUC than in the control study. At 120 minutes, only the diamorphine and combined groups had significantly lower AUC's.

6.4 DISCUSSION

The administration of diamorphine analgesia after hysterectomy was associated with a striking delay in the absorption of paracetamol on the day after surgery. This was presumably a result of

TABLE 6.6 AREAS UNDER THE PLASMA CONCENTRATION TIME CURVES (± SD) ug hr/ml

Group	0-45 min	p*	0-120 min	p*
Control	11.7 ± 6.6		39.4 ± 12.0	
Extradural	5.7 ± 5.4	< 0.05	28.3 ± 8.0	NS
Diamorphine	0.6 ± 0.8	< 0.01	13.3 ± 10.5	< 0.05
Combined extradural and diamorphine	4.6 ± 5.1	< 0.05	26.0 ± 17.0	< 0.05

* Extradural, diamorphine and combined groups compared with controls.

inhibition of gastric emptying. Plasma concentrations at 30, 45 and 60 minutes and the area under the concentration time curve from 0 to 45 minutes and from 0 to 120 minutes were significantly lower than those observed in the same patients studied one week after hysterectomy when results were similar to healthy volunteers. The study was carried out on average 3.1 hours after an intramuscular injection of diamorphine 5 mg. These results are not unexpected in view of the effect of diamorphine on paracetamol absorption observed in women during labour, reported in Chapter 4, and explored further in Chapter 7.

In contrast, in patients undergoing extradural analgesia alone (who had not received a narcotic analgesic since the premedication for surgery 24 hours before the study) paracetamol absorption was only moderately delayed. Concentrations at 15 minutes only were significantly lower than those of the controls and the area under the plasma concentration time curve was significantly lower only from 0 to 45 minutes. There was no significant difference from 0 to 120 minutes. Plasma concentrations at 30, 45 and 60 minutes were significantly greater than those observed after diamorphine analgesia.

Continuous extradural analgesia is titrated to keep the patient pain free and requires "top up" injections every 2 - 3 hours. These are given by anaesthetic staff and are time consuming. Thus a group of patients was studied who had extradural analgesia by day and diamorphine analgesia (given by nurses as required) overnight. At the time of the study at least 6 hours had elapsed since the last injection of diamorphine in an attempt to minimise any diamorphine effect on gastric emptying and paracetamol absorption. Certainly, the analgesic effect of diamorphine was absent 6 hours after administration and all patients had had an injection of bupivacaine into the extradural catheter. In this group, paracetamol absorption was almost identical with that observed in the group receiving extradural analgesia alone. Little is known of the influence of extradural analgesia on gastro-intestinal motility. To maintain analgesia after hysterectomy the dermatomes T10, 11, 12, L1 and L2 must be blocked and thus some sympathetic supply to the gastro-intestinal tract will be abolished. This may result in acceleration of intestinal motility but a higher block would be necessary to influence gastric motility. In a study of patients undergoing cholecystectomy, extradural blockade from T5 to L1

resulted in a small contracted gut due to parasympathetic dominance (Gelman et al 1977). In patients without extradural analgesia, the electrical activity of the stomach and intestine decreased after surgery and did not return to normal until the third or forth postoperative day. However a marked increase in amplitude and frequency of electrical oscillations was recorded in 80% of patients who received extradural block. Eating markedly increased electrical activity in patients whose postoperative pain was treated by extradural blockade, whereas eating in association with nicomorphine injection resulted in no change in electrical activity. The authors suggested that intra and postoperative extradural blockade might prevent or treat postoperative adynamic ileus.

The extent of the extradural blockade in my study was less than that of Gelman et al., but paracetamol absorption and presumably gastric emptying was significantly better on the day after surgery in patients undergoing extradural analgesia than in patients receiving diamorphine. Spence and Smith (1971) demonstrated that continuous lumbar extradural analgesia after vagotomy and drainage operations reduced the degree of postoperative lung dysfunction and hypoxia when compared with

intermittent morphine 10 mg intramuscularly. It may be that delayed gastric emptying with possible distension after narcotic administration contributed to postoperative lung dysfunction. Extradural analgesia after operation is an alternative to narcotic analgesia and is free of central effects, particularly respiratory depression. The lack of important effects on gastric emptying and drug absorption is another advantage.

CHAPTER 7

INHIBITION OF GASTRIC EMPTYING AND DRUG ABSORPTION BY NARCOTIC ANALGESICS

7.1 INTRODUCTION

The correlation between gastric emptying rate and paracetamol absorption and the consequences of modification of gastric emptying had not been established on the basis of simultaneous measurements. In the study of obstetric patients, I observed that the administration of narcotic analgesics to women in labour was associated with a striking reduction in the rate of absorption of orally administered paracetamol (Nimmo et al, 1975, Chapter 4). It seemed likely that this delay was due to delayed gastric emptying and the magnitude of the observed effect demanded further study. Narcotic analgesics have marked effects on the human gastro-intestinal tract and the use of opium for symptomatic relief of diarrhoea and dysentery preceded, by many centuries, its use as an analgesic drug (Jaffe 1970). Morphine and its analogues cause some decrease in the secretion of hydrochloric acid which can be overcome by chemical or psychic stimulation. There is a decrease in motility of the stomach with an increase in tone of the antrum and first part of the

duodenum (Cairnie et al 1961; Burks and Long 1967). Both biliary and pancreatic secretions are diminished by morphine and digestion of food in the small intestine is delayed. There is an increase in resting tone of the small intestine. The amplitude of non-propulsive rhythmic contractions is enhanced but propulsive contractions are markedly decreased (Chapman et al 1950; Daniel et al 1959). Large doses of atropine may antagonise partially these responses to morphine but resection of the extrinsic nerves and ganglionic blocking agents do not. It is thought that the effect is exerted on nerve plexuses within the bowel wall. Propulsive peristaltic waves in the colon are also diminished or abolished after morphine and tone is increased (Garrett et al 1967). Therapeutic doses of morphine result in an increase in biliary tract pressure and a rise in serum amylase and lipase (Bogoch et al 1954). However there is little information on the effects on gastric emptying and drug absorption. In the present study, the effect of narcotic analgesics on gastric emptying and paracetamol absorption was examined simultaneously in healthy volunteers.

7.2 /

7.2 SUBJECTS AND METHODS

Gastric emptying and paracetamol absorption were measured simultaneously in eight healthy adult male volunteers aged 26 to 39 years (mean 29.9 $\pm$ 4 years) mean weight 71.3 $\pm$ 6.7 Kg. All were members of the medical staff of the Department of Therapeutics and Clinical Pharmacology of the Royal Infirmary, Edinburgh. None was receiving any other medication during the study.

After an overnight fast, each subject drank orange juice (400 ml) containing paracetamol (20 mg/Kg) in solution together with ^{113m}In DTPA (300 uCi) as an non-absorbable isotopic marker for the emptying measurement (Chapter 3). The drink was consumed in 2 minutes. Serial blood samples were taken at intervals for 8 hours after ingestion for assessment of paracetamol absorption and urine was collected at intervals for 24 hours. No food, drink or tobacco was permitted for 4 hours after ingestion of the solution and the subjects remained supine throughout this period. Each subject was studied on two occasions at least 7 days apart. On one occasion, an intramuscular injection of pethidine (150 mg) or diamorphine (10 mg) was given 30 minutes before the paracetamol and on the other

occasion, subjects received a placebo injection of saline intramuscularly. All injections were given into the deltoid muscle.

Four subjects (age 29.3 $\pm$ 1 years; weight 71.4 $\pm$ 4.8 Kg) were given pethidine and four (age 30.5 $\pm$ 5.9 years; weight 71.2 $\pm$ 9.0 Kg) received diamorphine.

The order of narcotic and placebo administration was determined on a random basis and the subjects were not told beforehand which injection they would receive. Howevér, following the administration of the active drug, all subjects developed typical narcotic effects such as lightheadedness and drowsiness and were thus aware of the treatment they had received.

7.3 RESULTS

Gastric emptying was rapid in all the control studies following placebo injection (Table 7.1). The time for 50% emptying of the ingested solution from the stomach ranged from 4 to 22 minutes (mean 11.9 min). Paracetamol absorption was correspondingly rapid with a mean peak plasma concentration of 20.0 $\pm$ 5.2 ug/ml occurring 22 $\pm$ 8.8 minutes after injection (Table 7.2, Figure 7.1).

TABLE 7.1 TIME TO EMPTY 50% OF GASTRIC CONTENTS (MINUTES)

Subject	Control	Pethidine	Diamorphine
WN	21.5	73	
HB	20	130	
JP	14	30	
JM	8	125	
LP	19		>130
RC	5		>130
GD	4		>130
JL	4		>130
Mean	11.9	89.5	>130
SD	7.5	47.5	-

TABLE 7.2 PARACETAMOL ABSORPTION IN 8 HEALTHY VOLUNTEERS
Each volunteer received paracetamol (20mg/Kg) in 400 ml solution

Subject	Plasma Paracetamol Concentrations (ug/ml)																
	3'	6'	10'	15'	20'	25'	30'	40'	50'	60'	75'	90'	2hrs	3hrs	4hrs	6hrs	8hrs
LP	-	5.6	22.7	27.9	24.4	26.9	24.0	20.1	17.4	12.9	13.1	9.9	8.1	5.6	3.9	1.7	1.0
WN	7.6	17.4	21.4	21.2	25.2	23.0	19.6	17.0	15.7	23.0	20.1	16.3	15.7	10.1	7.2	5.1	2.2
GD	0.8	9.4	24.4	16.0	19.6	19.6	19.2	15.6	16.0	16.0	12.9	11.5	11.2	7.4	5.6	2.4	1.0
HB	0	2.8	3.3	4.9	8.7	12.9	15.3	19.4	18.2	18.1	17.4	16.1	13.6	10.4	7.8	4.3	2.7
JP	1.0	6.4	14.1	28.2	31.1	26.9	25.0	21.2	16.7	15.1	13.8	12.8	10.9	7.7	5.1	2.6	1.3
RC	0.5	4.9	9.1	13.0	16.9	17.5	17.2	14.3	11.4	13.6	11.4	9.7	6.8	4.9	3.2	1.9	0.6
GM	1.5	7.7	12.3	15.4	17.7	17.3	15.0	13.1	12.3	11.5	-	8.8	7.3	4.6	3.8	1.5	1.1
JL	1.5	6.0	12.7	13.4	13.1	15.7	14.9	-	11.9	10.4	10.8	10.8	9.3	8.2	4.1	2.2	1.1
Mean	1.8	7.5	15.0	17.5	19.6	20.0	18.8	17.2	15.0	15.1	14.2	12.0	10.3	7.4	5.1	2.7	1.4
SD	2.6	4.4	7.3	7.9	7.2	5.2	4.0	3.1	2.7	4.0	3.3	2.9	3.1	2.2	1.7	1.3	0.7

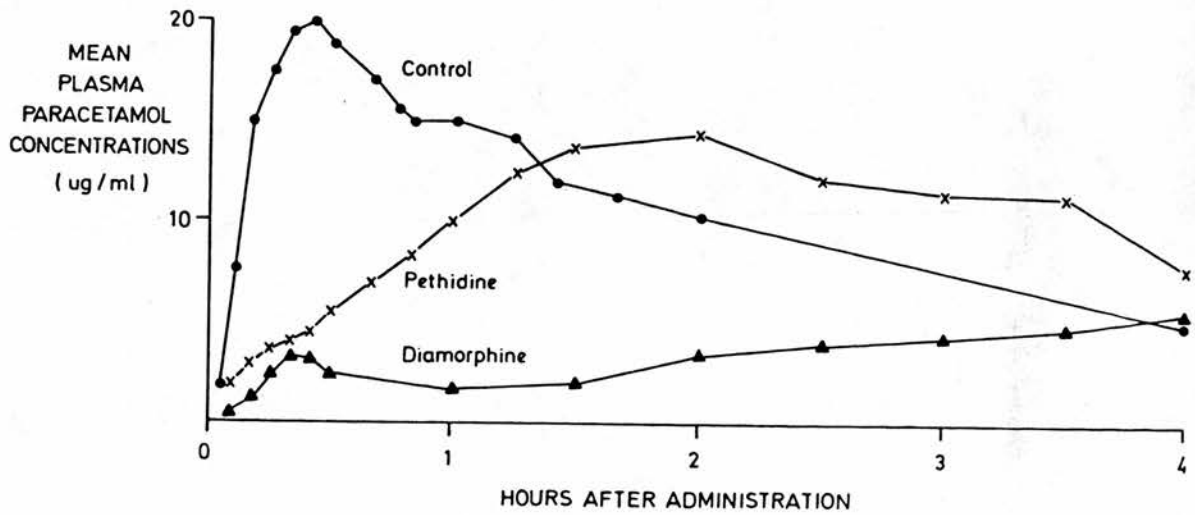


FIGURE 7.1

Mean plasma paracetamol concentrations after 20 mg/Kg paracetamol in 400 ml solution

● - ● = control (n = 8)

x - x = after pethidine 150 mg i.m. (n = 4)

▲ - ▲ = after diamorphine 10 mg i.m. (n = 4)

After pethidine, however, the mean time for 50% emptying of the ingested solution was prolonged to 89.5 minutes (Table 7.1). Similarly, the mean peak plasma concentration was only 14.3 $\pm$ 4.9 ug/ml and was delayed until 114 $\pm$ 74 minutes after injection (Table 7.3). The effects of pethidine on gastric emptying and paracetamol absorption in one subject (GM) are shown in Figure 7.2.

Diamorphine completely inhibited gastric emptying for more than 90 minutes in three of the four subjects and none achieved 50% emptying in two hours. One subject (LP) vomited at 60 minutes and subsequent plasma paracetamol concentrations were disregarded. Subject RC had some emptying of the stomach after diamorphine. He had undergone a Ramstedt operation in infancy for congenital pyloric stenosis. The mean peak plasma paracetamol concentration was only 5.2 $\pm$ 2.9 ug/ml and was not reached until 142 $\pm$ 108 minutes after ingestion (Table 7.4). An example of the marked inhibitory effects of diamorphine on gastric emptying and paracetamol absorption in one subject (JL) is shown in Figure 7.3.

Statistical comparisons of the 3 groups are given in Table 7.5. The time to empty 50% of the

TABLE 7.3 PARACETAMOL ABSORPTION AFTER PETHIDINE 150 mg INTRAMUSCULARLY

Subject	Plasma Paracetamol Concentrations (ug/ml)																	
	5'	10'	15'	20'	25'	30'	40'	50'	60'	75'	90'	2hrs	2½hrs	3hrs	3½hrs	4hrs	6hrs	8hrs
WN	0	0	0.5	0.6	0.7	1.0	1.2	10.0	15.3	23.0	22.3	19.2	15.0	14.3	10.8	10.0	6.0	3.5
HB	0.7	0.3	0.5	0.6	0.8	0.7	1.3	2.1	5.4	8.2	10.9	16.3	14.0	15.6	16.8	14.4	7.4	3.9
JP	6.1	10.4	12.0	13.2	15.1	18.9	24.1	19.4	16.9	15.4	17.6	13.8	11.9	9.6		7.7	3.1	1.3
GM	0	0	0.4	0.7	0.7	0.7	0.7	1.1	2.2	2.7	4.4	7.7	7.4	6.6	6.6	6.9	3.7	1.5
Mean	1.7	2.7	3.4	3.8	4.3	5.3	6.8	8.2	10.0	12.3	13.8	14.3	12.1	11.5	11.4	9.8	5.1	2.6
SD	±2.9	±5.2	±5.7	±6.3	±7.2	±9.1	±11.5	±8.5	±7.3	±8.8	±7.8	±4.9	±3.4	±4.2	±5.1	±3.4	±2.0	±1.3

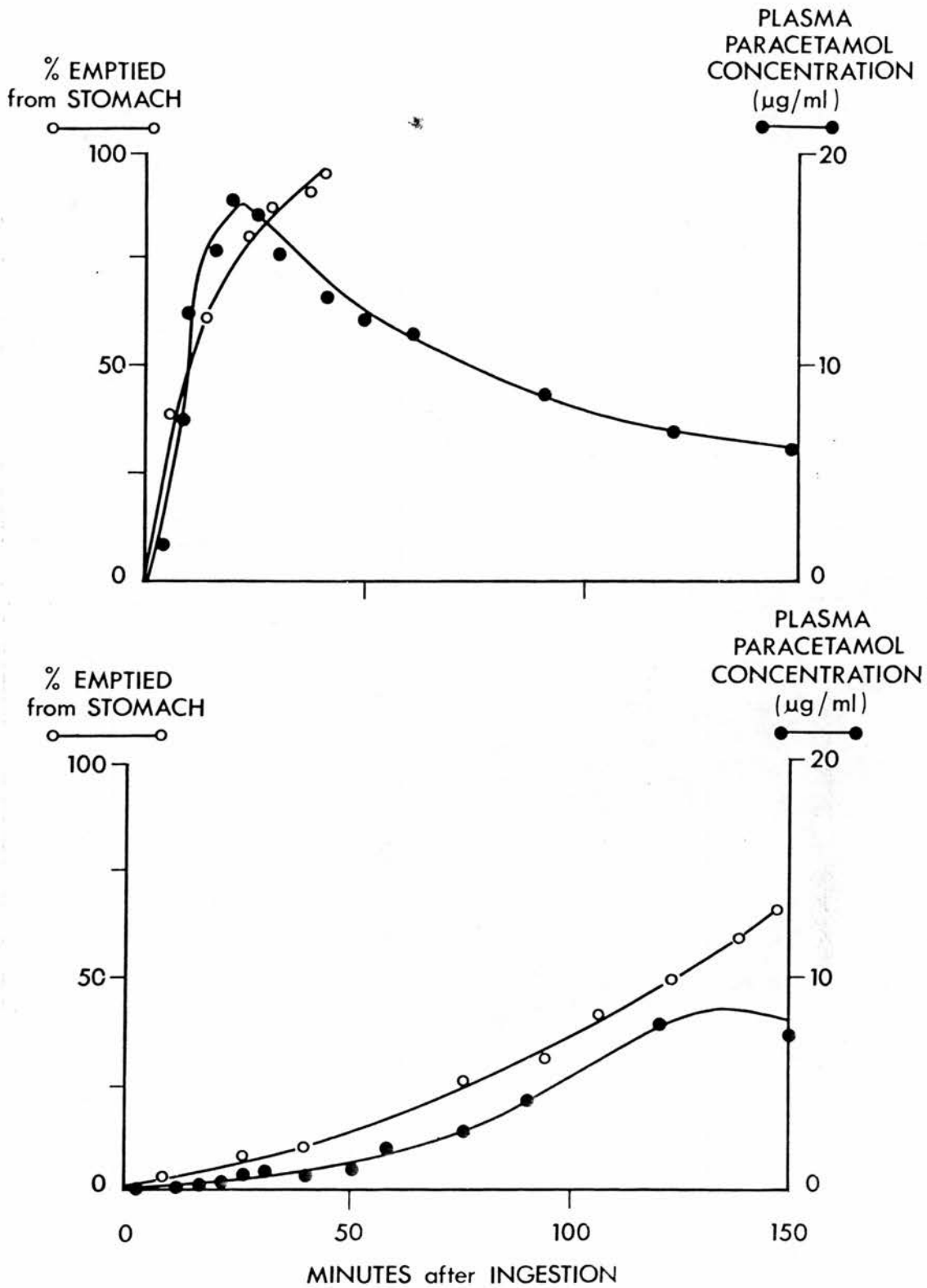


FIGURE 7.2

Gastric emptying and paracetamol absorption measured simultaneously in one healthy volunteer.

Top = control

Bottom = after pethidine 150 mg i.m.

TABLE 7.4 PARACETAMOL ABSORPTION AFTER DIAMORPHINE 10 mg INTRAMUSCULARLY

Subject	Plasma Paracetamol Concentrations (ug/ml)																	
	5'	10'	15'	20'	25'	30'	40'	50'	60'	75'	90'	2hrs	2½hrs	3hrs	3½hrs	4hrs	6hrs	8hrs
LP	0	0	0	0	0	0	0	0	0.5	0.6	0.6	0.6	0.8	0.9	1.4	1.3	2.5	1.2
GD	0	0	0	0	0	0	0	0	0.3	0.7	1.5	5.9	7.7	6.8	6.8	6.4	6.4	3.7
RC	1.5	4.5	10.2	13.3	12.5	10.2	-	-	5.3	-	4.9	6.1	5.3	5.7	-	4.9	4.5	2.3
JL	0	0	0	0.4	0.2	0.3	0.6	0.8	0.9	0.9	1.2	1.9	2.7	4.6	6.7	8.0	5.3	2.9
Mean	0.4	1.1	2.6	3.4	3.2	2.6			1.8		2.1	3.6	4.1	4.5	5.0	5.2	4.7	2.5
SD	±0.75	2.3	5.1	6.7	5.8	5.1			2.4		1.9	2.8	±3.0	2.6	±3.1	2.9	1.6	1.1

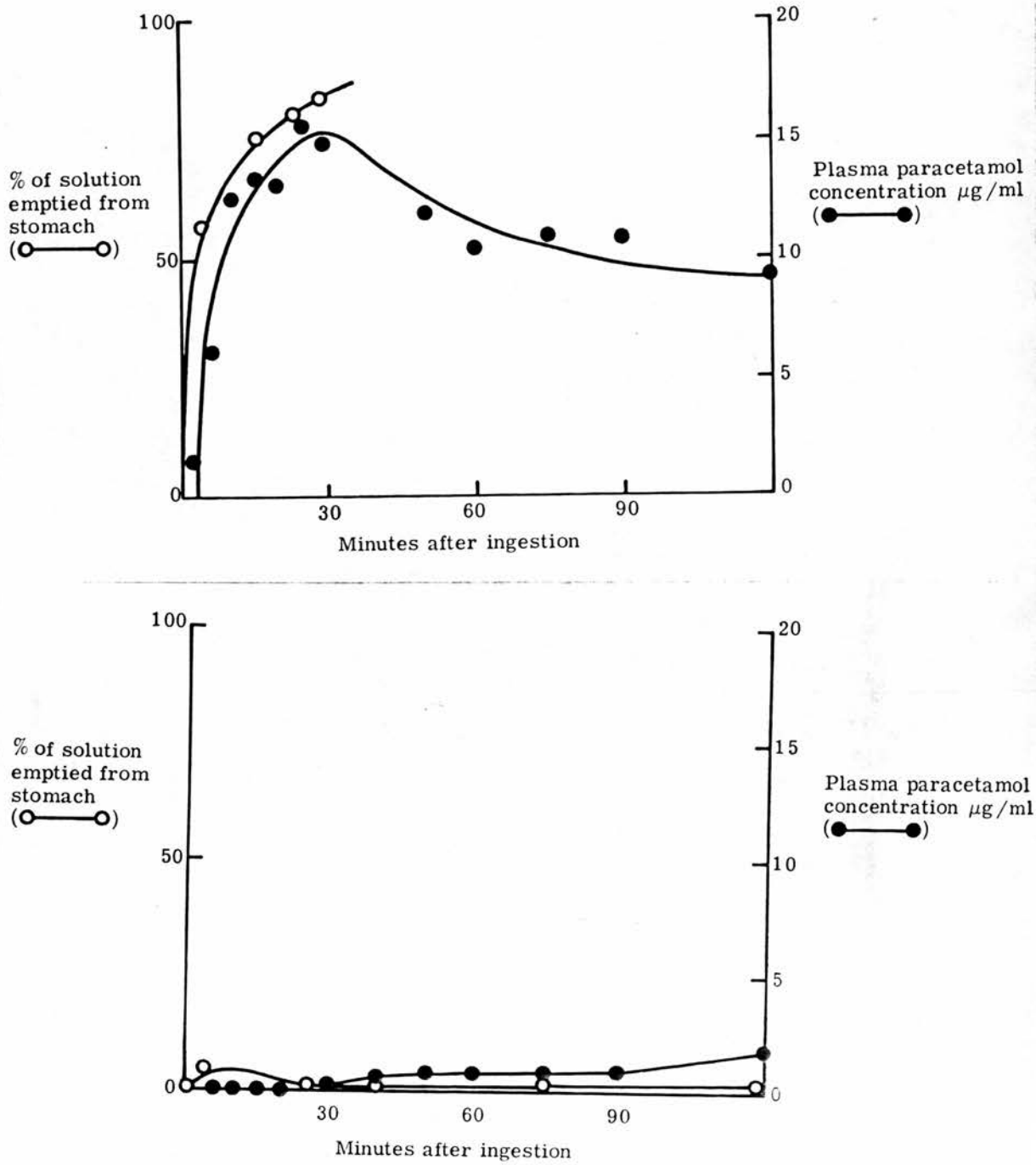


FIGURE 7.3

Gastric emptying and paracetamol absorption measured simultaneously in one healthy volunteer.

Top = control

Bottom = after diamorphine 10 mg i.m.

TABLE 7.5 EFFECT OF PETHIDINE AND DIAMORPHINE ON GASTRIC EMPTYING RATE AND PARACETAMOL ABSORPTION. RESULTS ARE MEAN ± S.E. MEAN

Group	Time to empty 50% of gastric contents (minutes)	p*	Peak plasma paracetamol concentration (ug/ml)	p**	Time of peak (minutes)	p**
Control (n = 8)	11.9 ± 2.5	-	20.0 ± 1.8	-	22 ± 3.1	-
Pethidine (n = 4)	89.5 ± 24	< 0.01	14.3 ± 2.5	0.05	114 ± 36	< 0.05
Diamorphine (n = 4)	> 130	< 0.01	5.2 ± 1.5	0.01	142 ± 72	< 0.01

* Pethidine and diamorphine compared with controls (Mann Whitney U test)

** Paired t test with controls

gastric contents was significantly delayed by pethidine and diamorphine ($p < 0.01$ Mann Whitney U test). Both pethidine and diamorphine significantly lowered and delayed the peak plasma paracetamol concentrations ($p < 0.05$ and $p < 0.01$ respectively).

The areas under the plasma concentration time curves from 0 to 4 hours and from 0 to 8 hours are shown in Table 7.6. Only the area from 0 to 4 hours after diamorphine differed significantly from control values. In the pethidine study and from 0 to 8 hours after diamorphine the results did not differ significantly.

The areas under the plasma concentration time curve at 1 hour were plotted against the percentage of the ingested solution emptied from the stomach at one hour for each subject. A significant correlation was obtained ($r = 0.94$, $p < 0.01$, Figure 7.4).

It was not possible to obtain 2 hourly urine collections on all subjects after the narcotic injection. This was presumably due to the fact that narcotics have an antidiuretic effect as well as delaying absorption of the ingested solution. However the recovery of paracetamol from urine at

TABLE 7.6 AREAS UNDER THE PLASMA CONCENTRATION TIME CURVES AFTER 20 mg/Kg PARACETAMOL IN SOLUTION (ug min/ml)

Subject	Control		Pethidine		Diamorphine	
	0-4 hrs	0-8 hrs	0-4 hrs	0-8 hrs	0-4 hrs	0-8 hrs
WN	3485	4661	3096	4626		
HB	2887	4033	2587	4573		
JP	2827	3523	3128	4040		
JM	1918	2992	1146	2094		
LP	2471	2969			-	-
RC	1937	2321			960	2334
GD	2649	3333			1440	2412
JL	2227	2803			656	1946
Mean	2550	3329	2489	3833	1019	2231
SD	529	741	929	1189	395	250
p*			NS	NS	$p < 0.02$	NS

* Pethidine and diamorphine compared with controls.

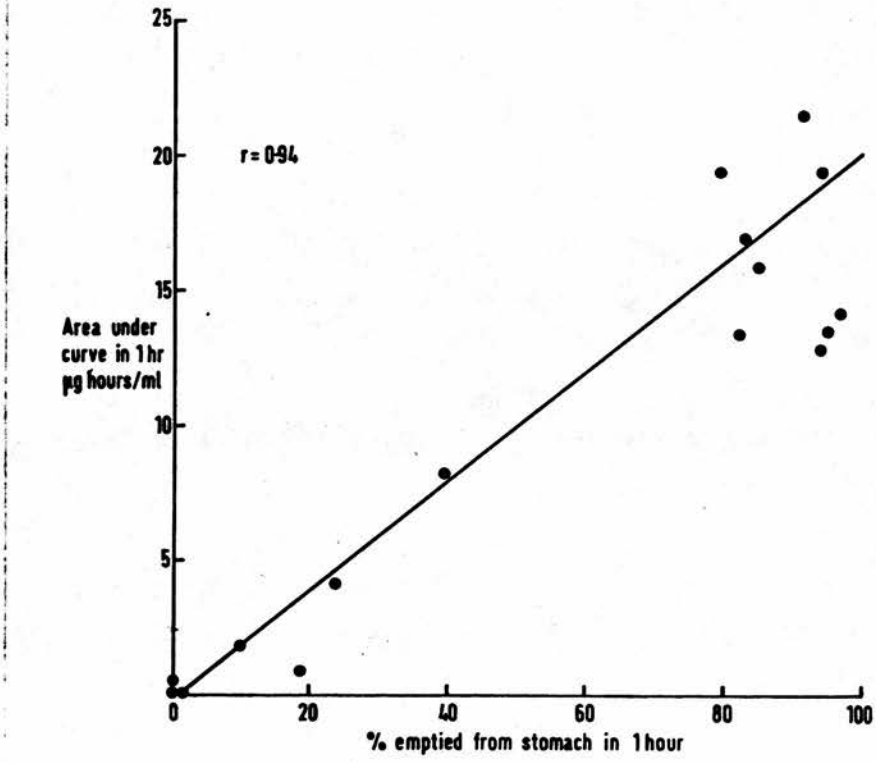


FIGURE 7.4

The area under the plasma concentration time curve at 1 hour plotted against the percentage of the ingested solution emptied from the stomach at 1 hour, r = 0.94.

4 hours was reduced following narcotic administration (Table 7.7).

The mean percentage of the ingested dose recovered in 4 hours was 37.1% in controls, 24.9% after pethidine and 13.1% after diamorphine. Only after diamorphine was the recovery significantly reduced ($p < 0.05$).

The total amount of paracetamol appearing in the urine in 24 hours was not affected by narcotic administration. The mean recovery was 77.2% of the administered dose in the controls, 74.8% after pethidine and 76.0% after diamorphine.

7.4 DISCUSSION

These results clearly demonstrate that pethidine and diamorphine induced a marked inhibition of gastric emptying and greatly retarded the absorption of orally administered paracetamol. The effect of diamorphine was particularly striking in 3 of the 4 subjects with complete inhibition of gastric emptying for more than 1.5 hours. The fourth subject had undergone a Ramstedt operation for congenital pyloric stenosis and it seems possible that this may have influenced the effect of diamorphine on gastric emptying. In keeping

TABLE 7.7 PERCENTAGE URINARY RECOVERY OF PARACETAMOL AFTER 20 mg/Kg PARACETAMOL IN SOLUTION

Subject	Control		Pethidine		Diamorphine	
	0-4 hours	0-24 hours	0-4 hours	0-24 hours	0-4 hours	0-24 hours
WN	32.3	75.6	18.9	70.0		
HB	29.5	78.8	20.8	80.1		
JP	36.3	79.5	35.1	81.4		
JM	-	71.7	-	67.7		
RC	40.8	72.5			26.3	77.2
GD	43.4	90.0			3.4	77.7
JL	40.4	72.2			9.7	73.1
Mean	37.1	77.2	24.9	74.8	13.1	76.0
SD	5.4	6.5	8.9	7.0	11.8	2.5

- No 4 hour sample was passed.

with other narcotic actions, the effect of diamorphine seemed to be of longer duration than that of pethidine. Both pethidine and diamorphine had a greater inhibitory effect than propantheline (30 mg) given intramuscularly (Nimmo et al, 1973). The data suggest that the slow absorption of paracetamol previously observed in women during labour might be almost entirely attributed to delayed gastric emptying produced by the administration of narcotic analgesics. In previous reports describing delayed gastric emptying in women during labour, the role of narcotics had not been considered (Davison et al 1970; Howard and Sharp 1973). These findings relate only to the period beginning 30 minutes after administration of the narcotic and may correspond to the later inhibitory phase of morphine's action on gastric motility observed by Crone and Ardran (1957).

These workers carried out barium meal investigations in 20 healthy male volunteers before and after an injection of 4 to 6 mg of morphine sulphate intravenously. The first effect of morphine was observed 2 to 4 minutes after the injection and for a variable length of time peristalsis was increased considerably in 8 of

the 20 individuals. This was followed by a longer period in which the contractions of the stomach became so shallow that one had difficulty in identifying them on the films. The duration of the period of increased peristalsis was less than 30 minutes. There was no evidence of a persistent contraction of the pylorus.

Although paracetamol absorption was delayed by administration of the narcotic, the urinary recovery over a period of 24 hours was not reduced, demonstrating that the amount of paracetamol absorbed was not influenced by this marked inhibition of gastric emptying. Although after diamorphine the area under the plasma paracetamol concentration time curve was significantly reduced up to 4 hours, this was not the case after pethidine, where no differences from controls were demonstrated. This suggests that the amount of "first-pass" loss of paracetamol was not influenced by the delayed gastric emptying induced by pethidine.

Narcotic analgesics are widely used in all branches of clinical practice. The magnitude of the effect observed in this study on gastric emptying and drug absorption seems likely to have wide therapeutic implications and to result in a

source of important drug absorption interactions. Many drugs which are given by mouth are probably not absorbed from the stomach to any significant extent and it seems inevitable that their absorption, like that of paracetamol, will be greatly retarded by administration of narcotic analgesics. This effect may be of greatest importance when rapid absorption of an orally administered drug is desired. For example, in a study of mexiletine absorption in coronary care patients, Pottage et al (1978) observed delayed and possible imcomplete absorption in patients who had received a narcotic analgesic. The mean plasma mexiletine concentrations after narcotics were significantly lower from 1 to 3 hours and up to 3 hours, the means were less than half those observed in patients not given narcotics.

In a study of 57 women before surgery, Gamble et al (1976) reported delayed diazepam absorption at least for 90 minutes after pethidine, morphine or atropine. Patients were given diazepam 10 mg orally 60 minutes after morphine 10 mg, pethidine 100 mg or atropine 0.6 mg. The decrease in plasma diazepam concentrations was more marked following morphine than with the other drugs studied.

In my study, in which gastric emptying and paracetamol absorption were measured simultaneously, the correlation coefficient between emptying and absorption at 1 hour was 0.94. This is a convincing demonstration of the dependence of drug absorption on stomach emptying. In none of the previous studies relating drug absorption and gastric emptying (Heading et al 1973; Nimmo et al 1973; Finch et al 1974) had such a relationship been established on the basis of simultaneous measurements. More recently Clark et al (1980) and Rees et al (1980) studied gastric emptying and paracetamol absorption in 26 healthy volunteers and 9 patients. Paracetamol tablets (1.5 g) were crushed and dissolved in 10 ml of water. They demonstrated that isoprenaline delayed and propranolol accelerated both gastric emptying and paracetamol absorption. The changes in paracetamol absorption correlated with the alterations in gastric emptying. Holt et al (1979) studied gastric emptying and paracetamol absorption simultaneously in 14 patients. In 8 of these the study was repeated after addition of the gel forming carbohydrates guar gum and pectin which are types of dietary fibre that resist digestion and absorption by the human alimentary tract. Both gastric

emptying and paracetamol absorption were slower after gel fibre but the total absorption of the drug, reflected in urinary recovery, was not significantly reduced. The area under the plasma concentration time curve from 0 to 30 minutes showed a significant correlation with the percentage of the solution emptied from the stomach at 30 minutes.

Harasawa et al (1979) used the rate of paracetamol absorption as an index of the rate of gastric emptying in 15 normal subjects, 52 gastric ulcer patients and 65 duodenal ulcer patients. They demonstrated accelerated paracetamol absorption in patients with duodenal ulcers and delayed paracetamol absorption in those with gastric ulcers. Goldstraw and Bach (1981) studied paracetamol absorption in patients at least 2 months after oesophagectomy for oesophageal carcinoma and found no difference from healthy controls.

Thus, in my study, the correlation between the rate of paracetamol absorption and the rate of gastric emptying was established for the first time on the basis of simultaneous measurements. This has allowed the rate of paracetamol absorption to be used as an index of gastric emptying rate in a variety of clinical situations. Narcotic analgesics

markedly delay gastric emptying and drug absorption. This is an important drug interaction with widespread therapeutic implications.

CHAPTER 8

REVERSAL OF NARCOTIC INDUCED DELAY IN GASTRIC EMPTYING AND PARACETAMOL ABSORPTION BY NALOXONE

8.1 INTRODUCTION

Since metoclopramide (10 mg) intramuscularly did not reverse the narcotic induced delay in paracetamol absorption during labour (Chapter 4, page 92), the effect of naloxone, a specific narcotic antagonist, was studied. Naloxone is the N-allyl derivative of the narcotic analgesic oxymorphone and differs from other N-allyl narcotic derivatives (nalorphine and levallorphan) in two respects - it has no agonist activity and it is the only specific antagonist to pentazocine (Editorial, Lancet 1975). Given intravenously, it acts within 1 or 2 minutes and its duration of action is of the order of 20 minutes probably due to its rapid exit from the brain and metabolism in the liver. Naloxone is a potent drug partly due to its high lipid solubility which allows a high brain concentration (Berkowitz 1976). An intravenous bolus dose of 0.4 mg reverses all the actions (including analgesia) of narcotic analgesics. In the present study, healthy volunteers were studied since it seemed unethical to give naloxone to patients prescribed narcotic analgesics for relief of pain.

Because volunteers were studied, pentazocine (a drug with less risk of addiction) was used to produce the delay in gastric emptying. Pentazocine is in some ways a poor choice because it is an agonist/antagonist narcotic and its effects may be less well antagonised by naloxone. Thus the dose of naloxone studied was 1.2 mg.

8.2 PATIENTS AND METHODS

Gastric emptying and paracetamol absorption were measured simultaneously in 4 healthy male fasting volunteers (age 31.8 $\pm$ 5.0 years; weight 72.8 $\pm$ 3.0 Kg) as described in Chapter 7. Each subject was studied "blind" on three occasions in random order at least 7 days apart:- once 30 minutes after pentazocine 60 mg intramuscularly and immediately after naloxone 1.2 mg intravenously; once 30 minutes after pentazocine and immediately after placebo saline; and once after placebo injections of saline. The subjects were able to detect which treatment they had received since 5 - 10 minutes after pentazocine they experienced typical narcotic effects which were reversed by naloxone.

8.3 RESULTS

8.3 RESULTS

Gastric emptying and paracetamol absorption were rapid in all the control studies (Tables 8.1 and 8.2, Figure 8.1). The mean time to empty half of the ingested dose from the stomach was 13 minutes and the mean peak plasma paracetamol concentration was 23.8 $\pm$ 3.8 ug/ml 22.5 $\pm$ 2.6 minutes after ingestion (Table 8.5). After pentazocine, however, gastric emptying was greatly delayed in all subjects. The mean time to empty 50% of the gastric contents was 97 minutes ($p < 0.05$). Paracetamol absorption was also markedly delayed (Tables 8.3 and 8.5) with a mean peak concentration of 10.8 $\pm$ 1.2 ug/ml at 160 $\pm$ 32 minutes after ingestion ($p < 0.05$ and $p < 0.01$ respectively). Plasma concentrations from 10 to 75 minutes were significantly less than in the control study ($p < 0.05$). One subject (LP) vomited at 60 minutes and therefore his subsequent plasma paracetamol concentrations were ignored.

The inhibition of gastric emptying and paracetamol absorption was largely reversed by naloxone (Tables 8.1 ; 8.4 and 8.5). The mean time to empty 50% of the gastric contents after pentazocine and naloxone was 28 minutes which did not differ significantly from the control measurements

TABLE 8.1 EFFECT OF PENTAZOCINE AND PENTAZOCINE/ NALOXONE ON GASTRIC EMPTYING RATE

Subject	Time to empty 50% of gastric contents (mins)		
	Control	Pentazocine	Pentazocine/ Naloxone
WN	21.5	150	46
GD	4	71	34
JM	8	108	27
LP	19	60	4
Mean	13.1	97 *	27.8 ** ***
SD	8.4	40.7	17.7

* $p < 0.05$ (compared with control)

** $p > 0.05$ (compared with control) NS

*** $p < 0.02$ (compared with pentazocine)

TABLE 8.2 PARACETAMOL ABSORPTION IN 4 HEALTHY VOLUNTEERS - EACH SUBJECT RECEIVED PARACETAMOL 20 mg/Kg ORALLY IN 400 ml SOLUTION

Time / Subject	Plasma paracetamol concentrations (ug/ml)																
	3'	6'	10'	15'	20'	25'	30'	40'	50'	60'	75'	90'	2h	3h	4h	6h	8h
WN	7.6	17.4	21.4	21.2	25.2	23.0	19.6	17.0	15.7	23.0	20.1	16.3	15.7	10.1	7.2	5.1	2.2
GD	0.8	9.4	24.4	16.0	19.6	19.6	19.2	15.6	16.0	16.0	12.9	11.5	11.2	7.4	5.6	2.4	1.0
JM	1.5	7.7	12.3	15.4	17.7	17.3	15.0	13.1	12.3	11.5	-	8.8	7.3	4.6	3.8	1.5	1.1
LP	0	5.6	22.7	27.9	24.4	16.9	14.0	20.1	17.4	12.9	13.1	9.9	8.1	5.6	3.9	1.7	1.0
Mean	3.3	10.0	20.2	20.1	21.6	21.7	19.5	16.5	15.4	15.9	15.4	11.6	10.6	6.9	5.1	2.7	1.3
SD	3.1	4.5	4.7	5.0	3.2	3.6	3.2	2.5	1.9	4.4	3.3	2.9	3.3	1.6	1.4	1.4	0.5

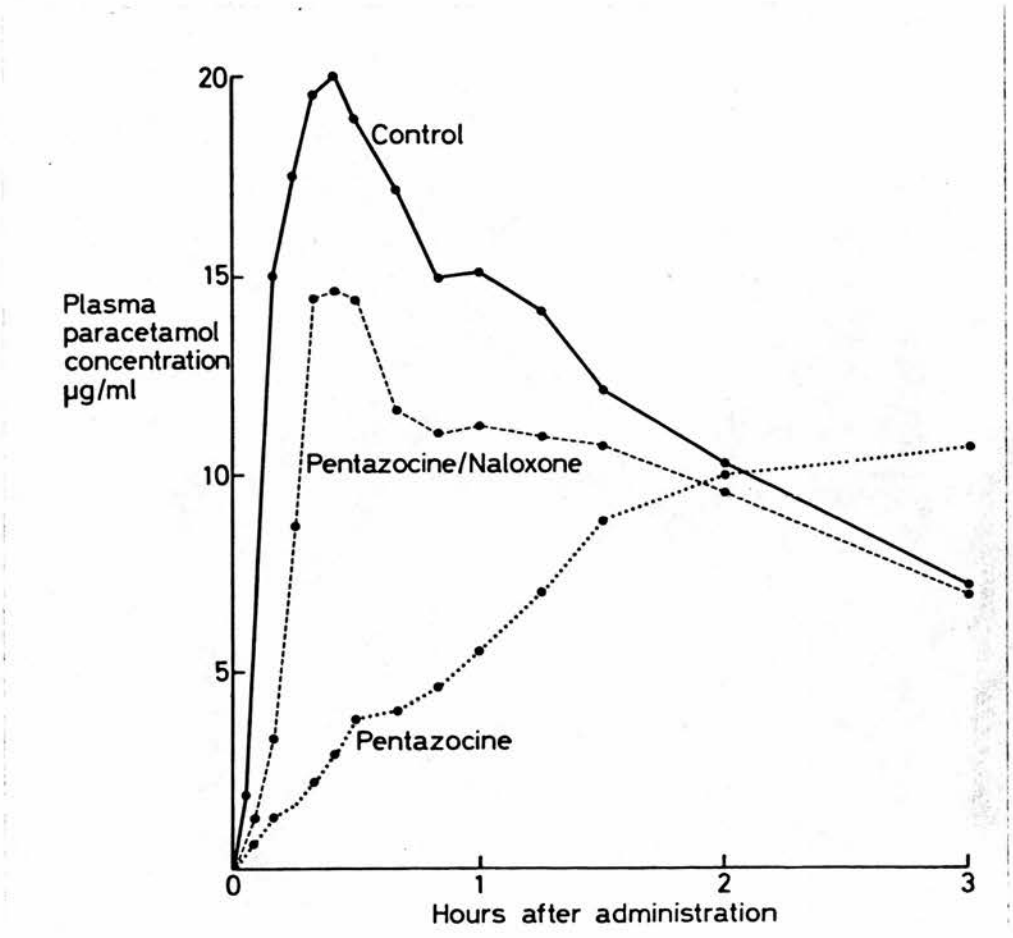


FIGURE 8.1

Mean plasma paracetamol concentrations in 4 volunteers after 20 mg/Kg paracetamol orally in 400 ml solution.

TABLE 8.3 PLASMA PARACETAMOL CONCENTRATIONS AFTER PENTAZOCINE 60 mg i.m. (ug/ml)

Time / Subject	5'	10'	15'	20'	25'	30'	40'	50'	60'	75'	90'	2h	2.5h	3h	4h	6h	8h
WN	2.2	5.2	6.3	6.3	6.3	8.2	8.9	9.7	11.9	10.1	11.2	11.9	10.8	11.6	9.3	5.6	3.7
GD	0	0	0	2.3	5.2	6.0	5.0	6.5	6.9	7.4	7.7	8.7	-	9.2	6.6	2.9	1.5
JM	0	0	0	0	0	0.9	1.5	1.8	2.4	3.4	7.4	9.3	9.8	11.2	6.4	4.6	1.8
LP	0	0	0	0	0	0	0.51	0.53	0.78	-	-	-	-	-	-	-	-
Mean	0.5	1.3	1.6	2.2	2.9	3.8	4.0	4.6	5.5	7.0	8.8	10.0	10.3	10.7	7.4	4.4	2.8
SD	1.1	2.6	3.2	3.0	3.4	4.0	3.8	4.2	5.0	3.4	2.1	1.7	0.7	1.3	1.6	1.4	1.3

TABLE 8.4 PLASMA PARACETAMOL CONCENTRATIONS AFTER PENTAZOCINE 60 mg i.m. AND NALOXONE 1.2 mg i.v. (ug/ml)

Time / Subject	5'	10'	15'	20'	25'	30'	40'	50'	60'	75'	90'	2h	2.5h	3h	4h	6h	8h
WN	0	3.5	10.5	18.3	20.8	21.1	15.0	14.8	15.2	14.1	14.1	12.3	11.2	8.9	7.2	3.6	2.4
GD	0	2.3	3.6	14.1	11.8	11.8	10.0	8.6	8.6	9.0	9.0	9.0	-	6.8	5.0	2.7	1.8
JM	1.4	2.7	6.2	11.0	12.7	12.7	11.3	12.1	12.7	12.1	12.1	9.7	-	7.3	4.9	2.7	1.4
LP	1.2	4.8	14.5	14.5	13.2	12.0	10.0	8.4	8.4	8.4	7.6	6.8	-	4.4	3.9	1.6	0.8
Mean	1.3	3.3	8.7	14.5	14.6	14.4	11.6	11.0	11.2	10.9	10.7	9.5	-	6.9	5.3	2.7	1.6
SD	0.1	1.1	4.8	3.0	4.2	4.5	2.4	3.1	3.3	2.7	2.9	2.3	-	1.9	1.4	0.8	0.7

TABLE 8.5 EFFECT OF PENTAZOCINE AND PENTAZOCINE/ NALOXONE ON PARACETAMOL ABSORPTION

Study	Mean ($\pm$ SE) peak plasma paracetamol concentration (ug/ml)	Mean ($\pm$ SE) time to peak concentration (minutes)
Control	23.8 $\pm$ 1.9	22.5 $\pm$ 1.3
Pentazocine	10.8 $\pm$ 0.6 *	160 $\pm$ 16.3 **
Pentazocine/ Naloxone	15.0 $\pm$ 1.8 *	25.0 $\pm$ 1.8 ***

* $p < 0.05$ compared with control

** $p < 0.01$ compared with control

*** $p < 0.05$ compared with pentazocine

but which was significantly shorter than after pentazocine alone ($p < 0.02$). The mean peak plasma paracetamol concentration was 15.0 ± 3.6 ug/ml which was significantly lower than the control measurements ($p < 0.05$) but not significantly different from those observed after pentazocine alone. The mean time to peak concentration was 25.0 ± 3.6 minutes which did not differ significantly from the controls but was significantly shorter after pentazocine alone ($p < 0.05$) (Table 8.5). Plasma concentrations at 20 and 25 minutes differed significantly from those in the control study ($p < 0.05$). The areas under the plasma concentration time curves from 0 to 4 hours and from 0 to 8 hours are shown in Table 8.6. Only the area from 0 to 8 hours after pentazocine differed significantly from controls. From 0 to 4 hours after pentazocine and at both times after pentazocine and naloxone, the areas did not differ from control values. It was not possible to collect 4 hourly urine samples in 2 of the 4 subjects. The total urinary recovery of paracetamol in 24 hours was not influenced by treatment with pentazocine or pentazocine and naloxone (Table 8.7). The mean percentage recovery was 75%, 79% and 74% respectively in controls, after pentazocine and after pentazocine and naloxone.

TABLE 8.6 AREAS UNDER THE PLASMA CONCENTRATION TIME CURVES AFTER 20 mg/Kg PARACETAMOL IN SOLUTION (ug min/ml)

Subject	Control		Pentazocine		Pentazocine/Naloxone	
	0-4hrs	0-8hrs	0-4hrs	0-8hrs	0-4hrs	0-8hrs
WN	3485	4661	2413	3865	2744	3752
GD	2649	3333	1719	2554	1841	2574
JM	1918	2992	1556	2600	2277	2979
LP	2471	2969	-	-	1808	2282
Mean	2631	3489	1896	3006	2168	2897
SD	649	799	455	744	440	638
p (compared with controls)			NS	< 0.05	NS	NS
p (compared with pentazocine)					NS	NS

TABLE 8.7 % URINARY RECOVERY OF PARACETAMOL IN 24 HOURS AFTER 20 mg/Kg ORALLY IN SOLUTION

Subject	Control	Pentazocine	Pentazocine/ Naloxone
WN	76%	70%	76%
GD	72%	90%	84%
JM	64%	78%	55%
LP	86%	-	82%
Mean	75	79	74
SD	9.2	10.1	13.2

8.4 DISCUSSION

Gastric emptying and paracetamol absorption were significantly delayed in all subjects by pentazocine 60 mg intramuscularly. The mean time to empty 50% of the gastric contents was prolonged from 13 minutes to 97 minutes, the mean peak paracetamol concentration was significantly reduced and the mean time to peak concentration was delayed. These results are similar to those observed after pethidine and diamorphine (Chapter 7) and suggest that the delay in paracetamol absorption seen in women during labour (Chapter 4) is due to delayed gastric emptying.

Pentazocine is an agonist/antagonist narcotic analgesic and is known to delay gastric emptying in the rat probably by inducing pylorospasm (Danhof *et al* 1966). In human subjects, pentazocine in small doses delayed gastric emptying and in larger doses it delayed small intestinal propulsive motility, prolonging stomach to rectum transit time of an oxygen bolus (Danhof 1967). Thus the present study confirms these findings with respect to the delayed gastric emptying and its effect on drug absorption.

Naloxone largely reversed the effects of

pentazocine on gastric emptying and drug absorption. The mean time to empty 50% of the gastric contents after pentazocine and naloxone did not differ from controls but was significantly shorter than after pentazocine alone. Paracetamol absorption was not identical to the control study, however. The mean peak plasma paracetamol concentration was significantly lower after pentazocine and naloxone and did not differ from the values seen after pentazocine alone. This may reflect incomplete reversal of the effects of pentazocine by naloxone or the shorter duration of action of naloxone compared with pentazocine (Houde 1979). Little is known of the effects of naloxone alone on gastric emptying and in this respect the controls of this study are inadequate since I did not study the effect of naloxone alone. However, after naloxone and pentazocine, gastric emptying and paracetamol absorption were significantly more rapid than after pentazocine alone.

The total amount of paracetamol absorbed was not influenced by pentazocine administered alone or with naloxone since the total urinary recovery of paracetamol in 24 hours was almost identical in the three studies.

Gastric emptying and paracetamol absorption are inhibited by narcotic analgesics and the delay in gastric emptying observed in women during labour is largely due to narcotic administration. Metoclopramide does not reverse this delay. Naloxone largely reverses the narcotic effect on gastric emptying in healthy volunteers though its effect is probably shorter. Larger doses of naloxone may produce a greater reversal of pentazocine's effects, and naloxone may more effectively reverse the effects of a pure narcotic agonist such as pethidine. When reversal of the effects of narcotic analgesics on gastric emptying is desirable - for example, immediately before anaesthesia during labour or in recurrent vomiting - intravenous naloxone may reverse the delay in gastric emptying as well as the other effects of narcotics.

CHAPTER 9

PHARMACOKINETICS OF PARACETAMOL ABSORPTION AND GASTRIC EMPTYING

9.1 INTRODUCTION

In pharmacokinetic analysis of drug absorption with plasma concentration-time data, a first-order rate constant (Ka) may be calculated for absorption of the drug from the gastrointestinal tract (Goldstein et al 1974; Gibaldi and Perrier 1975). This is a hybrid rate constant which depends on many factors, e.g. if the drug is given in a tablet, disintegration and dissolution have an important role (Wagner 1971; Bowman and Rand 1980). If the drug is administered in solution and pH changes do not result in precipitation of the drug, gastric emptying rate, mucosal transfer and blood flow are contributing processes to the overall absorption rate constant which will be governed primarily by the slowest or rate limiting step (Gibaldi 1971; Morris et al 1972). Thus drug absorption may not be a monexponential process and thus the classical methods of deriving Ka the first order rate constant have shortcomings.

The hypothesis that gastric emptying rather than transmucosal transfer from the lumen of the

small intestine is rate-limiting for rapidly absorbed drugs has not been tested by appropriate pharmacokinetic analysis. In this chapter I describe a pharmacokinetic model with four compartments - two body compartments and one each for the stomach and the site of most rapid absorption in the small intestine. The model was tested on the data obtained from simultaneous measurement of gastric emptying and paracetamol absorption in healthy volunteers and was found to be consistent with the experimental data.

9.2 SUBJECTS AND METHODS

The data were obtained from the studies described in Chapters 7 and 8. Only the results after diamorphine were omitted because of the difficulty in quantifying gastric emptying rate, such was the delay produced by diamorphine. Gastric emptying and paracetamol absorption were measured simultaneously in 8 healthy volunteers (age 29.9 $\pm$ 4 years; weight 71.3 $\pm$ 6.7 Kg) on 2 occasions. On one occasion, each volunteer was studied 30 minutes after an intramuscular injection of pethidine 150 mg or diamorphine 10 mg and on the other occasion after a placebo injection of saline. Four received pethidine and 4 received diamorphine. The data obtained after diamorphine were not used in the

analysis.

Four of the 8 subjects were studied on 2 further occasions - (1) 30 minutes after intramuscular pentazocine 60 mg and (2) 30 minutes after intramuscular pentazocine and immediately after intravenous naloxone 1.2 mg (Table 9.1).

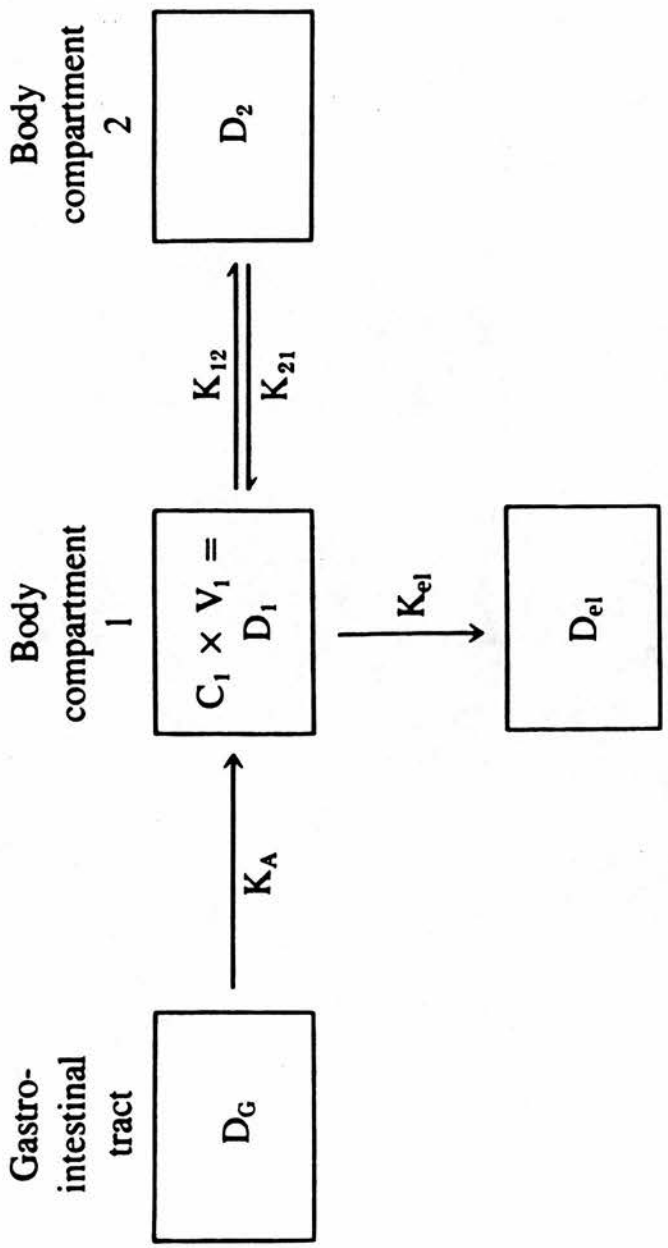
9.3 PHARMACOKINETIC MODELS

Two different compartmental models were used and compared for the analysis of the plasma paracetamol concentrations.

Scheme 1 (Figure 9.1) was a conventional compartmental model with one compartment representing the gastro-intestinal tract and 2 compartments representing the body (Greenblatt and Koch-Weser 1975). The apparent absorption rate constant (Ka) is the assumed first order rate constant for the transfer of the drug from the gastro-intestinal into the central body compartment (compartment 1), K_{12} and K_{21} are the rate constants for transfer into and out of the second body compartment (compartment 2) respectively and Kel is the elimination rate constant from the central compartment. D_G, D_1, D_2 and Del are the quantities in the gastro-intestinal tract, compartment 1, compartment 2 and the quantity of

TABLE 9.1 GASTRIC EMPTYING AND PARACETAMOL ABSORPTION STUDIES

Study	Control	30' after pethidine 150 mg i.m.	30' after pentazocine 60 mg i.m.	30' after pentazocine 60 mg i.m. and immediately after naloxone 1.2 mg i.v.
Subjects	Subjects 1-8	Subjects 2,4,5,7	Subjects 1,2,3,7	Subjects 1,2,3,7
Age (years)	29.9 $\pm$ 4.0	29.3 $\pm$ 1.0	31.8 $\pm$ 5.0	31.8 $\pm$ 5.0
Weight (Kg)	71.3 $\pm$ 6.7	71.4 $\pm$ 4.8	72.8 $\pm$ 3.0	72.8 $\pm$ 3.0



Two-compartment open model for oral administration.

FIGURE 9.1

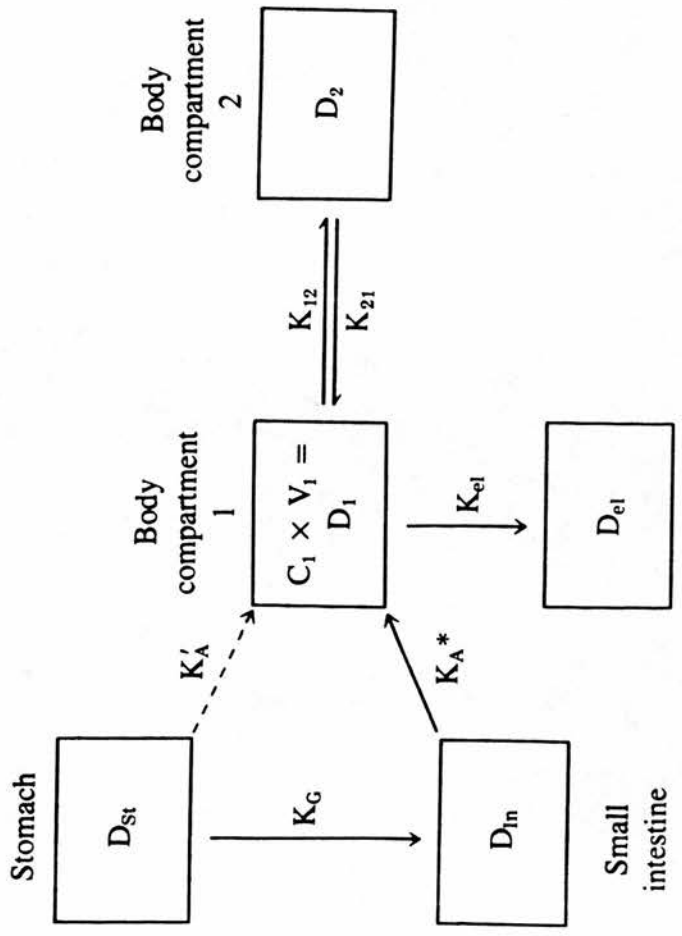
Scheme 1

eliminated drug, respectively.

Scheme 2 (Figure 9.2) shows a similar model but with the gastro-intestinal tract represented by 2 compartments to correspond to the stomach and the small intestine. The constant K_G is the first order rate constant for gastric emptying and Ka* is the rate constant for transfer of drug from the small intestine into the systemic circulation. K_A' is the rate constant for absorption from the stomach. It is known to be small for paracetamol (Heading et al 1973, Levine 1970; Prescott 1974; Chapter 7) and was neglected subsequently. Dst, D_{In}, D_1, D_2 and Del are the quantities of drug in the stomach, small intestine, body compartment 1, 2 and the quantity of drug eliminated respectively. Thus, using this model, if K_G is measured the true rate constant (Ka*) for transfer of the drug from the small intestine into the systemic circulation can be calculated. This calculation has not been made previously for any rapidly absorbed drug whose rate of absorption depends on the rate of gastric emptying.

9.4 COMPUTER ANALYSIS

All computer analyses were done by Dr. John A. Clements, Lecturer in Pharmacy, Heriot Watt



Proposed model with two body compartments and separate compartments representing the stomach and the small intestine.

FIGURE 9.2

Scheme 2.

University, Edinburgh.

Analogue computer programmes were constructed for these two models and the line of best fit to the data points was drawn by eye using an X - Y recorder. In the model shown in Scheme 2, the value of K_G found from the gastric emptying measurements was used as a constant in the computer programme. In many studies, monoexponential emptying was preceded by a short period during which a proportion of the dose passed rapidly through the pylorus as a bolus or "squirt". The computer programme was modified to accommodate this and other types of gastric emptying in the study (see results).

The equation for C_1, the concentration of drug in the central compartment for the model of Scheme 1, was that given in standard texts (Wagner 1971). The equation for C_1 for the model of Scheme 2 is given in the Appendix.

A glossary of symbols used is given in Table 9.2. It was assumed that the fraction of the dose reaching the systemic circulation was the same for the initial bolus and the exponentially released portions.

In this study a nonlinear optimization method

TABLE 9.2 GLOSSARY OF SYMBOLS

K_A	Apparent absorption rate constant for transfer of drug from the gastro-intestinal tract into the central body compartment.
K_{12}	Rate constant for transfer into compartment 2.
K_{21}	Rate constant for transfer out of compartment 2.
Kel	Elimination rate constant.
D_G	Quantity of drug in gastro-intestinal tract.
D_1	Quantity of drug in compartment 1.
D_2	Quantity of drug in compartment 2.
Del	Quantity of drug eliminated.
K_G	Rate constant for gastric emptying.
Ka*	Rate constant for transfer of drug from small intestine into systemic circulation.
K_A^1	Rate constant for absorption from the stomach.
Dst	Quantity of drug in stomach.
DIn	Quantity of drug in small intestine.
C_1	Concentration of drug in central compartment.
V_1	Apparent volume of distribution for central body compartment.
Do	Administered dose.
F	Fraction of administered dose that reaches systemic circulation.
f_1	Fraction of dose emptied rapidly from stomach as an initial bolus or 'squirt'.

f_2 Fraction of dose emptied exponentially from stomach with rate constant K_G (min^{-1}).

t Time elapsed after ingestion.

t_{LAG} Interval between ingestion and the start of gastric emptying.

α and β The fast and slow disposition rate constants for the 2 compartmental body model as defined by:

$$\alpha + \beta = K_{12} + K_{21} + Kel$$

$$\alpha \cdot \beta = K_{21} \cdot Kel$$

based on the simplex algorithm of Nelder and Mead (1965) was used to refine the estimates found from the analogue computer. The parameter estimates optimized on the digital computer were FDo/V_1 ; K_{12} ; K_{21} ; Kel ; K_A (Scheme 1) or Ka* (Scheme 2) ; t_{LAG}. From the model of Scheme 2, values of K_G, f_1 and f_2 were constants derived from analysis of gastric emptying. Individual data points were weighted by the method recommended by Ottaway (1973).

Multicompartmental analysis of plasma concentration-time data points yields estimates for the (assumed) first order rate constants for absorption, distribution and elimination. The general form of the equation relating C_1 to t for the model of Scheme 1 is

$$C_1 = \sum_{i=1}^{3} Ai \cdot e^{-ai \cdot (t-t_{LAG})}$$

Although the exponential terms a_1 a_2 and a_3 for a 2 compartment model may be assigned values equal to K_A, α and β , they are not necessarily in this order.

For absorption of paracetamol from aqueous solution, the slow disposition rate constant (β) is smaller than the apparent absorption rate constant

(K_A) and is smaller than the fast disposition rate constant (α). The two remaining exponential terms cannot be assigned to α and K_A unless experimental data are available from intravenous studies or comparing several different oral formulations (Ronfeld and Benet 1977). In the present studies, the main effect was on gastric emptying (and thus K_A). The procedure adopted for each subject who received up to 4 treatments was allocation of the smallest exponential term to β and the near-constant remaining term to α. Values of K_A were then found to alter with treatment in the expected way. The general form of the equation for Scheme 2 is

$$C_1 = \sum_{i=1}^{4} Ai \cdot e^{-a_i(t-t_{LAG})}$$

In the non-linear optimization, a_1 was a supplied constant equal to K_G and a_3 was identified as β. Values of a_2 or a_4 were assigned to α after comparing them with the estimates of α obtained from the analysis according to Scheme 1. The remaining exponential term was assigned to Ka*. In all cases, good agreement was found between the pharmacokinetic values obtained by the analogue and digital methods.

9.5 RESULTS

9.5.1 Gastric emptying

Three different types of gastric emptying were identified (Figure 9.3).

Type 1 Monoexponential gastric emptying pattern commencing immediately after ingestion of the solution or preceded by an interval or lag period during which no emptying occurs.

Type 2 A biphasic gastric emptying pattern in which a fraction (f_1) of the total administered dose emptied rapidly from the stomach within the first 10 - 15 minutes followed by a monoexponential decrease in the remaining fraction (f_2). The small number of points in the first short time interval did not allow a distinction to be drawn between a fast monoexponential emptying and an "instantaneous" squirt or bolus. Preliminary analysis showed that the calculated plasma-concentration-time curves were virtually identical for both cases and so the early emptying pattern was regarded as an initial bolus.

Type 3 A biphasic gastric emptying pattern

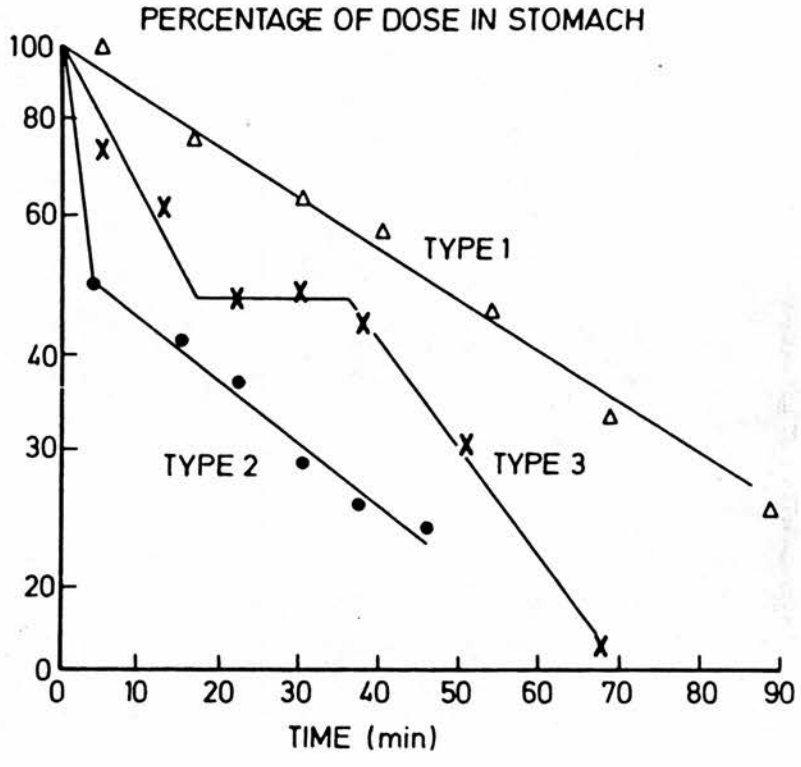


FIGURE 9.3

Gastric emptying pattern observed in
subject 2, (pentazocine, naloxone study) (type 1)
subject 3, (control) (type 2)
& subject 2, (control) (type 3)

in which there were two periods of monoexponential emptying, interrupted by an interval with no emptying.

In the control studies, 50% of ingested solution was emptied in a mean time of 12 minutes (range 4 to 22 minutes) (Tables 9.3; 9.4; 9.5). Gastric emptying was usually of the type 2 pattern with a very fast initial "squirt" of 30% (range 9% to 65%) followed by a slower monoexponential emptying with a mean $t_{\frac{1}{2}}$ of 25 minutes.

Following narcotic analgesics, emptying was either type 1 or type 3. The mean time for 50% gastric emptying was increased to 90 minutes (range 30 to 127 minutes). After pentazocine and naloxone, the time for 50% emptying was 30 minutes (range 4 to 46).

With types 1 and 3 emptying, a lag period was observed ranging from 0 to 36 minutes. Longer lag periods were associated with narcotic administration.

9.5.2 Paracetamol absorption

The mean plasma concentrations are summarised in Table 9.6. In all the control studies paracetamol absorption was rapid with a mean peak plasma

TABLE 9.3 RATE CONSTANT FOR GASTRIC EMPTYING (K_G) AND LAG TIME IN STUDIES EXHIBITION A MONOEXPONENTIAL EMPTYING PATTERN (TYPE 1)

Subject	Treatment	K_G (min^{-1})	Lag time (min)
1	Control	0.0420	5
2	Pethidine	0.0172	35
2	Pentazocine	0.0063	0
2	Pentazocine/naloxone	0.0146	0
3	Pentazocine	0.0132	0
7	Pentazocine/naloxone	0.0293	8

TABLE 9.4 FRACTION (f_1) OF DOSE EMPTIED AS AN INITIAL BOLUS AND RATE CONSTANT FOR SUBSEQUENT GASTRIC EMPTYING (K_G): TYPE 2 EMPTYING PATTERN

Subject	Treatment	f_1 (%)	K_G (min^{-1})
1	Pentazocine/naloxone	60	0.0147
3	Control	46	0.0184
3	Pentazocine/naloxone	21	0.0123
4	Control	15	0.0268
5	Control	9	0.0386
6	Control	34	0.0503
7	Control	19	0.0533
8	Control	65	0.0174

TABLE 9.5 VALUES FOR EMPTYING PATTERN CHARACTERIZED BY TWO MONOEXPONENTIAL PHASES SEPARATED BY A LAG PHASE; TYPE 3 EMPTYING PATTERN

Subject	Treatment	$K_G(min^{-1})$ for first phase	Duration of lag (min)	$K_G(min^{-1})$ for second phase
2	Control	0.0524	20	0.0315
4	Pethidine	0.0047	50	0.0084
5	Pethidine *	0.0112	0	0.0385
7	Pethidine	0.0036	0	0.0094
7	Pentazocine +	0.0047	0	0.0105

* In this experiment there was an initial "squirt" of 30% of the stomach contents into the small intestine.

\+ In this experiment there was an initial lag period of 25 min during which no emptying was observed.

TABLE 9.6 MEAN PLASMA CONCENTRATIONS (UG ML^{-1}) OF UNCONJUGATED PARACETAMOL AFTER ORAL DOSE OF AN AQUEOUS SOLUTION (20 MG KG^{-1})

	Time after administration (min)																		
	3	5	6	10	15	20	25	30	40	50	60	75	90	120	150	180	210	240	360	480
Control study, 8 subjects																				
Mean	1.8	-	7.5	15.0	17.5	19.6	20.0	18.8	17.2	15.0	15.1	14.2	12.0	10.3	-	7.4	-	5.1	2.7	1.4
SD	2.6	-	4.4	7.3	7.9	7.2	5.2	4.0	3.1	2.7	4.0	3.3	2.9	3.1	-	2.2	-	1.7	1.5	0.7
150 mg IM pethidine 30 min before ingestion, 4 subjects																				
Mean	-	1.7	-	2.7	3.4	3.8	4.3	5.3	6.8	8.2	10.0	12.3	13.8	14.3	12.1	11.5	11.4	9.8	5.1	2.6
SD	-	2.9	-	5.2	5.7	6.3	7.2	9.1	11.5	8.5	7.3	8.8	7.8	4.9	3.4	4.2	5.1	3.4	2.0	1.3
60 mg IM pentazocine 30 min before ingestion, 4 subjects																				
Mean	-	0.6	-	1.3	1.6	2.2	2.9	3.8	4.0	4.6	5.5	7.0	8.8	10.0	10.3	10.7	-	7.4	4.4	2.8
SD	-	1.1	-	2.6	2.7	3.0	3.4	4.0	3.8	4.2	5.0	3.4	2.1	1.7	0.7	1.3	-	1.6	1.4	1.3
60 mg IM pentazocine 30 min before and 1.2 mg IV naloxone immediately before ingestion, 4 subjects																				
Mean	-	1.3	-	3.3	8.7	14.5	14.6	14.4	11.6	11.0	11.2	10.9	10.7	9.4	-	6.9	-	5.3	2.7	1.6
SD	-	0.1	-	1.1	4.8	3.0	4.2	4.5	2.4	3.1	3.3	2.7	2.9	2.3	-	1.9	-	1.4	0.8	0.7

concentration of 20.0 ± 5.2 ug/ml at 25 minutes. After pethidine and pentazocine, absorption was delayed in all subjects. The mean peak concentrations were 14.3 ± 4.9 ug/ml at 2 hours and 10.7 ± 1.3 at 3 hours respectively. Naloxone partially reversed the pentazocine induced delay. The mean peak concentration was 14.6 ± 4.2 ug/ml at 25 minutes.

9.5.3 Pharmacokinetic analysis

Scheme 1

Based on the model of Scheme 1, the apparent absorption rate constant was estimated (Ka, Table 9.7). In some studies, after pethidine and pentazocine there was a "lag period" during which plasma concentrations rose only very slowly before the rapid rise at the end of the "lag period". These early points were not included in the calculated curve and so K_A was based only on the rapidly ascending part of the curve. In subject 2, two peaks were observed in the control study and no attempt was made to draw a curve to fit these data.

Overall, there was no significant correlation between K_A and K_G ($r = 0.31$, $n = 13$, $p < 0.05$). However, for type 1 emptying the individual observed values for K_A and K_G were similar (Table 9.8).

TABLE 9.7 KINETIC VALUES FOR PARACETAMOL AFTER ORAL ADMINISTRATION TO HUMAN VOLUNTEERS (20 MG KG^{-1} BODY WEIGHT)

Subject	Treatment	Peak plasma concentrations ug ml^{-1}	Time of peak (min)	Apparent absorption rate constant * (K_A) min^{-1}	True absorption rate constant + (K_A*) min^{-1}
1	Control	27.9	15	0.054	0.255
1	Pentazocine/naloxone	14.5	15	0.076	0.071
2	Control	25.2, 23.0	20, 60	++	0.134
2	Pethidine	23.0	75	0.020	0.077
2	Pentazocine	11.9	60	0.005	0.214
2	Pentazocine/naloxone	21.1	30	0.019	0.209
3	Control	24.4	10	0.066	0.061
3	Pentazocine	9.2	180	0.013	0.066
3	Pentazocine/naloxone	14.1	20	0.031	0.077
4	Control	19.4	40	0.017	0.082
4	Pethidine	16.8	210	0.008	0.047
5	Control	31.1	20	0.049	0.171
5	Pethidine	24.1	40	0.015	0.118
6	Control	17.5	25	0.035	0.153
7	Control	17.7	20	0.046	0.218
7	Pethidine	7.7	120	0.014	0.256
7	Pentazocine	11.2	180	0.009	0.210
7	Pentazocine/naloxone	12.7	25	0.027	0.173
8	Control	15.7	25	0.038	0.050
	Mean				0.139
	SD				0.073

* Based on model of Scheme 1
\+ Based on model of Scheme 2
++ Conventional analysis of these data was inappropriate

TABLE 9.8 VALUES OF K_G AND K_A IN STUDIES OF TYPE 1 GASTRIC EMPTYING

SUBJECT AND STUDY		K_G (min^{-1})	K_A (min^{-1})
1.	Control	0.042	0.054
2.	Pethidine	0.017	0.020
2.	Pentazocine	0.006	0.005
2.	Pentazocine/naloxone	0.015	0.019
3.	Pentazocine	0.013	0.013
7.	Pentazocine/naloxone	0.029	0.027

There was a highly significant correlation ($r = 0.97$, $n = 6$, $p < 0.01$) and the slope of the regression line did not differ significantly from unity ($p < 0.05$) (Fig. 9.4).

Thus, in most cases, the values of K_A and K_G were not equal because gastric emptying was not a single exponential process. The model of scheme 1 therefore has limited application for the description of the kinetics of absorption of drugs such as paracetamol.

Scheme 2

Analysis of the data using the model of scheme 2, revealed excellent agreement between observed and calculated plasma concentration-time curves in all subjects, regardless of the type of gastric emptying pattern. The analysis provided an estimate of K_A^*, the rate constant for transfer of drug from the small intestine into the systemic circulation. The values of K_A^* were greater than K_G, indicating that the rate-limiting step in the overall absorption of paracetamol is the rate of gastric emptying.

In figure 9.5, the observed and calculated plasma concentrations and the observed (type 1) gastric

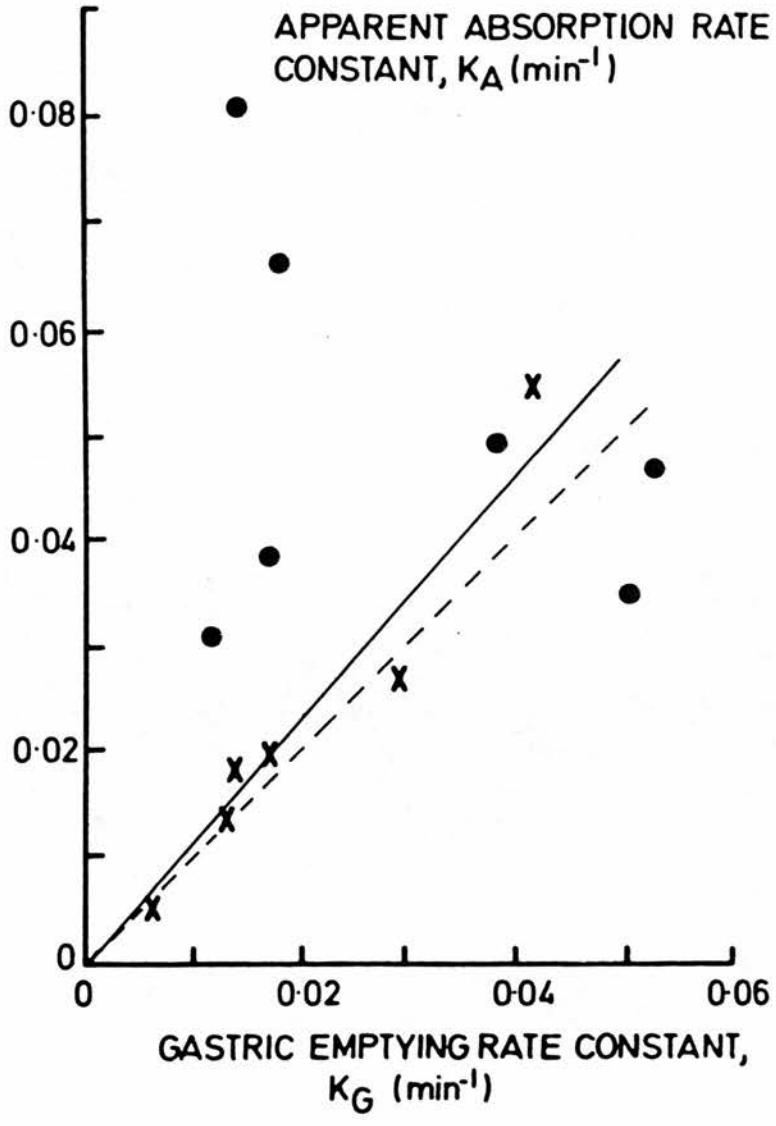


FIGURE 9.4

Apparent absorption rate constant (K_A) plotted against gastric emptying rate constant (K_G) in studies of type 1 (x) and type 2 (•) gastric emptying.

-------- is line of identity

_____ is regression line for type 1 gastric emptying

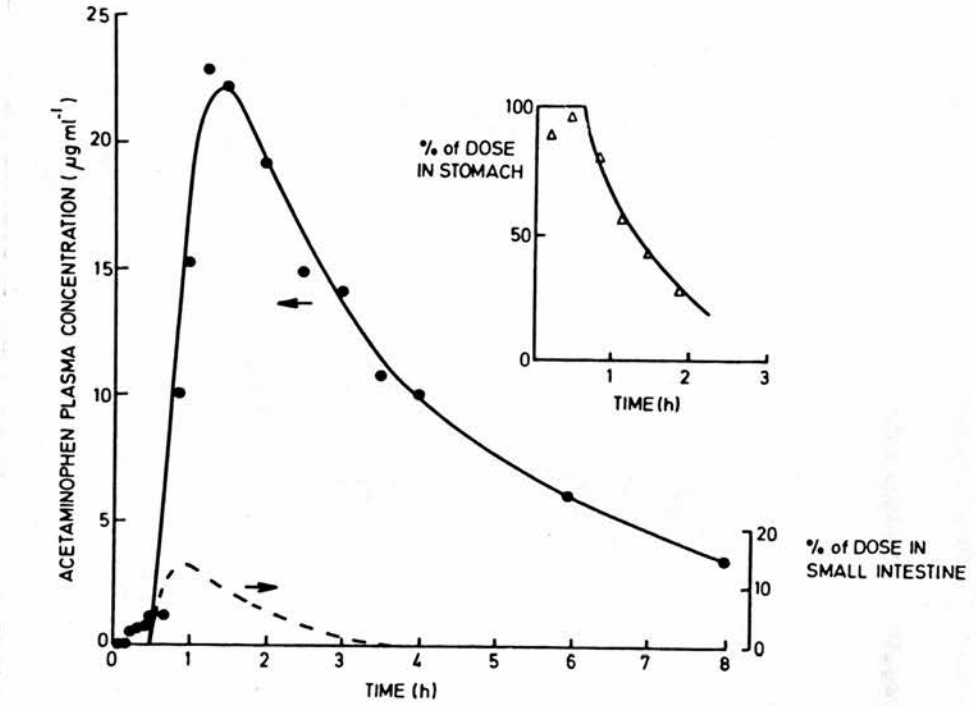


FIGURE 9.5

Plasma paracetamol concentration plotted against time for type 1 emptying with a lag period (subject 2, pethidine)

● data points

____ Calculated curve

---- predicted percentage of dose in small intestine

Inset - Gastric emptying pattern

△ data points

____ calculated curve

emptying pattern in subject 2 are shown. Pethidine delayed the onset of emptying for about 35 minutes and this was reflected in a delay before plasma concentrations rose. The data suggest that a small amount of solution had emptied from the stomach in this quiescent period and this is seen as a small rise in plasma concentrations.

In figure 9.6, the plasma concentration-time profile and gastric emptying pattern for type 2 gastric emptying in subject 6 is shown. About one third of the dose left the stomach rapidly and the plasma concentration rose correspondingly. In the subsequent exponential phase, gastric emptying was rapid (K_G = 0.050 min^{-1}). Since K_A* was even larger (0.153 min^{-1}), the quantity of paracetamol in the small intestine fell rapidly.

The measured plasma paracetamol concentrations in one subject showed two peaks. Gastric emptying pattern indicated that there were two exponential portions separated by an interval of about 20 minutes during which there was no emptying. Using an analogue computer programme with the times of start (t_1) and end (t_2) of the quiescent interval, and the rate constants K_{G1} and K_{G2} for the first and second exponential emptying periods respectively,

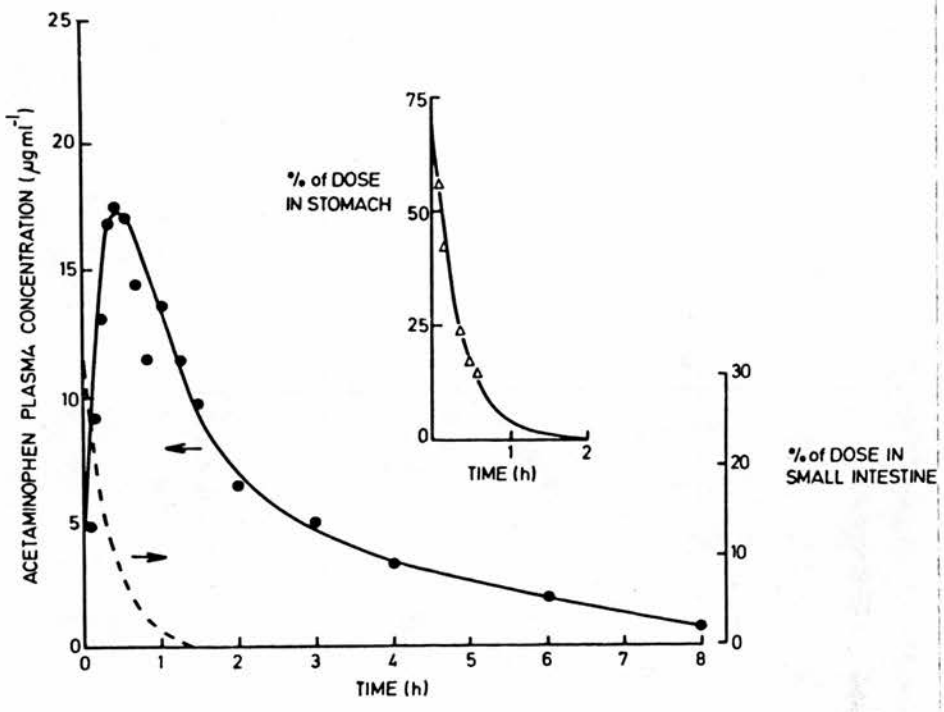


FIGURE 9.6

Plasma paracetamol concentration plotted against time for type 2 gastric emptying (subject 6, control)

- ● data points
- ____ calculated curve
- ---- predicted percentage of dose in small intestine

Inset - gastric emptying pattern
- △ data points
- ____ calculated curve

he calculated plasma concentration-time curve agreed remarkably well with the observed points (Fig. 9.7).

In a process with 2 consecutive steps, estimation of the rate constant for the faster step is subject to some error. Successive increases in K_A^*, with K_G held constant and of similar magnitude to K_A^*, make substantial changes in the predicted curve (Fig. 9.8). However, if $K_A^* >> K_G$, the rate constant for the overall process of transfer from stomach to systemic circulation is approximately equal to K_G, and the predicted plasma concentration-time curve is influenced only slightly by small changes in K_A^*.

9.6 DISCUSSION

Gastric emptying patterns in the 20 studies showed considerable variation but could be conveniently classified into 3 types. Departures of emptying from the simple monoexponential pattern are well recognised (Hunt & Spurrell 1951; Colmer et al 1973).

Inspection of the emptying pattern and plasma paracetamol concentration-time curve for each experiment showed that the two were closely related. In particular, where the start of gastric emptying

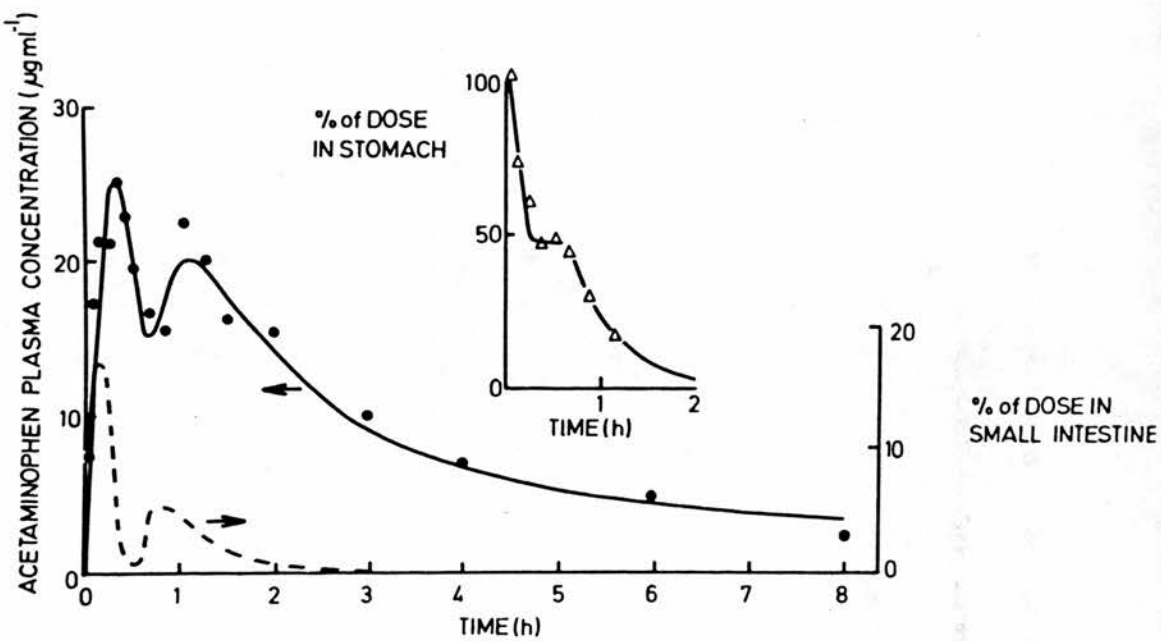


FIGURE 9.7

Plasma paracetamol concentrations plotted against time for type 3 gastric emptying (subject 2, control)

● data points

____ calculated curve

---- predicted percentage of dose in small intestine

Inset - gastric emptying pattern

△ data points

____ calculated curve

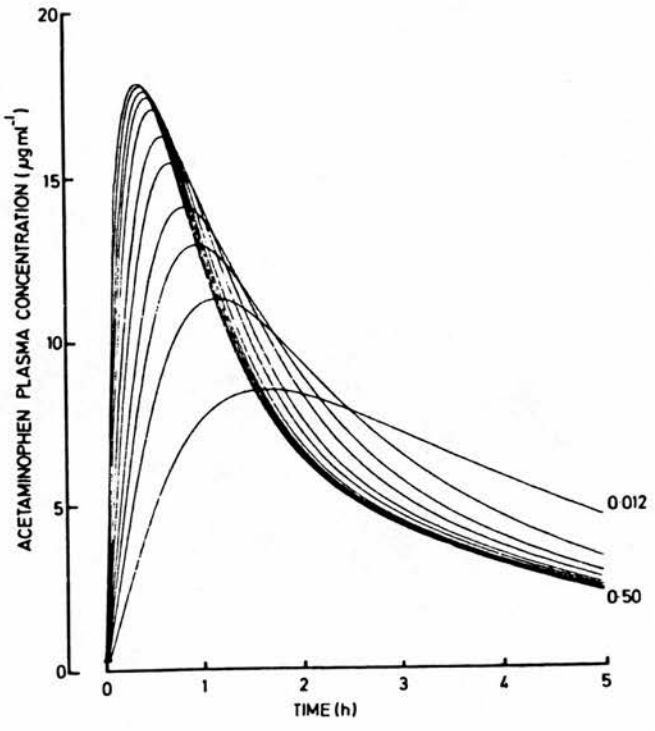


FIGURE 9.8

Predicted plasma concentration-time curves showing the effects of change in K_A*

(Subject 6, control study, type 2 emptying:
f1 = 34%, f2 = 66%, K_G = 0.050, K_{12} = 0.016,
K_{21} = 0.011, Kel = 0.010 min^{-1})

Values of K_A* for successive curves are 0.012, 0.025, 0.038, 0.05, 0.075, 0.10, 0.15, 0.20, 0.25, 0.35, and 0.50 min^{-1}

was delayed there was a corresponding "lag" period during which the plasma concentration did not rise or rose only very slightly and slow gastric emptying was associated with a slow rise in plasma concentration. Conversely, the most rapid increase in paracetamol concentrations were found with type 2 gastric emptying, particularly when a substantial proportion of the dose emptied in the initial "squirt". This obvious relationship between gastric emptying and the initial rise in plasma concentration strongly suggests that gastric emptying was the rate-limiting step in the absorption of paracetamol.

Overall, the values obtained for K_A using conventional pharmacokinetic analysis did not correspond to the observed values of K_G, but these two values were in excellent agreement when there was type 1 gastric emptying. This is to be expected since emptying is then a single exponential process which limits absorption. There was no significant correlation between K_G and K_A with types 2 and 3 gastric emptying patterns and Scheme 2 was developed to take these patterns into account. Using this model there was good agreement between calculated and actual plasma concentrations in all cases. Even when gastric emptying was interrupted by a quiescent

period and the plasma concentration-time curve had two peaks, satisfactory agreement was found using the model. The occurrence of two peaks early in the plasma concentration-time curve observed here and in other studies is seen to be due to an interruption in gastric emptying. The first rapid decline in plasma concentration starts at the time when emptying from the stomach ceases temporarily.

As expected, the true absorption rate constant K_A^* (Scheme 2) exceeded the apparent absorption rate constant K_A. Since there was no significant correlation between K_A^* and K_A, the true absorption rate constant cannot be predicted from K_A obtained by conventional pharmacokinetic analysis.

The absolute bioavailability was not determined in this investigation. Since Rawlins, Henderson and Hijab (1977) found that the mean bioavailability of paracetamol from two 500-mg tablets was 89%, the apparent absorption rate constants should be corrected for incomplete bioavailability, but this does not alter the conclusions drawn. The concurrent administration of narcotic analgesics does not influence the total urinary excretion of paracetamol and its major metabolites (Chapters 7 and 8).

The value of K_A* was greater than K_G in all experiments and confirms that gastric emptying is the rate-limiting step in the absorption of paracetamol given orally in solution. Absorption from the small intestine is rapid, and the estimated mean $t_{\frac{1}{2}}$ for absorption is 6.8 $\pm$ 3.9 min. The results confirm that absorption of paracetamol was highly dependent on the kinetics of gastric emptying.

Most control studies showed type 2 gastric emptying but the percentage of the dose emptied as an initial bolus varied from 9% to 65% When a large proportion of the dose rapidly entered the small intestine, plasma paracetamol concentration rose rapidly and the apparent absorption rate constant (K_A) approached that for the true absorption rate constant (K_A*). However, when only a small amount was released from the stomach in the first bolus, K_A* was 3 to 5 times as great as K_A.

Premedication with a narcotic analgesic abolished the initial bolus in seven out of eight studies and emptying was arrested or greatly reduced. Plasma concentrations remained at or close to zero for about 30 to 40 min. In some cases a very slow rise

was observed to concentrations of about 5% to 10% of the peak values: this may be due to a small amount of solution passing through the pylorus (since the emptying measurements did show a small loss of solution from the stomach), or to a small amount of paracetamol that may have been absorbed from the stomach.

In one study (Subject 5, after pethidine) an initial bolus of 30% of the dose entered the small intestine. The plasma concentration rose immediately after ingestion of the solution. Subsequent gastric emptying was much slower than in the control and the peak plasma concentration was lower. The reason for the reduced or delayed effect of pethidine on this subject is not known.

Measurements of gastric emptying have confirmed that it is not usually a simple monoexponential process in supine individuals. Type 2 gastric emptying is more common, and when a large proportion of the dose passes through the pylorus, absorption is very rapid. Using a model in which separate compartments represent the stomach and the small intestine, it is possible to calculate plasma concentrations arising from several patterns of gastric emptying and to estimate the true absorption

rate constant K_A^* for absorption from the small intestine. Although simpler models such as that of Scheme 1 may sometimes be consistent with experimental data, the proposed model seems to be more appropriate for the description of drug absorption from orally administered solutions if gastric emptying is to be taken into account.

CHAPTER 10

THE EFFECTS OF POSTURE ON PARACETAMOL ABSORPTION

Since gastric emptying rate probably determines the rate of absorption of most orally administered drugs, it follows that factors influencing gastric emptying rate will in turn influence the rate of drug absorption. In neonates, the stomach empties more rapidly in the prone and right lateral positions than in the supine and left lateral positions (Yu, 1975) but there are little data in man relating gastric emptying or drug absorption with posture. In the present study the effect of posture on the rate of paracetamol absorption was measured.

PATIENTS AND METHODS

Eight healthy volunteers (seven male) with a mean age of 29 $\pm$ 1.8 years and a mean weight of 68.8 $\pm$ 8.2 Kg were studied twice. On one occasion, the subjects were ambulant throughout the study and on the other, they lay on the left side for 2 hours and were then ambulant. On both occasions, after an overnight fast, each subject received 1.5 g paracetamol as three Panadol tablets with 200 ml water. Blood samples were taken at intervals for 4 hours for paracetamol measurement by gas liquid

chromatography. No food, fluid or tobacco was allowed during the study.

RESULTS

Paracetamol absorption was significantly delayed in all subjects lying on the left side (Table 10.1 and 10.2, Fig. 10.1). Plasma concentrations at 15 minutes and 30 minutes were significantly lower in the supine subjects. The mean concentrations at 15 minutes were 12.5 $\pm$ 13.6 ug/ml and 0.18 $\pm$ 0.49 ug/ml ambulant and lying respectively ($p < 0.05$). At 30 minutes, the concentrations were 20.8 $\pm$ 9.4 ug/ml and 7.8 $\pm$ 8.8 ug/ml ($p < 0.05$). After 45 minutes, plasma concentrations did not differ between the two groups.

The area under the plasma concentration time curve from 0 to 45 minutes was significantly greater in the ambulant study (10.9 $\pm$ 5.6 ug hr/ml) than in the lying study (4.5 $\pm$ 2.8 ug hr/ml ; $p < 0.02$). The total amount of paracetamol absorbed in 4 hours was probably not influenced by posture since the areas under the plasma concentration time curve from 0 to 4 hours were almost identical in the two studies (49.5 $\pm$ 12.3 ug hr/ml ambulant and 45.5 $\pm$ 7.8 ug hr/ml lying).

TABLE 10.1 PLASMA PARACETAMOL CONCENTRATIONS IN 8 AMBULANT VOLUNTEERS

Subject	Plasma Paracetamol Concentration (ug/ml)									AUC	
	15'	30'	45'	60'	75'	90'	2hr	3hr	4hr	0-45m ug hr/ml	0-4h ug hr/ml
WSN	31.5	28.2	24.6	26.1	19.0	17.9	15.4	10.9	8.2	I8.0	65.6
AP	10.7	29.2	28.0	23.3	20.7	18.4	16.7	12.2	9.2	13.5	64.2
JM	0	18.1	21.8	20.1	16.9	15.9	14.5	10.2	7.3	7.3	49.9
RHR	3.9	11.4	16.2	16.5	16.4	14.7	14.0	12.8	9.3	5.9	42.1
JP	35.2	24.6	20.0	16.2	14.7	13.7	12.2	8.1	6.0	17.5	53.1
GBD	0	3.0	11.1	14.2	12.3	11.1	9.9	6.4	4.2	2.1	27.7
AN	12.0	23.0	24.2	19.7	18.5	16.2	12.5	9.5	6.0	11.8	49.8
PB	6.8	28.5	18.8	15.4	13.7	12.2	10.2	7.9	5.0	I1.2	43.4
Mean	12.5	20.8	20.6	18.9	16.5	15.0	13.2	9.8	6.9	10.9	49.5
SD	13.6	9.4	5.3	4.2	2.9	2.6	2.4	2.2	1.9	5.6	12.3

TABLE 10.2 PLASMA PARACETAMOL CONCENTRATIONS IN 8 VOLUNTEERS LYING ON THE LEFT SIDE

Subject	Plasma Paracetamol Concentration (ug/ml)									AUC	
	15'	30'	45'	60'	75'	90'	2hr	3hr	4hr	0-45m ug hr/ml	0-4h ug hr/ml
WSN	1.4	25.7	18.6	20.1	17.6	15.3	13.1	10.7	8.1	9.1	51.2
AP	0	1.5	2.0	4.9	9.2	11.9	13.0	18.1	11.4	0.75	42.4
JM	0	0.5	3.6	11.8	17.8	18.9	13.9	11.4	8.5	0.58	41.6
RHR	0	6.8	29.2	23.6	20.5	18.3	14.6	11.0	7.7	5.4	52.7
JP	0	0	45.2	24.7	20.2	19.3	15.8	10.7	7.4	5.7	45.7
GBD	0	8.6	19.4	14.3	12.8	11.3	9.5	7.4	4.8	4.6	34.9
AN	0	4.4	23.7	26.9	26.3	23.3	18.4	11.4	7.3	4.1	57.9
PB	0	15.0	15.6	15.8	15.8	12.9	10.5	7.8	3.9	5.7	38.0
Mean	0.18	7.81	19.6	17.8	17.5	16.4	13.6	11.1	7.4	4.5	45.5
SD	0.49	8.78	13.9	7.5	5.2	4.2	2.8	3.3	2.3	2.8	7.8

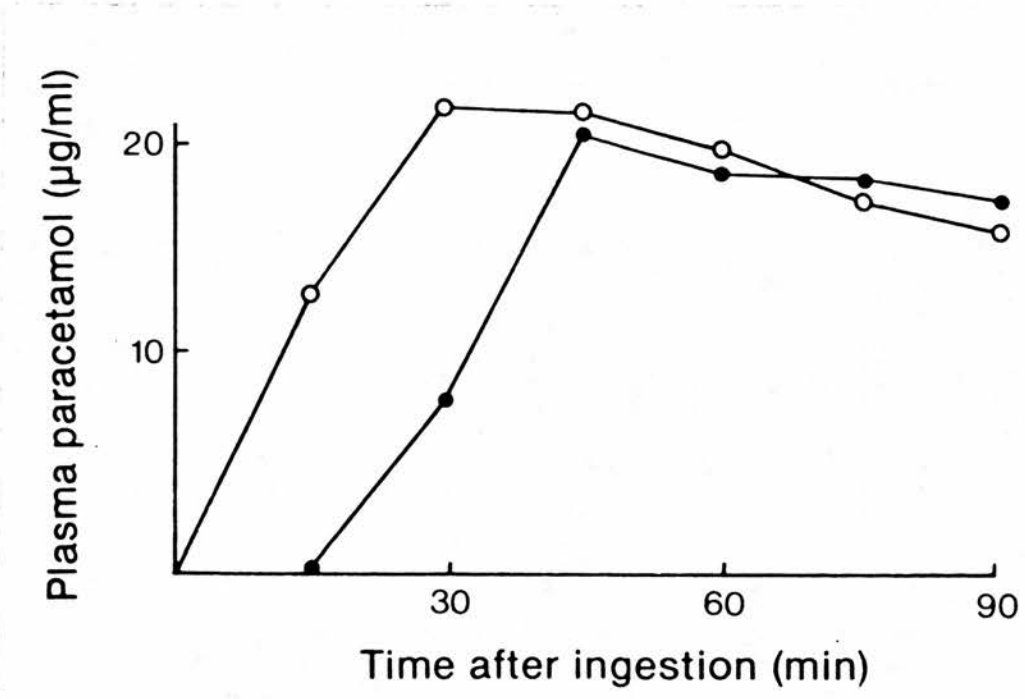


FIGURE 10.1

Mean plasma paracetamol concentrations in 8 healthy volunteers studied on 2 occasions after paracetamol 1.5 g orally with 200 ml water.

(o——o = ambulant ●——● = lying on left side)

DISCUSSION

The delay in paracetamol absorption observed in subjects lying on the left side was probably due to slower gastric emptying in that position. Martin (1971) commented on a similar delay in the absorption of aspirin solution in five subjects in the "left supine position" and also attributed this to delayed gastric emptying. Unfortunately, no actual plasma concentration data was given but plasma concentrations were reported to be higher in sitting subjects at 10 and 20 minutes than in subjects in the left supine position.

Patients who take tablets while in bed on their left side will be likely to have delayed absorption and it is obvious that the position of subjects must be taken into account in drug absorption studies.

CHAPTER 11

PARACETAMOL AND ASPIRIN ABSORPTION FROM SAFAPRYN AND SAFAPRYN-CO

Although narcotic analgesics delay gastric emptying and greatly slow the rate of paracetamol absorption, Bajorek, Widdop and Volans (1978) demonstrated that oral codeine phosphate (15-30 mg) does not delay the absorption of paracetamol (1.5 g) when given 30 minutes previously. Crone and Ardran (1957) found that intravenous morphine (4 - 6mg) increased the amplitude of gastric peristalsis and "propulsive power" of the stomach for approximately 30 minutes in 20 healthy volunteers; this "augmented activity" being followed by a longer phase of inhibition of peristalsis. This could conceivably explain the failure of inhibition of paracetamol absorption by codeine in the studies of Bajorek et al (1978) and it may be that low doses of narcotics initially have a stimulating effect on gastric emptying.

When codeine phosphate syrup (10 ml) was given to six volunteers every 30 minutes for 2 hours before a dose of ethanol (0.4 g/Kg) there was a significant reduction in the ethanol absorption for at least the

two hours of the study (Cudworth et al 1975). The mean peak alcohol concentration was 29.7 ± 7 mg/100 ml after codeine phosphate and 35 ± 7 mg/100 ml after placebo. The dose of codeine phosphate used in this study was very large (200 mg) and all of the subjects experienced central side effects such as headache, dizziness, euphoria and disorientation.

Little is known of the absorption of paracetamol and aspirin from codeine-containing compound analgesics after single or repeated doses. In the present study, the absorption of aspirin and paracetamol from two doses of Safapryn and Safapryn-Co (Pfizer Ltd.) was measured. Each Safapryn tablet contains aspirin 300 mg as an enteric coated core surrounded by an outer layer of paracetamol 250 mg. Safapryn-Co has aspirin 300 mg as an enteric coated core surrounded by an outer layer of paracetamol 250 mg and codeine 8 mg. Both tablets are sugar coated.

PATIENTS AND METHODS

Four healthy male volunteers with a mean age of 29.0 ± 2.1 years and a mean weight of 68.2 ± 3.2 Kg were studied twice with at least one week between each study. On one occasion, the fasting subjects received 4 tablets of Safapryn with 200 ml of water

at 0900 h followed by a further 4 tablets in the same way at 1500 h. A light lunch consisting of a cheese or salad sandwich and coffee was taken at 1200 h. No tobacco was allowed and the subjects were ambulant throughout the study. The study was repeated with Safapryn-Co.

Blood was taken at intervals for 10 hours and the plasma was separated for estimation of unchanged paracetamol and salicylate by gas liquid chromatography and fluorimetry (Schachter and Mahis 1958) respectively.

RESULTS

Following the first dose of Safapryn and Safapryn-Co, plasma paracetamol concentrations were the same (Table 11.1; Figure 11.1). Absorption was rather slow with peak concentrations occurring at 2 hours. Paracetamol concentrations in all 4 subjects were greater following Safapryn-Co, 30 and 60 minutes after the second dose. The mean concentrations at 30 minutes were 7.6 ± 3.9 ug/ml and 3.3 ± 1.3 ug/ml after Safapryn-Co and Safapryn respectively and at 60 minutes the values were 14.5 ± 6.8 ug/ml and 7.2 ± 3.6 ug/ml ($p < 0.05$).

Following the first dose of either preparation,

TABLE 11.1 PARACETAMOL ABSORPTION FOLLOWING 4 TABLETS OF SAFAPRYN OR SAFAPRYN-CO AT TIME 0 AND 6 HOURS

	Plasma paracetamol concentrations (ug/ml)								
	0.5h	1h	2h	4h	6h	6.5h	7h	8h	10h
SAFAPRYN									
1	2.6	10.4	7.3	6.0	2.7	3.9	9.5	12.8	5.7
2	3.7	8.3	9.3	5.6	3.5	2.9	2.7	6.7	9.7
3	1.7	5.6	9.8	6.1	3.4	4.7	10.7	13.4	5.6
4	5.1	10.1	9.3	4.8	2.0	1.7	5.9	12.6	5.6
Mean	3.3	8.6	8.9	5.6	2.9	3.3	7.2	11.4	6.7
SD	1.5	2.2	1.1	0.6	0.7	1.3	3.6	3.1	2.0
SAFAPRYN-CO									
1	4.3	8.1	10.1	5.8	2.9	8.1	21.3	12.1	6.0
2	3.5	7.2	12.1	6.1	3.1	4.1	5.1	10.7	7.3
3	5.2	10.1	10.1	6.3	3.7	12.9	16.7	12.6	6.6
4	6.0	8.8	7.6	5.1	2.9	5.2	14.9	15.7	7.1
Mean	4.8	8.6	10.0	5.9	3.2	7.6	14.5	12.8	6.8
SD	1.1	1.2	1.8	0.53	0.38	3.9	6.8	2.1	0.58

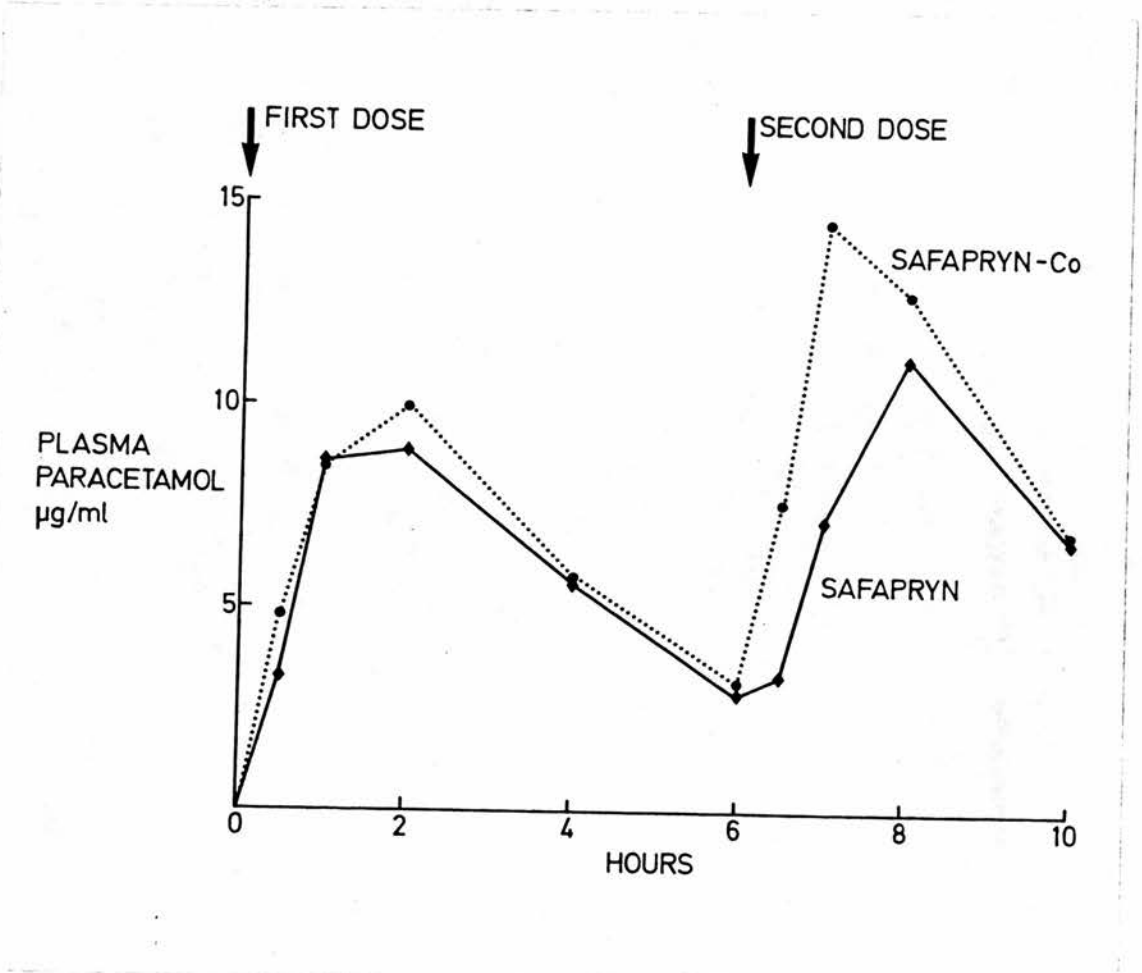


FIGURE 11.1

MEAN PLASMA PARACETAMOL CONCENTRATIONS FOLLOWING SAFAPRYN (◆) AND SAFAPRYN-CO (●). FOUR TABLETS WERE ADMINISTERED AT TIME 0 AND 6 HOURS. EACH TABLET CONTAINS 250 mg PARACETAMOL.

TABLE 11.2 PLASMA SALICYLATE CONCENTRATIONS FOLLOWING 4 TABLETS OF SAFAPRYN OR SAFAPRYN-CO AT TIME 0 AND 6 HOURS

	Plasma salicylate concentrations (ug/ml)								
	0.5h	1h	2h	4h	6h	6.5h	7h	8h	10h
SAFAPRYN									
1	0	0	0	5.0	33.0	37.0	40.0	54.0	81.0
2	0	0	0	32.5	87.0	92.0	89.0	91.0	87.0
3	0	0	0	18.0	19.0	32.0	18.0	21.0	11.0
4	0	0	0	55.0	88.0	82.0	80.0	80.0	125.0
Mean	0	0	0	27.6	56.8	60.0	56.8	61.5	76.0
SD	0	0	0	21.4	36.0	30.7	33.5	31.1	47.5
SAFAPRYN-CO									
1	0	0	0	0	63.0	63.0	63.0	73.0	111.0
2	0	0	0	54.0	166.0	160.0	136.0	124.0	98.0
3	0	0	0	31.0	77.0	72.0	75.0	77.0	97.0
4	0	0	0	14	48	56	56	70	87
Mean	0	0	0	24.8	88.5	87.8	82.5	86.0	98.3
SD	0	0	0	23.3	53.0	48.6	36.5	25.5	9.8

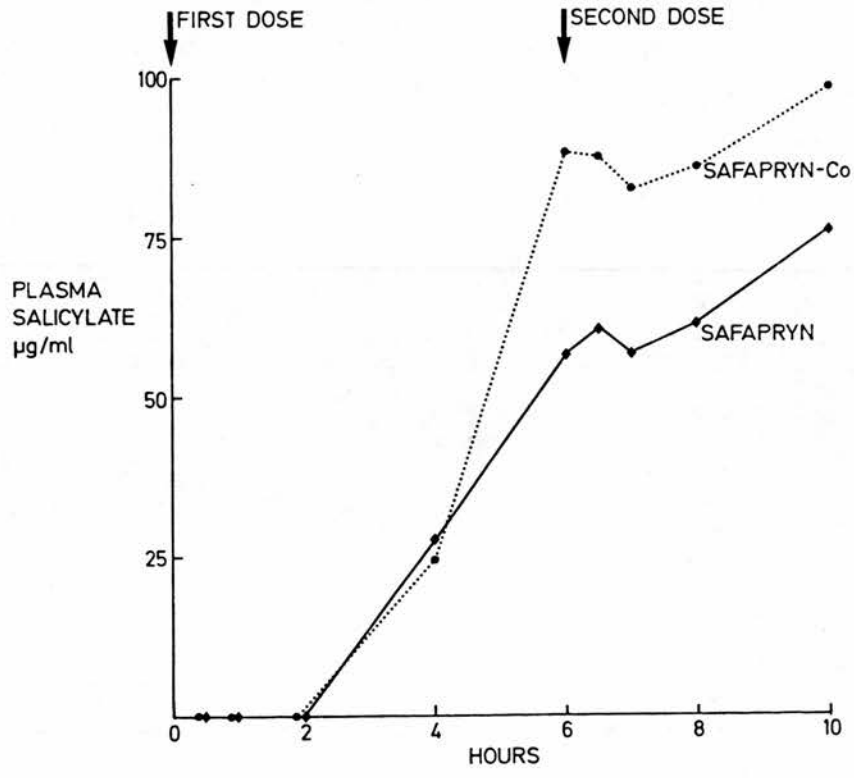


FIGURE 11.2

MEAN PLASMA SALICYLATE CONCENTRATIONS FOLLOWING SAFAPRYN (◆) AND SAFAPRYN-CO (●). FOUR TABLETS WERE ADMINISTERED AT TIME 0 AND 6 HOURS. EACH TABLET CONTAINS 300 mg ASPIRIN AS AN ENTERIC COATED CORE.

plasma salicylate concentrations were the same (Table 11.2; Figure 11.2). Absorption was slow with plasma concentrations still rising 6 hours after administration. Following the second dose, plasma salicylate concentrations were greater in 3 of the 4 subjects after Safapryn-Co compared with Safapryn but the differences did not reach statistical significance.

DISCUSSION

Codeine phosphate, in a dose of 32 mg, seems unlikely to inhibit the absorption of aspirin and paracetamol from compound analgesic preparations. If anything, absorption after the second dose of Safapryn-Co was more rapid than from Safapryn and this is consistent with a time and dose-dependent effect of narcotic analgesics on gastric emptying.

CHAPTER 12

CONCLUSION

The major theme of this thesis has been to relate drug absorption and gastric emptying and to identify physiological, pathological and pharmacological factors which influence drug absorption by their effect on gastric emptying.

Paracetamol has been used as a model drug for absorption studies because it is a safe, simple analgesic drug which is acceptable to patients and volunteers as a test drug and because its rate of absorption after oral administration depends on the rate of gastric emptying. The peak plasma paracetamol concentration and the time taken to achieve the peak concentration correlates with liquid gastric emptying.

This correlation has been used to assess indirectly the rate of gastric emptying in a variety of clinical situations in which direct measurement of gastric emptying rate, although desirable, is impracticable.

The rate of gastric emptying is important in women during labour because delayed gastric emptying

may contribute to maternal death. From studies of paracetamol absorption, gastric emptying seems to be normal in early labour and only slightly delayed in late labour. If extradural analgesia is used, gastric emptying rate is probably not affected. Administration of narcotic analgesics, however, is associated with a striking delay in gastric emptying which is not influenced by metoclopramide 10 mg i.m. Patients with delayed paracetamol absorption following narcotic administration have returned to normal when studied 2 to 5 days after delivery.

In similar studies carried out in the early postoperative period after abdominal hysterectomy, paracetamol absorption and thus gastric emptying was only slightly delayed in patients undergoing extradural analgesia but was markedly delayed in those receiving narcotic analgesic drugs. It seems likely that narcotic analgesics administered to alleviate pain, contribute significantly to any alteration in gastro-intestinal function which has been recorded in patients in pain or in the postoperative period.

In healthy volunteers, I have confirmed that narcotic analgesics alone can produce a striking delay in gastric emptying and paracetamol absorption

measured simultaneously. The magnitude of the delay in absorption is similar to that observed in the patient studies and is partially antagonized by naloxone.

Using pharmacokinetic analysis in which 2 compartments represent the gastro-intestinal tract (one for the stomach and one for the small intestine) the measured rate constant for gastric emptying was always smaller than that for transfer from the small intestine to the systemic circulation. Thus, the rate limiting step in the overall absorption of paracetamol is the rate of gastric emptying.

In healthy volunteers, codeine present in Safapryn-Co did not inhibit paracetamol absorption. In fact, after the second dose, paracetamol absorption was enhanced. Thus, small doses of narcotics may initially stimulate gastric emptying before producing a delay and these data are compatible with those of Crone and Ardran (1958).

Paracetamol absorption rate as an index of the rate of gastric emptying has been used in a variety of clinical situations since publication of my early results. Attention to detail is of great importance to avoid physiological factors which may

influence gastric emptying. For example in healthy volunteers paracetamol absorption is delayed for more than 30 minutes by lying down compared with being ambulant.

In conclusion, this thesis contains information on gastric emptying and drug absorption in a variety of situations. The clinical relevance has been extended by studies of physiological, pathological and pharmacological modifications. The results may have wide therapeutic implications.

APPENDIX

Equation used for C_1 for the model of scheme 2 Chapter 9

For description of symbols, see Table 9.2

$$C_1 = \frac{F.Do.K_A^*}{V_1}\left[\frac{f_2K_G(K_{21}-K_G).e^{-K_G(t-t_{LAG})}}{(K_A^*-K_G)(\alpha-K_G)(\beta-K_g)} + \frac{f_2K_G+f_1(K_G-K_A^*)}{(K_G-K_A^*)(\alpha-K_A^*)(\beta-K_A^*)}.(K_{21}-K_A^*).e^{-K_A^*(t-t_{LAG})}\right.$$

$$\left. + \frac{f_2K_G+f_1(K_G-\alpha)}{(K_G-\alpha)(K_A^*-\alpha)(\beta-\alpha)}.(K_{21}-\alpha)e^{-\alpha(t-t_{LAG})} + \frac{f_2K_G+f_1(K_G-\beta)}{(K_G-\beta)(K_A^*-\beta)(\alpha-\beta)}.(K_{21}-\beta).e^{-\beta(t-t_{LAG})}\right]$$

LIST OF ABBREVIATIONS

The following special abbreviations have been used in this thesis.

AUC	Area under the plasma concentration time curve.
C	Centigrade
C_t	Plasma concentration at time t
g	Gram
hr	Hour
i.d.	Internal diameter
i.m.	Intramuscular
i.v.	Intravenous
Ka	First order absorption rate constant
kg	Kilogram
l	Litre
M	Molar
mg	Milligram
min(')	Minute
ml	Millilitre
ng	Nanogram
NS	Not significant
rpm	Revolutions per minute
SD	Standard deviation
SEM	Standard error of the mean
$t_{1/2}$	Half-life
uCi	Microcurie

ug	Microgram
ul	Microlitre
Σ	Algebraic sum

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PUBLICATIONS

Reprinted from THE LANCET, *April* 19, 1975, *p.* 890

NARCOTIC ANALGESICS AND DELAYED GASTRIC EMPTYING DURING LABOUR

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Summary The rate of gastric emptying in women during labour was estimated indirectly from the kinetics of absorption of orally administered paracetamol (acetaminophen). Gastric emptying was normal in patients who had not received a narcotic analgesic but was markedly delayed in women given pethidine, diamorphine, or pentazocine. The inhibitory effect of diamorphine and pethidine on gastric emptying was not reversed by metoclopramide.

Introduction

UNEXPECTED vomiting or regurgitation with aspiration of gastric contents during induction of anæsthesia in labour remains an important cause of maternal death. Despite a significant decrease in the total number of maternal deaths in the years 1952 to 1969,[1] the number of fatalities related to anæsthesia has not decreased. At least half these deaths were caused by the inhalation of gastric contents. This tendency to vomit or regurgitate has been attributed in part to the delayed gastric emptying which is known to occur during labour.[2–4] The present studies were undertaken to investigate gastric emptying during labour and the effects of drugs such as metoclopramide. However, it immediately became apparent that significant delay occurred only in patients receiving narcotic analgesics. These drugs are widely used for obstetric analgesia. They cause vomiting and have been shown to influence gastrointestinal motility,[5–7] but the possibility that delayed gastric emptying in labour might be due to the administration of narcotics does not seem to have been considered. Howard and Sharp [3] demonstrated that metoclopramide increased the rate of gastric emptying in labour, but no distinction was made between those patients who received pethidine and those who did not.

Because gastric emptying cannot be readily measured during labour, an indirect estimate was obtained in the present studies from the kinetics of paracetamol (acetaminophen) absorption after an oral dose. The rate of gastric emptying determines the rate of absorption or orally administered paracetamol, since this drug is not absorbed to any extent from the stomach but is rapidly absorbed from the upper small intestine.[8] This method has recently been validated by simultaneous measurements of the rate of gastric emptying and paracetamol absorption.[9] We report our observations on the effects of pethidine, diamorphine (heroin), pentazocine, and metoclopramide on gastric emptying, as demonstrated by paracetamol absorption in women during labour.

Patients and Methods

Paracetamol-absorption studies were carried out in 56 patients during labour and in the post-partum period. Their ages ranged from seventeen to thirty-four years (mean twenty-three years). Each had given informed consent and none had clinical evidence of gastrointestinal, hepatic, renal, or cardiovascular disease. The obstetric management of the patients was not influenced by their participation in the study, and intravenous or buccal oxytocin was given as required.

Pethidine and diamorphine.—Initially, the absorption of paracetamol was studied in 28 women in labour receiving pethidine 150 mg. or diamorphine 10 mg. intramuscularly as required. The narcotic was usually given with cyclizine 50 mg. The test dose of paracetamol was given at varying times in relation to the injection of the narcotic and the imminence of delivery.

Pentazocine.—Similar studies were performed in 8 women in labour who received pentazocine 60 mg. and cyclizine 50 mg. intramuscularly thirty minutes before the administration of paracetamol.

Metoclopramide.—Additional studies were performed to assess the possible effects of metoclopramide on the inhibition of paracetamol absorption produced by the narcotic analgesics. 5 women in labour received diamorphine 10 mg. and metoclopramide 10 mg. intramuscularly at the same time, and 5 were given pethidine 150 mg. with metoclopramide 10 mg. In both groups these drugs were given thirty minutes before the ingestion of paracetamol.

Post-partum studies.—The absorption of paracetamol was also studied in 10 patients two to five days after vaginal delivery. They had all received a narcotic analgesic during labour—6 had had pethidine, 1 pethidine and diamorphine, and 3 had received diamorphine alone. None had received any type of analgesic for at least sixteen hours before paracetamol was given.

TABLE I—PLASMA-PARACETAMOL CONCENTRATIONS IN WOMEN DURING LABOUR AND POST PARTUM

Treatment *	Plasma-paracetamol concentration (μg./ml.) (mean ± S.E.)										
	15 min.	30 min.	45 min.	60 min.	75 min.	90 min.	2 hr.	3 hr.	4 hr.	6 hr.	8 hr.
No narcotic (12) ..	..	21 ± 4·7	..	18·7 ± 2·1	..	14·5 ± 1·8	12·4 ± 1·5	9 ± 0·8	6·7 ± 0·7	3·2 ± 0·4	2 ± 0·3
Post partum (10) ..	..	17 ± 3·9	..	19 ± 1·9	..	16·8 ± 1·4	15·6 ± 1·0	..	..	..	..
Pethidine (8)	..	0·8 ± 0·4	..	1·9 ± 0·5	..	2·8 ± 0·6	3·0 ± 0·5	7·2 ± 1·9	14·0 ± 3·8	7·6 ± 1·5	3·9 ± 0·4
Diamorphine (8) ..	..	2·2 ± 1·1	..	3·3 ± 0·8	..	4·5 ± 1·4	5·9 ± 1·3	6·8 ± 1·5	8·6 ± 2·1	5·8 ± 1·0	2·9 ± 3·4
Pentazocine (8) ..	0·1 ± 0·09	0·9 ± 0·4	1·4 ± 0·6	2 ± 0·7	2·1 ± 0·6	2·5 ± 0·6	..	..	..	..	..
Pethidine and metoclopramide (5) ..	1·2 ± 0·8	2·5 ± 2·1	3 ± 2·2	4·7 ± 2·7	4·3 ± 2·8	5·3 ± 2·7	..	..	..	..	..
Diamorphine and metoclopramide (5)	0·2 ± 0·07	1 ± 0·6	1·5 ± 0·8	2·5 ± 0·9	3·6 ± 1·3	3·3 ± 0·7	..	..	..	..	..

* Numbers of patients are given in parentheses.

Paracetamol absorption.—In all studies, each patient was given 1·5 g. of paracetamol as 3 'Panadol' tablets with 200 ml. of water after a fast of at least four hours. No food or fluid was allowed for two hours, and all patients remained in bed during the period of observation. Venous blood-samples were taken at intervals and the plasma was separated and stored frozen. Unchanged paracetamol was estimated by gas/liquid chromatography.[10] Paracetamol absorption was assessed by determining the maximum plasma-paracetamol concentration and the time taken to reach this maximum concentration.

Results

Control Studies

Of the 28 women receiving pethidine and diamorphine, maximum plasma-paracetamol concentrations had been reached in 12 before they received their first injection of narcotic analgesic. Therefore, the narcotic could not have influenced the initial paracetamol absorption and these women formed a control group. In these 12 patients, paracetamol absorption, and hence gastric emptying, was not delayed and seemed normal (fig. 1). A mean maximum concentration of $21{\cdot}0 \pm 4{\cdot}7$ μg. per ml. (mean $\pm$ S.E.) was achieved thirty minutes after ingestion.

The 10 women studied post partum comprised an additional control group, although blood-samples were taken for only two hours. Paracetamol absorption was again normal, and the results were similar to those obtained in the first control group (fig. 1). A mean maximum concentration of $19{\cdot}0 \pm 1{\cdot}9$ μg. per ml. was achieved sixty minutes after ingestion.

The mean plasma-paracetamol concentrations in all the groups studied are shown in table I. The intervals between the ingestion of the test dose of paracetamol and delivery and the numbers in each group given oxytocin appear in table II.

Pethidine

8 women were given 150 mg. of pethidine before maximum paracetamol concentrations were attained. In this group, paracetamol absorption was markedly delayed. The mean maximum plasma concentration was only $14{\cdot}0 \pm 3{\cdot}8$ μg. per ml. and was not achieved until four hours after ingestion (fig. 1).

Diamorphine

Paracetamol absorption was also strikingly delayed in all 8 women who received diamorphine before maximum paracetamol concentrations were achieved. The mean maximum plasma-paracetamol concentra-

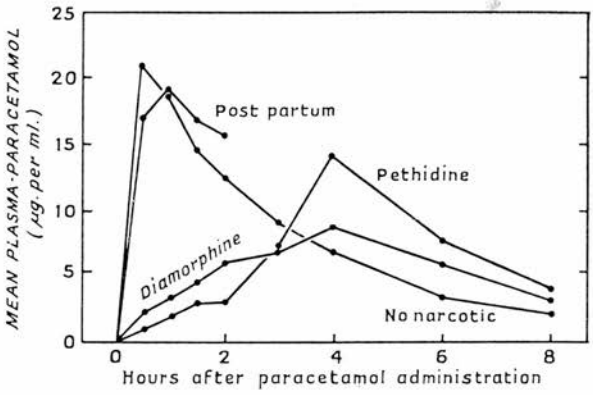

Fig. 1—Effect of pethidine and diamorphine on paracetamol absorption in women during labour.

tion was only $8{\cdot}6 \pm 2{\cdot}1$ μg. per ml. and was not reached until four hours after ingestion (fig. 1).

Both pethidine and diamorphine significantly reduced paracetamol absorption as judged by plasma-paracetamol concentrations up to two hours after ingestion and the time taken to reach maximum levels ($P<0{\cdot}05$). Of the patients given diamorphine and pethidine, six in each group were also given cyclizine. Paracetamol absorption in these patients was the same as in the women receiving diamorphine or pethidine alone.

Pentazocine

After an intramuscular injection of 60 mg. pentazocine and 50 mg. cyclizine, paracetamol absorption was markedly delayed in all 8 women, at least for the ninety minutes during which blood-samples were taken. The mean paracetamol level at ninety minutes was only $2{\cdot}5 \pm 0{\cdot}6$ μg. per ml. and the concentrations were increasing at this time (fig. 2). Concentrations at thirty, sixty, and ninety minutes were significantly lower than those observed in the control group ($P<0{\cdot}01$).

TABLE II—INTERVALS BETWEEN INGESTION OF PARACETAMOL AND DELIVERY AND NUMBER OF PATIENTS IN EACH GROUP RECEIVING OXYTOCIN

Treatment	Paracetamol ingestion-delivery (hr.) interval (mean ± S.E.)	No. given oxytocin
No narcotic	$10{\cdot}6 \pm 1{\cdot}9$	10/12
Pethidine	$2{\cdot}6 \pm 0{\cdot}6$	7/8
Diamorphine	$4{\cdot}2 \pm 0{\cdot}9$	3/8
Pentazocine	$4{\cdot}7 \pm 1{\cdot}1$	1/8
Pethidine and metoclopramide	$1{\cdot}5 \pm 0{\cdot}4$	5/5
Diamorphine and metoclopramide ..	$6{\cdot}7 \pm 1{\cdot}9$	5/5

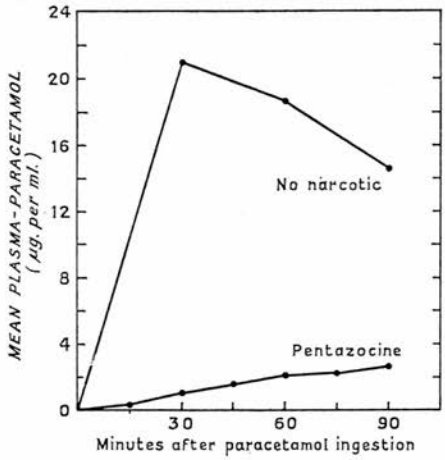

Fig. 2—Inhibitory effect of pentazocine on paracetamol absorption in women during labour.

Metoclopramide

Paracetamol absorption was abnormally slow in all women who received metoclopramide at the same time as pethidine or diamorphine (figs. 3 and 4). The mean plasma concentrations at ninety minutes were only $5{\cdot}3 \pm 2{\cdot}7$ and $3{\cdot}3 \pm 0{\cdot}7$ μg. per ml., respectively, and at this time the concentrations were still rising.

Plasma-paracetamol concentrations at thirty, sixty, and ninety minutes after pethidine and metoclopramide did not differ significantly from those in the women who received pethidine alone or with

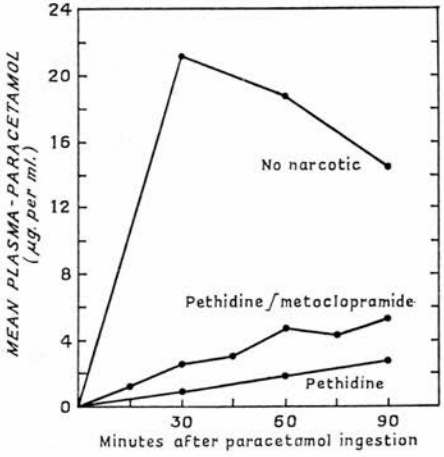

Fig. 3—Effects of pethidine alone and pethidine and metoclopramide on paracetamol absorption in women during labour.

cyclizine ($P>0.05$). Metoclopramide obviously did not significantly enhance the rate of paracetamol absorption in patients given diamorphine. Indeed, if anything, it seemed to make things worse.

Discussion

Paracetamol absorption was normal in 12 women in labour before narcotic administration and in 10 postpartum patients. Absorption was markedly delayed in women receiving pethidine, diamorphine, or pentazocine; and metoclopramide did not increase the rate of absorption of paracetamol after pethidine or diamorphine. There was no relation between delayed paracetamol absorption and the parity of the patients or the administration of cyclizine or oxytocin.

Unfortunately, it was not possible to demonstrate that labour itself had no effect on paracetamol absorption, since the controls were not ideal. The women in labour who had not received a narcotic were studied on average 10.6 ± 1.9 hours before delivery while those receiving pethidine and diamorphine were studied 2.6 ± 0.6 and 4.2 ± 0.9 hours, respectively, before delivery. Therefore the observed delay in paracetamol absorption could either have been due to the pain and distress of labour and approaching delivery or to the administration of the narcotic itself. Morphine is known to decrease gastric motility and it may delay the passage of gastric contents through the duodenum for as long as twelve hours.[11] Thus, the narcotics are

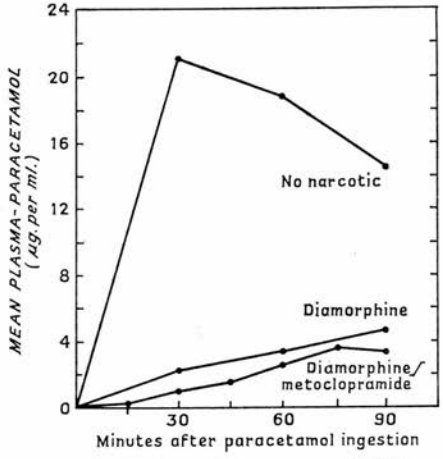

Fig. 4—Failure of metoclopramide to reverse inhibitory effect of diamorphine on absorption of paracetamol in women during labour.

likely to have been responsible for the inhibition of gastric emptying which delayed paracetamol absorption. In addition, we have studied the effects of pethidine and diamorphine on gastric emptying and paracetamol absorption measured at the same time in healthy volunteers and shown that these drugs delay both emptying of the stomach and absorption of orally administered paracetamol.[9]

Workers who demonstrated delayed gastric emptying in labour and the effects of metoclopramide gave no details of the administration of narcotics or of the imminence of delivery in the patients.[2,3] Metoclopramide probably accelerates gastric emptying in patients not given narcotics, but in the present studies it was clearly without significant effect when given at the same time as pethidine or diamorphine.

Delayed gastric emptying is at least partly responsible for maternal death related to anæsthesia, and the number of deaths has not decreased over a period of seventeen years.[1] The use of pethidine, diamorphine, or pentazocine for the relief of pain in labour may well be a major factor. Women who have received these analgesics before coming to anæsthesia will be more likely to vomit or to have increased gastric contents because of delayed gastric emptying, and they are unlikely to be helped by metoclopramide.

We thank the consultant obstetricians of the Simpson Memorial Maternity Pavilion for permission to study their patients, and we gratefully acknowledge the technical assistance provided by Mrs I. Darrien.

Requests for reprints should be addressed to W. S. N.

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Printed in Great Britain

Br. J. clin. Pharmac. (1975), 2, 509-513

INHIBITION OF GASTRIC EMPTYING AND DRUG ABSORPTION BY NARCOTIC ANALGESICS

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1 The effect of intramuscular pethidine or diamorphine on gastric emptying and the absorption of orally administered paracetamol was assessed in eight normal subjects.

2 Both drugs produced a significant and striking delay in gastric emptying and absorption of paracetamol.

3 It seems inevitable that pethidine and diamorphine will retard the absorption of other orally administered drugs.

Introduction

In a previous study of obstetric patients, we observed that the administration of narcotic analgesics to women in labour was associated with a striking reduction in the rate of absorption of orally administered paracetamol (Nimmo. Wilson & Prescott, 1975). Since paracetamol absorption is dependent on gastric emptying (Heading, Nimmo. Prescott & Tothill, 1973) it seemed likely that this delay in paracetamol absorption was due to delayed gastric emptying. However, it was not possible to distinguish between the effects of the narcotics themselves and any delay associated with the increasing distress of labour and approaching delivery which constituted the clinical indication for narcotic administration. Although narcotic analgesics undoubtedly have marked effects on the smooth muscle of the gastrointestinal tract and interfere with normal peristalsis (Daniel, Suther land & Bogoch, 1959, Burks & Long, 1967 Cairnie, Kosterlitz & Taylor, 1961) their effects on gastric emptying in man are not clear. A radiological study has suggested that morphine has a diphasic effect, initially stimulating and then inhibiting gastric emptying of a barium sulphate suspension (Crone & Ardran, 1957).

Interference with the absorption of orally administered drugs is not a recognised consequence of the clinical use of narcotic analgesics. The magnitude of the effect we observed in the obstetric patients seemed sufficient to justify further study and we have now examined the effects of pethidine and diamorphine on gastric emptying and paracetamol absorption in healthy volunteers to define more precisely the effect of narcotic administration on the absorption of an orally administered drug.

Methods

Gastric emptying and paracetamol absorption were measured simultaneously in eight adult male volunteers aged 26 to 39 years. After fasting overnight, each subject drank orange juice (400 ml) containing paracetamol (20 mg/kg) in solution together with ^{113m}In DTPA (300 μCi) as a non-absorbable isotopic marker for the emptying measurement. The drink was consumed within 2 minutes. The gastric emptying rate was determined directly by serial scintiscans of the subject's abdomen and counting the dots in the stomach area (Heading, Tothill, Laidlaw & Shearman, 1971). A quantitation of emptying between the times of ingestion of the drink and performance of the first scan was included (Colmer, Owen & Shields, 1973). After correcting for isotopic decay, the results were expressed as the time taken to empty 50% of the ingested dose from the stomach.

Serial blood samples were taken at intervals for 8 h after ingestion for assessment of paracetamol absorption. The plasma was stored frozen and the concentration of unchanged paracetamol was measured by gas-liquid chromatography (Prescott, 1971). Urine was collected for 24 h and where possible, 2 hourly collections were made for the first 12 hours. The total unchanged and conjugated paracetamol in each sample was estimated by gas-liquid chromatography (Prescott, 1971).

No food, drink or tobacco was permitted for 4 h after ingestion of the solution and the subjects remained supine throughout this period. Each subject was studied on two occasions at least 7 days apart. On one occasion an intramuscular injection of pethidine (150 mg) or diamorphine (10 mg) was given 30 min before the paracetamol

and on the other occasion subjects received a placebo injection of 0.9% w/v NaCl (saline). Four subjects were given pethidine and four received diamorphine. The order of narcotic and placebo administration was determined on a random basis and the subjects were not told beforehand which injection they would receive. However, following the administration of the active drug all subjects developed typical narcotic effects such as lightheadedness and drowsiness and were thus aware of the treatment they had received.

Results

Gastric emptying was rapid in all the control studies following placebo injection. The time for 50% emptying of the ingested solution from the stomach ranged from 4 to 22 min (mean 11.9 min) (Table 1). Paracetamol absorption was correspondingly rapid with a mean peak plasma concentration of 20.0 μg/ml occurring 22 min after ingestion (Table 2).

After pethidine, however, the mean time for 50% emptying of the ingested solution was prolonged to 89.5 min (Table 1). Similarly, the mean peak paracetamol concentration was only 13.8 μg/ml and was delayed until 114 min after ingestion (Table 2). The effects of pethidine on gastric emptying and paracetamol absorption in one subject are shown in Figure 1.

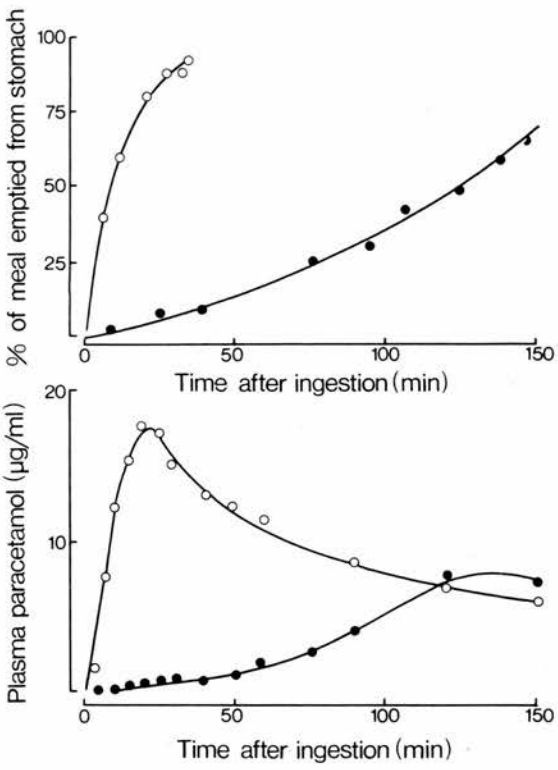

Figure 1 The effect of pethidine (150 mg i.m., •) on gastric emptying and paracetamol absorption compared with saline injection (○) in one volunteer.

Table 1 Effect (mean ± s.e. mean) of pethidine and diamorphine on gastric emptying rate

	Time to 50% gastric emptying of ingested solution (min)	P*
Control (n = 8)	11.9 ± 2.5	–
Pethidine (n = 4)	89.5 ± 24	<0.01
Diamorphine (n = 4)	>130	<0.01

* Pethidine and diamorphine compared with control (Mann Whitney U test).

Diamorphine completely inhibited gastric emptying for more than 90 min in three of four subjects and none achieved 50% emptying in two hours (Table 1). The mean peak plasma paracetamol concentration was only 5.2 μg/ml and was not reached until 142 min after ingestion. An example of the marked inhibitory effects of diamorphine on gastric emptying and paracetamol absorption in one subject is shown in Figure 2.

The mean paracetamol absorption curves are shown in Figure 3. Clearly the inhibition of

Table 2 Effect (mean ± s.e. mean) of pethidine and diamorphine on paracetamol absorption

Group	*Peak plasma paracetamol concentration (µg/ml)*	P*	*Time of peak (min)*	P*
Control (n = 8)	20.0 ± 1.8	–	22 ± 3.1	–
Pethidine (n = 4)	13.8 ± 3.9	<0.05	114 ± 36	<0.05
Diamorphine (n = 4)	5.2 ± 1.5	<0.01	142 ± 72	<0.01

* Paired t tests with controls.

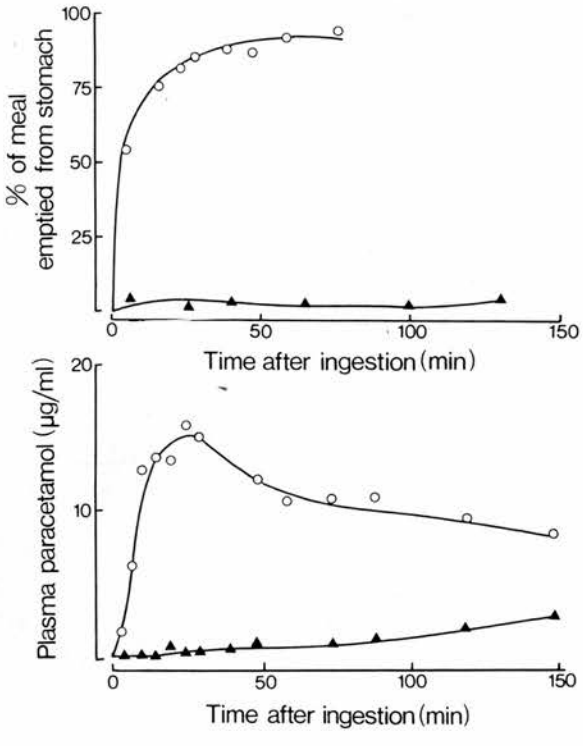

Figure 2 The effect of diamorphine (10 mg i.m., ▲) on gastric emptying and paracetamol absorption compared with saline injection (○) in one volunteer.

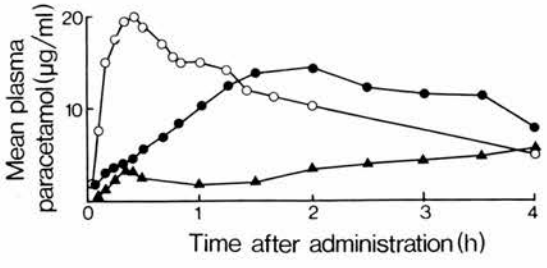

Figure 3 The absorption of paracetamol in eight healthy volunteers following i.m. pethidine (150 mg, ●), diamorphine (10 mg, ▲) or saline (○) as a control. Four volunteers received pethidine and four received diamorphine.

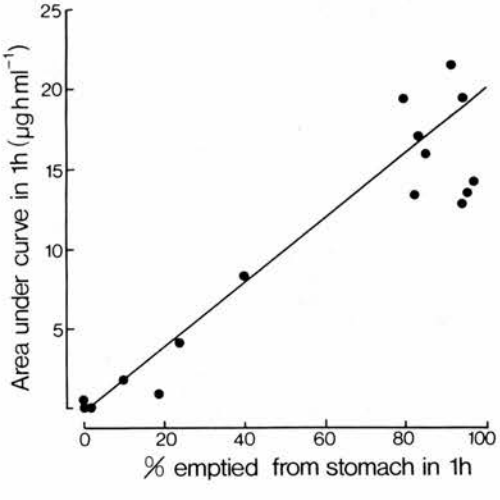

Figure 4 The area under the plasma concentration-time curve at 1 h plotted against % of the ingested solution emptied from the stomach at 1 h in each subject, $r = 0.94$.

absorption was greater and more prolonged with diamorphine than with pethidine, in accord with the gastric emptying measurements. The effects of both narcotic drugs on gastric emptying and paracetamol absorption were statistically significant (Tables 1 and 2).

It was not possible to obtain 2 hourly urine collections on all subjects after the narcotic injection. This was presumably due to the fact that narcotics themselves have an antidiuretic effect as well as inducing delay in absorption of the ingested solution. However, the recovery of paracetamol from urine at 4 h was reduced following narcotic administration. The mean percentage of the ingested dose recovered in 4 h was 37.1% in the controls, 24.9% after pethidine and 13.1% after diamorphine. The total amount of paracetamol appearing in the urine in 24 h was not affected by narcotic administration. The mean recovery was 77.2% of the administered dose in the controls and 75.3% after the narcotics.

The area under the plasma concentration-time curve at 1 h was plotted against the percentage of the ingested solution emptied from the stomach at one hour for each subject. A highly significant correlation was obtained ($r = 0.94$, Figure 4).

Discussion

These results clearly demonstrate that pethidine and diamorphine induced a marked inhibition of gastric emptying and greatly retarded the absorption of orally administered paracetamol. The effect of diamorphine was particularly striking with complete inhibition of gastric emptying in three of the four subjects for more than 1.5 hours. Both drugs had a much greater inhibitory effect

than propantheline (30 mg) given intramuscularly (Nimmo, Heading, Tothill & Prescott, 1973). The data imply that the slow absorption of paracetamol previously observed in women in labour (Nimmo *et al.*, 1975) can almost certainly be attributed entirely to delayed gastric emptying produced by administration of narcotic analgesics. In previous reports describing delayed gastric emptying in women during labour, the role of narcotics has not been considered (Davison, Davison & Hay, 1970; Howard & Sharp, 1973).

The present findings have wide therapeutic implications. There is an increasing awareness of the role of gastric emptying rate in influencing the absorption of orally administered drugs (Heading *et al.*, 1973; Nimmo *et al.*, 1973; Finch, Kendall & Mitchard, 1974; Volans, 1974; Ahmad, 1974). Many drugs which are given by mouth are probably not absorbed to any significant extent by the stomach and it seems inevitable that their absorption, like that of paracetamol, will be greatly retarded by administration of narcotic analgesics. This effect may be of great importance when rapid absorption of an orally administered drug is desired. For example, morphine prevents adequate absorption of an orally administered anti-arrhythmic drug in patients who have suffered myocardial infarction (Pottage & Prescott, unpublished observations). This action of narcotics appears to be shared by analogues such as pentazocine and is not reversible with metoclopramide (Nimmo *et al.*, 1975). The present findings relate only to the period beginning 30 min after administration of the narcotic and may correspond to the later inhibitory phase of morphine's action on gastric motility observed by Crone & Ardran (1957).

In this study in which gastric emptying and paracetamol absorption were measured simultaneously, the correlation coefficient between emptying and absorption at 1 h was 0.94. This is a convincing demonstration of the dependence of drug absorption on stomach emptying. In none of the previous studies relating drug absorption and gastric emptying (Heading *et al.*, 1973; Nimmo *et al.*, 1973; Finch *et al.*, 1974) has such a relationship been established on the basis of simultaneous measurements.

Although paracetamol absorption was delayed by administration of the narcotic, the urinary recovery over a period of 24 h was not reduced. In consequence, the administration of multiple oral doses of a drug to a patient who has also been given a narcotic analgesic may present a risk of abnormally high plasma concentrations of the drug when the effect of the narcotic on gastric emptying wears off.

Narcotic analgesics are widely used in all branches of medical practice. Because of their major inhibitory effect on gastric emptying they are likely to influence the absorption of most if not all orally administered drugs. This may represent one of the most important clinical drug absorption interactions.

We gratefully acknowledge technical assistance provided by Mr I. King, Mrs J. Maguire and Miss W. Fleming. This study was supported in part by grants from the Scottish Home and Health Department.

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(Received March 13, 1975)

Reprinted from the

British
Journal of Anaesthesia

GASTRIC EMPTYING FOLLOWING HYSTERECTOMY WITH EXTRADURAL ANALGESIA

W. S. NIMMO, D. G. LITTLEWOOD, D. B. SCOTT AND L. F. PRESCOTT

Br. J. Anaesth. (1978), **50**, 559

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W. S. NIMMO, D. G. LITTLEWOOD, D. B. SCOTT AND L. F. PRESCOTT

SUMMARY

Using the rate of absorption of paracetamol following oral administration of the drug, gastric emptying was measured in 21 patients following hysterectomy. Gastric emptying was inhibited markedly in patients receiving narcotic analgesia after operation, but only a moderate delay was observed in patients undergoing extradural analgesia.

In the first few days after abdominal surgery, gastrointestinal motility is commonly decreased and this is accompanied by anorexia, nausea, vomiting, diminished bowel sounds and, occasionally, paralytic ileus. Conventional analgesia with narcotic analgesic agents may contribute to this state since these drugs constrict smooth muscle, delay gastrointestinal transit and inhibit gastric emptying (Jaffe, 1970; Nimmo, Wilson and Prescott, 1975; Nimmo et al., 1975). Extradural analgesia (by means of an indwelling catheter introduced before operation) is an increasingly popular alternative to narcotic analgesia but little is known of its effect on gastrointestinal motility. In the present study, gastric emptying was measured in patients receiving narcotic analgesics or extradural analgesia following hysterectomy through a lower abdominal incision.

Gastric emptying rate was assessed by the rate of absorption of paracetamol following oral administration of the drug. Paracetamol is not absorbed from the stomach but is absorbed very rapidly from the upper small intestine and thus the rate of paracetamol absorption is an indirect measure of the rate of gastric emptying (Heading et al., 1973; Nimmo et al., 1973; Nimmo, Wilson and Prescott, 1975; Nimmo et al., 1975). Rapid absorption is associated with rapid emptying while delayed absorption reflects delayed emptying of the stomach.

PATIENTS AND METHODS

Twenty-one patients undergoing abdominal hysterectomy gave informed consent for the study (table I). None had clinical evidence of gastrointestinal, hepatic, cardiac or renal disease and none received any other medication during the study. After premedication with diamorphine 5 mg i.m., anaesthesia was induced in all patients with thiopentone 500 mg. For maintenance of anaesthesia, 14 patients received extradural analgesia at the level of L3/4 with 2% lignocaine 15–20 ml in combination with general anaesthesia maintained by nitrous oxide, oxygen and halothane (Scott, 1975); after operation the extradural cannula was left *in situ*. In a further seven patients, anaesthesia was maintained with halothane and nitrous oxide in oxygen and the lungs were ventilated with intermittent positive pressure ventilation following the injection of tubocurarine.

After operation, six of the 14 patients with an extradural cannulae *in situ* received extradural analgesia alone with 8–10 ml of bupivacine 0.5% as required. The other eight patients had the same mode of extradural analgesia by day (when medical staff were available to perform the injection) and diamorphine 5 mg i.m. 6-hourly at night. None of this group had been given diamorphine for at least 6 h before the study. The seven patients who did not receive extradural analgesia during surgery received only diamorphine 5 mg i.m. 6-hourly, and the last administration of diamorphine ranged from 1.5 to 4 h before the study (mean $\pm$ SD, 3.1 ± 1 h).

Each patient was studied on two occasions—once on the day after operation and again 1 week later, so that each patient served as her own control. After a fast of at least 4 h, each patient was given paracetamol 1.5 g (three "Panadol" tablets) with 200 ml of water. The patients remained at rest in bed and no food, fluid or tobacco was allowed throughout the study. Venous blood samples were taken at intervals for 120 min and the plasma was separated and stored frozen. Plasma paracetamol concentrations were measured by gas–liquid chromatography (Prescott, 1971).

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0007-0912/78/0050-0559 $01.00

TABLE I. *Details of the three groups of patients in the study*

Group	Mean age (yr ± SD)	Mean weight (kg ± SD)	Anaesthesia	Analgesia after operation
Extradural ($n = 6$)	48.7 ± 12.4	65.0 ± 10.8	Thiopentone, nitrous oxide, oxygen, halothane; lumbar extradural	Extradural analgesia only
Diamorphine ($n = 7$)	36.4 ± 13.8	61.7 ± 13.7	Thiopentone, tubocurarine, nitrous oxide, oxygen, halothane; IPPV	Diamorphine 5 mg i.m. 6-hourly
Combined extradural + diamorphine ($n = 8$)	46.1 ± 7.6	52.4 ± 7.3	Thiopentone, nitrous oxide, oxygen, halothane; lumbar extradural	Extradural analgesia by day, diamorphine by night

Statistical analyses were performed using the Student's *t* test.

RESULTS

Control measurements

One week after hysterectomy, the absorption of paracetamol was rapid in all patients. The mean peak plasma concentration, 25.8 ± 10.0 (SD) μg ml^{-1}, occurred 45 min after ingestion (fig. 1). Gastric emptying was presumably normal in these patients, since paracetamol absorption was almost identical to that observed in healthy volunteers (Heading et al., 1973; Nimmo et al., 1973; Nimmo et al., 1975).

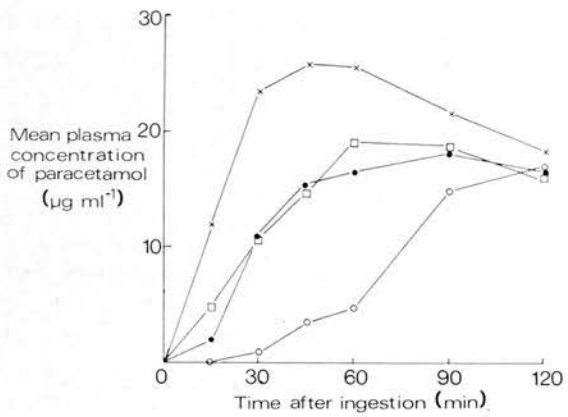

FIG. 1. Mean plasma paracetamol concentrations following an oral dose of 1.5 g in patients after hysterectomy. ×——× = 1 week after operation ($n = 21$); ○——○ = narcotic analgesia 1 day after operation ($n = 8$); □——□ = extradural analgesia 1 day after operation ($n = 6$); ●——● = combined extradural and narcotic analgesia 1 day after operation ($n = 7$).

Narcotic analgesia

There was a striking inhibition of paracetamol absorption and gastric emptying in patients who received diamorphine i.m. for analgesia after operation. The mean plasma paracetamol concentration at 45 min was only 3.5 ± 4.0 μg ml^{-1} and plasma concentrations were still increasing at 90 min after ingestion (fig. 1). The concentrations at 30, 45 and 60 min were significantly less than those in the control study ($P < 0.01$).

Extradural analgesia

In the patients who received extradural analgesia alone, there was a moderate delay in the rate of paracetamol absorption and thus gastric emptying (fig. 1). The mean peak plasma paracetamol concentration of 19.2 ± 9.0 μg ml^{-1} occurred 60 min after ingestion. Only the values at 15 min were significantly less than those in the control study ($P < 0.05$). The concentrations at 30, 45 and 60 min were greater than those in the narcotic study ($P < 0.05$).

Combined extradural and narcotic analgesia

Paracetamol absorption and therefore gastric emptying in these patients, who had not received a narcotic for 6 h, was almost identical to that in the patients receiving extradural analgesia alone. A peak concentration of 18.3 ± 11.8 μg ml^{-1} occurred 90 min after ingestion (fig. 1). Only the values at 15 min were significantly smaller than those in the control study ($P < 0.05$). The plasma concentrations at 30, 45 and 60 min were greater than those in patients who had received diamorphine within the previous 6 h.

The areas under the plasma concentration curves at 45 and 120 min are shown in table II.

DISCUSSION

The administration of diamorphine to patients after hysterectomy was associated with a striking delay in the absorption of paracetamol which was presumably a result of inhibition of gastric emptying. This is not surprising, since diamorphine 10 mg may produce

TABLE II. *Areas under the plasma concentration–time curves* (± *SD*)

Group	0–45 min	*P**	0–120 min	*P**
Control	11.7 ± 6.6		39.4 ± 12.0	
Extradural	5.7 ± 5.4	< 0.05	28.3 ± 8.0	n.s.
Diamorphine	0.6 ± 0.8	< 0.01	13.3 ± 10.5	< 0.005
Combined extradural and narcotic	4.6 ± 5.1	< 0.05	26.0 ± 17.0	< 0.05

* Extradural, diamorphine and combined groups compared with controls.

total inhibition of gastric emptying for at least 2 h in healthy volunteers (Nimmo et al., 1975). Other narcotic analgesic agents, including morphine, pethidine and pentazocine, have been shown also to delay gastric emptying and drug absorption. In patients undergoing extradural analgesia alone, there was only moderate delay in gastric emptying 1 day after hysterectomy. Thus these patients may be less likely to experience nausea or vomiting and it may be possible to commence oral feeding and medication sooner than is possible for those given conventional narcotic analgesia. Similar results have been obtained in patients having extradural analgesia during labour (Nimmo, Wilson and Prescott, 1977).

In those patients who received extradural analgesia by day and diamorphine by night, gastric emptying was very similar to that in patients who received extradural analgesia alone when no narcotic had been given for 6 h.

Extradural analgesia after operation as an alternative to narcotic analgesia is gaining popularity because it is more effective and free from central effects, particularly respiratory depression. The lack of important effects on gastric emptying is another advantage.

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VIDAGE GASTRIQUE APRES HYSTERECTOMIE EFFECTUEE SOUS ANALGESIE EXTRADURALE

RESUME

On a mesuré le vidage gastrique de 21 malades ayant subi une hystérectomie en se basant sur le taux d'absorption du paracétamol après administration orale de ce médicament. Le vidage gastrique a été nettement modéré sur les malades qui avaient été soumis à une analgésie par un narcotique après l'opération, mais on n'a observé qu'un léger retard chez les malades ayant été soumis à une analgésie extradurale.

MAGENENTLEERUNG NACH HYSTEREKTOMIE BEI EXTRADURALER ANALGESIE

ZUSAMMENFASSUNG

Unter Verwendung der Absorbierungsrate von Paracetamol nach oraler Verabreichung wurde die Magenentleerung bei 21 Patientinnen nach Hysterektomie gemessen. Die Magenentleerung wurde deutlich behindert bei den Patientinnen, die nach der Operation ein narkotisches Schmerzlinderungsmittel erhielten, während in Fällen von extraduraler Analgesie nur geringfügige Verzögerungen beobachtet wurden.

VACIAMIENTO GASTRICO SIGUIENDO HISTERECTOMIA CON ANALGESIA EXTRADURAL

SUMARIO

Aprovechando la rapidez de absorción del paracetamol siguiendo la administración oral de la droga, se midió el vaciamiento gástrico en 21 pacientes después de su histerectomía. El vaciamiento gástrico fue notablemente inhibido en aquellos pacientes que recibieron analgesia narcótica después de la operación, pero sólo se observó una demora moderada en los pacientes sometidos a analgesia extradural.

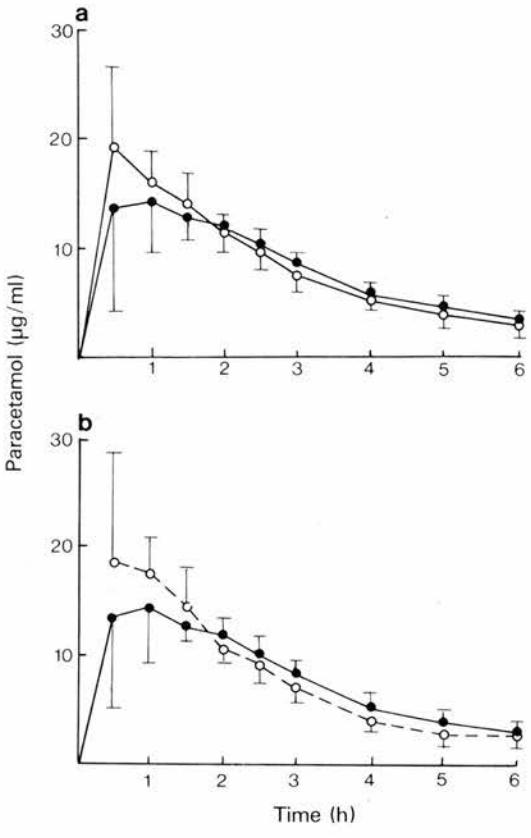

Figure 1 Mean plasma paracetamol levels (±s.d.) in six normal volunteers when 1.5 g of paracetamol was ingested 30 min after prior ingestion of (a) 15 mg codeine phosphate (○) and (b) 30 mg codeine phosphate (○---○). For ease of illustration the active treatments are compared separately with the placebo treatment (●).

their colleagues (PB), under supervision, as part of the course of study and was approved by the Guy's Hospital Ethical Committee.

Codeine was given as 15 mg tablets of codeine phosphate BP or matching placebo together with 75 ml water. Paracetamol was given as a single dose of 1000 mg (2 tablets of Panadol, Winthrop).

Each subject was tested on three days separated by an interval of at least 1 week. The subjects fasted from midnight on the day before the test. At approximately 09 h 30 min codeine phosphate or placebo was administered as two tablets to provide 0, 15 or 30 mg of codeine according to a double-blind, randomized, latin square design. Thirty minutes after the ingestion of codeine the subjects took the paracetamol together with a further 75 ml of water. The codeine was administered 30 min in advance of the paracetamol in a belief that this might increase any delay in paracetamol absorption relative to that which might occur if the drugs were administered simultaneously. Blood was collected into heparinized tubes via an indwelling venous catheter at timed intervals up to 6.5 h after ingestion of the codeine. Throughout this time the subjects carried out simple investigations into the analgesic and sedative effects of the drugs. A standard lunch with decaffeinated coffee was taken after 3.5 h.

Plasma paracetamol levels were estimated by gas-liquid chromatography using the method of Prescott (1971).

The mean plasma paracetamol levels (±s.d.) are shown in Figure 1. It can be seen that oral codeine (15 or 30 mg) taken 30 min before the paracetamol had no influence upon the rate or extent of absorption of the latter drug. This was confirmed by analysis of variance.

From the pronounced effects of the stronger narcotic analgesics upon the absorption of paracetamol (Nimmo *et al.*, 1975; Nimmo, Heading *et al.*, 1975) and from the time-honoured use of codeine to treat diarrhoea it might have been predicted that codeine would have also delayed paracetamol absorption. However, this experiment has failed to demonstrate any inhibition of paracetamol absorption using doses of up to 30 mg of codeine under conditions where paracetamol absorption would otherwise be expected to be maximal (McGilveray & Mattock, 1972).

There are currently at least seventeen compound analgesic preparations containing codeine and thirteen preparations containing codeine and paracetamol (MIMS, 1977). When taken in the recommended therapeutic dose these formulations would yield a dose of 10 to 20 mg codeine, an amount which we conclude to be unlikely to impair the absorption of the paracetamol or other drugs. Further investigation would be needed before this conclusion could be extended to include drug absorption after the larger single doses of codeine which may be used in the treatment of diarrhoea and after repeated dosage with codeine-containing compound preparations.

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Received November 15, 1977

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THE INFLUENCE OF POSTURE ON PARACETAMOL ABSORPTION

The rate of gastric emptying probably determines the rate of absorption of most orally administered drugs and it follows that factors influencing gastric emptying rate will in turn influence the rate of drug absorption (Prescott, 1974; Nimmo, 1976; Nimmo, Heading, Wilson, Tothill & Prescott, 1975). In neonates, the stomach empties more rapidly in the prone and right lateral positions than in the supine and left lateral positions (Yu, 1975), but there is little data in man relating gastric emptying or drug absorption with posture. The rate of paracetamol absorption correlates well with gastric emptying rate, and in the present report we describe the effect of posture on the rate of paracetamol absorption.

Eight healthy volunteers with a mean ± s.d. age of 29 ± 1.8 years and a mean ± s.d. weight of 68.8 ± 8.2 kg were studied twice. On one occasion the subjects were ambulant throughout the study and on the other they lay on the left side for 2 h and were then ambulant. On both occasions, after an overnight fast, each subject was given 1.5 g paracetamol as three Panadol tablets with 200 ml water. Blood samples were taken at intervals for 4 h for paracetamol measurements (Prescott, 1971). No food, fluid or tobacco was allowed during the study. Statistical analyses were carried out using the paired Student's *t*-test.

Paracetamol absorption was significantly delayed in all subjects lying on the left side (Figure 1). Plasma concentrations (mean ± s.e. mean) at 15 min and 30 min in the supine subjects were only 0.18 ± 0.18 μg/ml and 7.8 ± 3.1 μg/ml respectively and 12.5 ± 4.8 μg/ml and 20.8 ± 3.3 μg/ml in the ambulant subjects ($P < 0.05$ and < 0.01 respectively). Plasma concentrations after 45 min did not differ in the two groups.

The total amount of paracetamol absorbed in 4 h was not influenced by posture since the mean area under the plasma concentration time curve (0–4 h) was 49.5 ± 4.3 μg ml^{-1} h in the ambulant study and 45.5 ± 2.8 μg ml^{-1} h in the supine study.

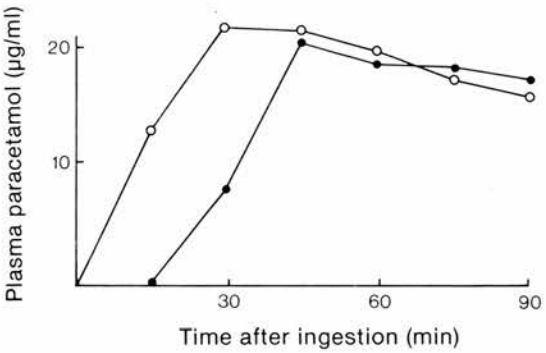

Figure 1 Mean plasma paracetamol concentrations after 1.5 g orally in ambulant (○) and supine (●) subjects ($n = 8$).

The delay in paracetamol absorption observed in subjects lying on the left side was probably due to slower gastric emptying in that position. Martin (1971) commented on a similar delay in the absorption of aspirin solution in five subjects in the 'left supine position' and also attributed this to delayed gastric emptying. Unfortunately no plasma concentration data was given. Patients who take tablets while in bed on their left side will be likely to have delayed absorption and it is obvious that the position of subjects must be taken into account in drug absorption studies.

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Received October 31, 1977

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PHYSICAL EXERCISE AND DISPOSITION OF DIAZEPAM

Diazepam, a widely used tranquilizer, exhibits strong binding to plasma and tissues. Its hepatic elimination is relatively slow (low hepatic extraction ratio) and independent of the liver blood flow (Klotz, Antonin & Bieck, 1976). With antipyrine, the non protein-bound model drug for hepatic elimination, significant differences in the volumes of distribution have been reported, if the subjects were exposed to heat and/or physical stress (Swartz, Sidell & Cucinell, 1974). In subjects performing physical exercise for 2 h an increase in V_d with a reciprocal fall in k_{el} resulting in an unchanged clearance rate was found with amylobarbitone (Balasubramanian, Mawer & Simons, 1970). We used diazepam as a kind of prototype for a drug with blood-flow independent elimination and extensive binding, to compare in healthy subjects the pharmacokinetics of this drug during rest and after maximal short-term stress. The blood perfusion of the different organs and tissues can change under these two experimental conditions. Consequently, the plasma level-time profile and the disposition of the drug might be altered by distribution changes or re-mobilization from a storage site.

Four healthy volunteers (25–30 years, 53–72 kg) received a single intravenous bolus of 0.1 mg diazepam/kg. Maximal exercise was performed in the sitting position on a computerized bicycle (dynavit®, meditronic) which calculated according to the age, weight and sex of the individuals the corresponding maximal heart rates. The work-load was progressively and automatically adjusted to maintain the continuously monitored heart rate for 5 min in this maximal range. Immediately before and after this physical stress venous blood samples were drawn into heparinized tubes from an indwelling catheter, or by venepuncture at 0.5, 1, 2, 4, 7, 10, 24, 36, 48, 60 and 72 h after administration. Subjects remained in the supine position for the first 10 h, except at the time of the test. Concentrations of diazepam were assayed in the different plasma samples by a specific and sensitive gaschromatographic procedure (Klotz, Avant, Hoyumpa, Schenker & Wilkinson, 1975). The plasma level-time curves were fitted according to a two compartment open model by the least squares iterative digital computer program SAAM-25 (Berman & Weis, 1974). This model and its pharmacokinetic parameter have been well described (Riegelman, Loo & Rowland, 1968). The biexponential decline of the plasma levels of diazepam after the single intravenous dose of 0.1 mg/kg in two representative individuals can be seen in Figure 1. The computer fitted curves, derived from the plasma concentrations measured just before and after the physical exercise, did not demonstrate statistically significant differences. The most important pharmacokinetic parameters calculated were also almost identical under the two experimental conditions (Table 1).

The motion of a patient taking diazepam can range from bed rest and moderate work to physical exercise. These different situations might alter the clinical response of the drug simply by changes in its distribution or elimination. After physical stress, changes in cardiac output can be observed. This can influence a drug's disposition via changes in an organ's or tissue's blood perfusion (Wilkinson, 1975). Hepatic elimination can be modified by changes in hepatic blood flow (Rowland, Benet & Graham, 1973) and during exercise this flow decreases. Since diazepam belongs to the group of drugs whose elimination is independent of the liver blood flow (Klotz *et al.*, 1975), it is not surprising that its total body clearance (Cl) and its half-life of elimination ($T_{\frac{1}{2}}\beta$) were unaffected by physical exercise. In addition, at the different times of blood sampling no significant increases or decreases in the plasma levels

Table 1 Pharmacokinetic parameters (mean ± s.d.) of diazepam as calculated from blood samples drawn before and after physical stress

Parameter	*Before exercise*	*After exercise*
$T_{\frac{1}{2}}\alpha$(h)	1.3 ± 0.3	1.1 ± 0.7
$T_{\frac{1}{2}}\beta$(h)	35.3 ± 3.0	29.8 ± 9.2
Cl(ml/min)	21.7 ± 2.9	26.3 ± 4.8
V_d (l/kg)	0.96 ± 0.10	0.98 ± 0.24
$V_d\beta$ (l/kg)	1.02 ± 0.13	1.10 ± 0.28
V_1 (l/kg)	0.36 ± 0.06	0.45 ± 0.06

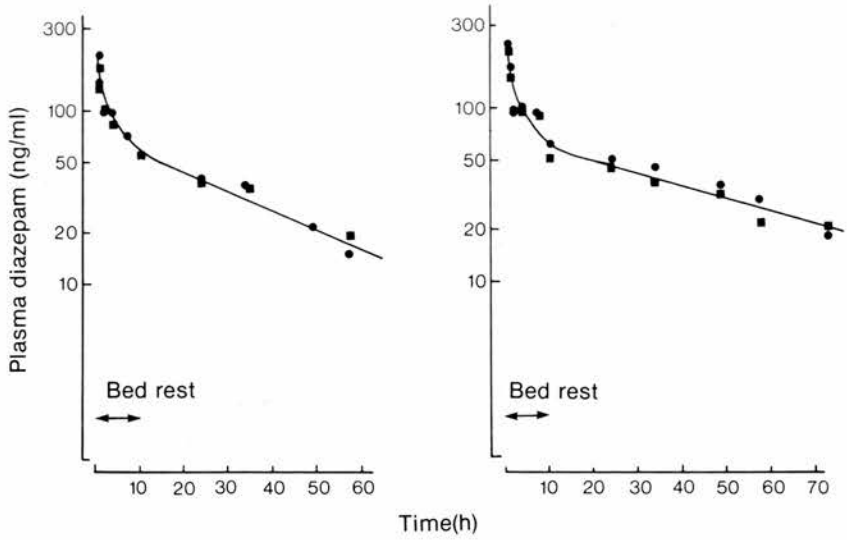

Figure 1 Plasma concentration-time profile of diazepam after intravenous injection of diazepam (0.1 mg/kg) in two healthy volunteers. Blood samples were drawn before (●) and after (■) physical exercise.

could be observed after a maximal work-load lasting for 5 min. This indicates that under our experimental conditions no change in the distribution has occurred. This can also be postulated from the unchanged volumes of distribution (V_1, V_d, $V_d\beta$). The minor changes in haematocrit, plasma volumes and plasma protein which were reported after different types of exercise (Novosadova, 1977) are probably not sufficient to modify the disposition of this liquid soluble and highly protein bound drug.

The results of this study would indicate that the pharmacokinetics of a single dose of diazepam is independent of the degree of motion of the patient since we could not demonstrate a difference between the opposite points of this range, bed rest and physical exercise.

This study was supported by the Robert Bosch Foundation, Stuttgart/W. Germany. We are grateful for the excellent technical assistance of Mrs E. Golbs.

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Received November 28, 1977

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KINETICS OF ACETAMINOPHEN ABSORPTION AND GASTRIC EMPTYING IN MAN

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Reprinted from
CLINICAL PHARMACOLOGY AND THERAPEUTICS
St. Louis

Vol. 24, No. 4, pp. 420-431, October, 1978

Kinetics of acetaminophen absorption and gastric emptying in man

Eight healthy male volunteers ingested an aqueous solution containing acetaminophen (20 mg/kg) and a nonabsorbable isotopic marker. The concentrations of unconjugated acetaminophen in samples of blood plasma taken at frequent intervals were measured by gas-liquid chromatography. The data points followed a smooth curve in most cases and were fitted to the classical two-compartment pharmacokinetic model to obtain K_A, the apparent first-order rate constant for absorption from the gastrointestinal tract. Gastric emptying was measured simultaneously from serial scintiscans of the subject's abdomen. The subjects were also studied after intramuscular injection of meperidine (150 mg) and pentazocine (60 mg) with and without naloxone (1.2 mg). The acetaminophen absorption curves and gastric emptying patterns were consistent with negligible absorption from the stomach. A new model is proposed in which the conventional single compartment used to represent the gastrointestinal tract is replaced by two compartments: one represents the stomach and the other the small intestine, from which absorption occurs rapidly. Pharmacokinetic analysis using this model showed good agreement in all cases, and provided an estimate of K_A^*, the first-order rate constant for drug transfer from the intestinal lumen into the systemic circulation. The mean half-time for transfer was 6.8 ± 0.9 min. As expected, K_A^* was greater than K_G (the first-order rate constant for gastric emptying), showing that gastric emptying was rate-limiting in the absorption of acetaminophen. The value of K_A^* was greater than K_A and the two were not related. The value of K_A was not equal to K_G in most studies because gastric emptying was not a single exponential process.

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Most drugs are believed to be absorbed from the alimentary tract by passive diffusion, and on theoretical grounds absorption from a solution should occur in accordance with a first-order process. When a drug is administered as a solid dosage-form deaggregation and particle dissolution precede absorption,[16] and absorption may not be a monoexponential process. If a drug is administered in aqueous solution (assuming that pH changes do not cause precipitation), it should be immediately available for absorption, but absorption of most drugs from the stomach is much slower than from the small intestine.[5, 7, 9, 13] Consequently, the rate at which a drug is transferred from the stomach to the duodenum is an important determinant of the

Received for publication Feb. 27, 1978.
Accepted for publication June 3, 1978.
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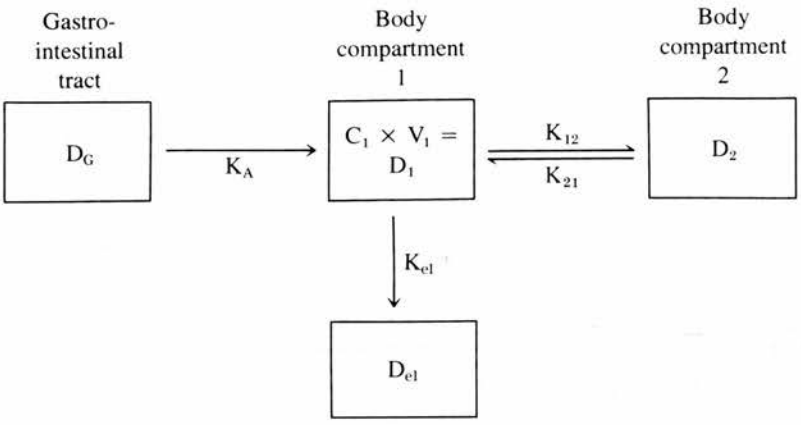


Schema 1. Two-compartment open model for oral administration.

overall absorption rate. We have previously shown that the area under the plasma concentration–time curve is proportional to the percentage of an orally administered solution of acetaminophen emptied from the stomach of normal subjects during the first hour.[9]

In pharmacokinetic analysis of plasma drug concentration–time data, a first-order rate constant (K_A) is often calculated for absorption from the gastrointestinal tract.[3] This constant is necessarily a hybrid, dependent upon the rates of all contributing processes but governed primarily by the slowest or rate-limiting step.

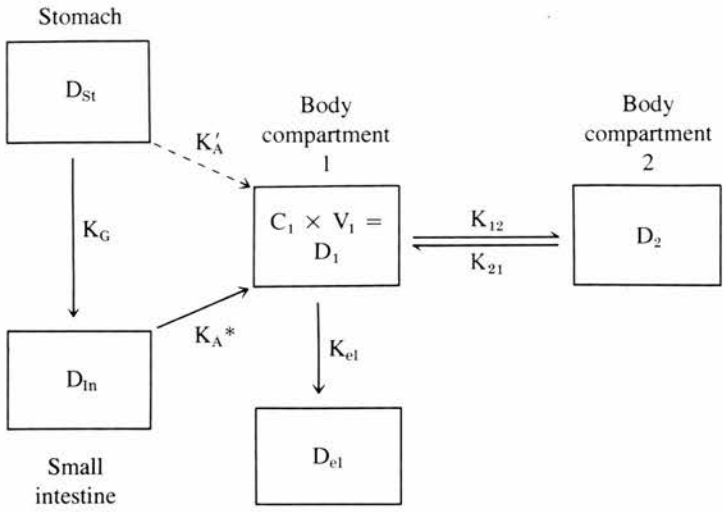
The hypothesis that gastric emptying rather than transmucosal transfer from the lumen of the small intestine is rate-limiting for rapidly absorbed drugs has apparently not been tested by the appropriate pharmacokinetic analysis. In this paper we describe a new pharmacokinetic model with four compartments, namely, two body compartments and one each for the stomach and the site of most rapid absorption in the small intestine. The model was tested by studying the absorption of orally administered acetaminophen in aqueous solution, with simultaneous radioisotopic measurement of gastric emptying in healthy volunteers, and was found to be entirely consistent with the experimental data.

Methods

Gastric emptying. Gastric emptying and acetaminophen absorption were measured simultaneously in eight adult male volunteers aged 26 to 39. After fasting overnight, within 2 min each subject drank orange juice (400 ml) containing acetaminophen (20 mg/kg) in solution together with ^{113m}In DTPA* (300 μCi) as a nonabsorbable isotopic marker for the emptying measurements. Gastric emptying rate was determined directly by serial scintiscans of the subject's abdomen and summing the counts over the stomach area.[4] The measurement of emptying between the time of ingestion of the drink and performance of the first scan was made by the method of Colmer, Owen, and Shields.[2] All results were corrected for isotopic decay, and the first-order rate constants for gastric emptying were determined by regression analysis.

Acetaminophen absorption. Serial blood samples were taken at frequent intervals for 8 hr after ingestion for assessment of absorption. The plasma was stored frozen and the concentration of unchanged acetaminophen was measured by gas-liquid chromatography.[12] No food, drink, or tobacco was permitted for 4 hr after acetaminophen, and the subjects remained supine throughout this period. Initially each subject was studied on two occasions at least 7 days apart. On one occasion an intramuscular injection of meperidine (150 mg) was given 30 min before the acetaminophen solution, and on the other occasion subjects received placebo injection of 0.9% saline. The order of narcotic

*Chelate of indium-113m with diethyltriaminepenta-acetic acid.



Schema 2. Proposed model with two body compartments and separate compartments representing the stomach and the small intestine.

and placebo administration was determined on a random basis. Four of the 8 subjects were studied on two further occasions: (1) 30 min after intramuscular pentazocine (60 mg) and (2) 30 min after intramuscular pentazocine (60 mg) and immediately after intravenous naloxone (1.2 mg).

Pharmacokinetic models. Two different compartmental models were used for the analysis of the plasma concentration of unconjugated acetaminophen at various times after ingestion.

Schema 1 shows a conventional compartmental model with one compartment representing the gastrointestinal tract and two compartments representing the body. The apparent absorption rate constant (K_A) is the assumed first-order rate constant for the transfer of drug from the gastrointestinal into the central body compartment (compartment 1), K_{12} and K_{21} are the rate constants for transfer into and out of the second body compartment (compartment 2), respectively, and K_{el} is the elimination rate constant from the central compartment. D_G, D_1, D_2, and D_{el} are the quantities in the gastrointestinal tract, compartment 1, compartment 2, and the quantity of eliminated drug, respectively.

Schema 2 shows a similar model but with the gastrointestinal tract represented by two compartments to correspond to the stomach and the small intestine. The constant K_G is the first-order rate constant for gastric emptying and K_A^* is the rate constant for transfer of drug from the small intestine into the systemic circulation. K_A' is the rate constant for absorption from the stomach. It was assumed to very small for acetaminophen and was neglected subsequently. D_{St}, D_{In}, D_1, D_2, and D_{el} are the quantities in the stomach, small intestine, body compartment 1, body compartment 2, and the quantity of eliminated drug, respectively.

Computer analysis. Analog computer programs were constructed for these two models and the line of best fit to the data points was drawn by eye using an X-Y recorder. In the model shown in Schema 2 the value of K_G found from measurements of gastric emptying was used as a constant in the computer program. The results of gastric emptying measurements showed that in many studies monoexponential emptying was preceded by a short period during which a proportion of the dose passed rapidly through the pylorus as a bolus or "squirt." The computer program was modified to accommodate this and other types of gastric emptying pattern observed in the study (see the section on results).

The equation for C_1, the concentration of drug in the central compartment for the model of Schema 1, was that given in standard texts.[16]

The equation for C_1 for the model in Schema 2 was found using Laplace transforms and the antitransform obtained by established methods.[1]

$$C_1 = \frac{F \cdot D_0 \cdot K_A^*}{V_1}\left[\frac{f_2K_G(K_{21} - K_G) \cdot e^{-K_G(t-t_{LAG})}}{(K_A^* - K_G)(\alpha - K_G)(\beta - K_G)} + \left\{\frac{f_2K_G + f_1(K_G - K_A^*)}{(K_G - K_A^*)(\alpha - K_A^*)(\beta - K_A^*)}\right\} \cdot (K_{21} - K_A^*) \cdot e^{-K_A^*(t-t_{LAG})} + \left\{\frac{f_2K_G + f_1(K_G - \alpha)}{(K_G - \alpha)(K_A^* - \alpha)(\beta - \alpha)}\right\} \cdot (K_{21} - \alpha) \cdot e^{-\alpha(t-t_{LAG})} + \left\{\frac{f_2K_G + f_1(K_G - \beta)}{(K_G - \beta)(K_A^* - \beta)(\alpha - \beta)}\right\} \cdot (K_{21} - \beta) \cdot e^{-\beta(t-t_{LAG})}\right] \quad (1)$$

where V_1– is the apparent volume of distribution for the central body compartment,

F– is the fraction of the administered dose (D_0) that ultimately reaches the systemic circulation,

f_1– is the fraction of this quantity of drug ($F.D_0$) that is emptied rapidly from the stomach in the first short interval of time as a bolus or "squirt,"

f_2– is the fraction that is emptied exponentially from the stomach with rate constant K_G (min^{-1}),

t– is elapsed time after ingestion,

t_{LAG}– is the interval between ingestion and the start of gastric emptying,

α and β– are, respectively, the fast and slow disposition rate constants for the two-compartmental body model, as defined by

$$\alpha + \beta = K_{12} + K_{21} + K_{el}$$
$$\alpha \cdot \beta = K_{21} \cdot K_{el}$$

and K_{12}, K_{21} and K_{el} are defined by Schema 2.

It is assumed that the fraction of the dose reaching the systemic circulation is the same for the initial bolus and the exponentially released portions. In the special case where f_1 is zero, Equation 1 reduces to the same equation as that for exponential drug release from a sustained-release preparation into the gastrointestinal tract.[17]

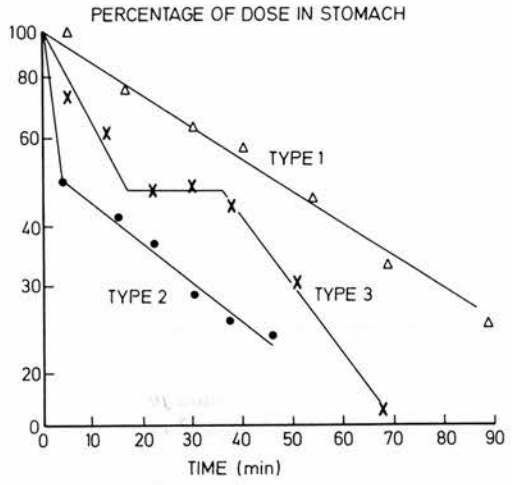


Fig. 1. Gastric emptying patterns in Subject 2, pentazocine-naloxone study (Type 1 gastric emptying), Subject 3, control study (Type 2 gastric emptying), and Subject 2, control study (Type 3 gastric emptying).

A nonlinear optimization method based on the simplex algorithm of Nelder and Mead[8] was used to refine the estimates found from the analog computer. The parameter estimates optimized on a digital computer were: FD_0/V_1; K_{12}; K_{21}; K_{el}; K_A (Schema 1) or K_A^* (Schema 2); t_{LAG}. For the model of Schema 2, values of K_G, f_1, and f_2 were constants derived from analysis of gastric emptying patterns. Individual data points were weighted by the method recommended by Ottaway.[11]

Multicompartmental analysis of plasma concentration–time data points following extravascular administration yields estimates of the rate constants for the (assumed) first-order processes of absorption, distribution, and elimination. The general form of the equation relating concentration (C_1) in compartment 1 to time after administration for the model of Schema 1 is:

$$C_1 = \sum_{i=1}^{3} A_i \cdot e^{-a_i \cdot (t - t_{LAG})}$$

Although the exponential terms a_1, a_2, and a_3 for a 2-compartment model may be assigned values equal to K_A, α, and β, they are not necessarily in this order.

Table I. *Rate constant for gastric emptying (K_G) and lag time in studies exhibiting a monoexponential emptying pattern (Type 1)*

Subject	*Treatment*	K_G (min^{-1})	*Lag time (min)*
1	Control	0.0420	5
2	Meperidine	0.0172	35
2	Pentazocine	0.0063	0
2	Pentazocine/naloxone	0.0146	0
3	Pentazocine	0.0132	0
7	Pentazocine/naloxone	0.0293	8

Table II. *Fraction (f_1) of dose emptied as an initial bolus and rate constant for subsequent gastric emptying (K_G); Type 2 emptying pattern*

Subject	*Treatment*	f_1 (%)	K_G (min^{-1})
1	Pentazocine/naloxone	60	0.0147
3	Control	46	0.0184
3	Pentazocine/naloxone	21	0.0123
4	Control	15	0.0268
5	Control	9	0.0386
6	Control	34	0.0503
7	Control	19	0.0533
8	Control	65	0.0174

For absorption of acetaminophen from an aqueous solution, the slow disposition rate constant (β) is smaller than the apparent absorption rate constant (K_A), and is by convention smaller than the fast disposition rate constant (α). The two remaining exponential terms cannot be assigned to α and K_A unless experimental data are available from studies using the intravenous route of administration or comparing several formulations given orally.[15] In the present study, however, the main effect of the narcotic analgesics was on gastric emptying (and thus K_A). The procedure adopted for each subject who received up to four treatments was allocation of the smallest exponential terms to β, and the near-constant terms to α: values of K_A were then found to alter with treatment in the expected way.

A similar dilemma arises in the identification of the exponential terms of the integrated equation for the model of Schema 2. The general form of Equation 1 is:

$$C_1 = \sum_{i=1}^{4} A_i \cdot e^{-a_i(t - t_{LAG})}$$

where the A_i terms are defined by the respective terms in Equation 1. In the nonlinear optimization, a_1 was a supplied constant equal to K_G and a_3 was identified as β. Values of a_2 or a_4 were assigned to α after comparing them with the estimates of α obtained from the analysis according to the model of Schema 1. The remaining exponential term was assigned to K_A*. In all cases good agreement was found between the pharmacokinetic values obtained by the analog and digital methods.

Results

Gastric emptying. Three different patterns of emptying were observed and were designated Type 1, 2, and 3 as follows:

Type 1. A monoexponential gastric emptying pattern commencing immediately after ingestion of the solution or preceded by an interval or lag period during which no emptying occurs.

Type 2. A biphasic gastric emptying pattern in which a fraction (f_1) of the total administered dose emptied rapidly from the stomach within the first 10 to 15 min, followed by a monoexponential decrease of the remaining fraction (f_2). The small number of points in the first short time interval did not allow a distinction to be drawn between a fast monoexponential emptying and an "instantaneous" squirt or bolus. Preliminary analysis showed that the calculated plasma concentration–time curves were virtually identical for both cases, and so the early emptying pattern was regarded as an initial bolus.

Type 3. A biphasic gastric emptying pattern in which there were two intervals of monoexponential emptying, interrupted by an interval with no emptying.

An example of each type of emptying pattern is shown in Fig. 1.

Table III. *Values for emptying pattern characterized by two monoexponential phases separated by a lag phase; Type 3 emptying pattern*

Subject	*Treatment*	$K_G(min^{-1})$ *for first phase*	*Duration of lag (min)*	$K_G(min^{-1})$ *for second phase*
2	Control	0.0425	20	0.0315
4	Meperidine	0.0047	50	0.0084
5	Meperidine*	0.0112	0	0.0385
7	Meperidine	0.0036	0	0.0094
7	Pentazocine†	0.0047	0	0.0105

*In this experiment there was an initial "squirt" of 30% of the stomach contents into the small intestine.
†In this experiment there was an initial lag period of 25 min during which no emptying was observed.

In the control studies, 50% of ingested solution was emptied in a mean time of 12 min (range, 4 to 22 min) (Tables I to III). Gastric emptying was usually of the Type 2 pattern with very fast initial emptying of a mean of 30% (range, 9 to 65%) followed by a slower monoexponential emptying with a mean t½ of 25 min (Table II).

With the narcotic analgesics emptying was either Type 1 or Type 3. The mean time for 50% gastric emptying was increased to 90 min (range, 30 to 127) and after pentazocine followed by naloxone the time for 50% gastric emptying was 30 min (range, 4 to 46).

With Types 1 and 3 emptying a lag period was observed, ranging from 0 to 36 min (Tables I and III). In most cases the longer lag periods were associated with pretreatment with a narcotic.

Acetaminophen absorption. The mean plasma concentrations of unconjugated acetaminophen are shown in Table IV.

In all the control studies acetaminophen absorption was rapid with a mean peak plasma concentration of 21.8 μg ml^{-1} occurring at 23 min. Following administration of the narcotic analgesics, absorption was delayed. The individual mean peak plasma concentrations were 17.9 μg ml^{-1} and 8.3 μg ml^{-1} at 111 and 120 min after meperidine and pentazocine, respectively.

Pharmacokinetic analyses.

Schema 1. The plasma acetaminophen concentration–time plots appeared to follow a smooth curve in most cases, and computer analyses provided an estimate of the apparent absorption rate constant (K_A) (Table V) based on the model of Schema 1. In some studies where meperidine and pentazocine were administered, there was a "lag" period during which the plasma concentration rose only slowly before the rapid rise at the end of the "lag" phase. These early points could not be included in the calculated curve, and so the apparent absorption rate constant was based on the rapidly ascending part of the curve. In Subject 2 two peaks were observed in the control study and no attempt was made to draw a calculated curve to fit these data.

Overall, there was no significant correlation between K_A and K_G ($r = 0.31$; $p' > 0.1$; $n = 13$), but, for the Type 1 emptying pattern the individual observed values for K_A and K_G were similar. There was a highly significant correlation ($r = 0.97$; $p' < 0.01$; $n = 6$) and the slope of the regression line did not differ significantly from unity ($p' = 0.10$) (Fig. 2).

Thus, the values of K_A and K_G were not equal in most cases because gastric emptying pattern was not a simple monoexponential process. The model shown in Schema 1 therefore has limited application for the description of the kinetics of absorption of drugs such as acetaminophen.

Schema 2. Analysis of the data using the model of Schema 2 revealed excellent agreement between observed and calculated plasma concentration–time curves in all subjects, regardless of the type of gastric emptying pattern. The analysis provided an estimate of K_A*, the rate constant for transfer of drug from the small intestine into the systemic circulation. The values of K_A* were greater than K_G, indicating that the rate-limiting step in the overall absorption of

Table IV. *Mean plasma concentrations ($\mu g\ ml^{-1}$) of unconjugated acetaminophen after oral dose of aqueous solution (20 mg kg^{-1})*

	Time after administration (min)								
	3	*5*	*6*	*10*	*15*	*20*	*25*	*30*	*40*
Control study, 8 subjects									
Mean	1.8	—	7.5	15.0	17.5	19.6	20.0	18.8	17.2
Standard deviation	2.6	—	4.4	7.3	7.9	7.2	5.2	4.0	3.1
150 mg IM meperidine 30 min before ingestion, 4 subjects									
Mean	—	1.7	—	2.7	3.4	3.8	4.3	5.3	6.8
Standard deviation	—	2.9	—	5.2	5.7	6.3	7.2	9.1	11.5
60 mg IM pentazocine 30 min before ingestion, 4 subjects									
Mean	—	0.6	—	1.3	1.6	2.2	2.9	3.8	4.0
Standard deviation	—	1.1	—	2.6	2.7	3.0	3.4	4.0	3.8
60 mg IM pentazocine 30 min before and 1.2 mg IV naloxone immediately before ingestion, 4 subjects									
Mean	—	1.3	—	3.3	8.7	14.5	14.6	14.4	11.6
Standard deviation	—	0.1	—	1.1	4.8	3.0	4.2	4.5	2.4

Table V. *Kinetic values for acetaminophen after oral administration to human volunteers (20 mg kg^{-1} body weight)*

Subject	*Treatment*	*Peak plasma concentration $\mu g\ ml^{-1}$*	*Time of peak (min)*	*Apparent absorption rate constant* (K_A), min^{-1}*	*True absorption rate constant† (K_A*), min^{-1}*
1	Control	27.9	15	0.054	0.255
1	Pentazocine/naloxone	14.5	15	0.076	0.071
2	Control	25.2, 23.0	20,60	‡	0.134
2	Meperidine	23.0	75	0.020	0.077
2	Pentazocine	11.9	60	0.005	0.214
2	Pentazocine/naloxone	21.1	30	0.019	0.209
3	Control	24.4	10	0.066	0.061
3	Pentazocine	9.2	180	0.013	0.066
3	Pentazocine/naloxone	14.1	20	0.031	0.077
4	Control	19.4	40	0.017	0.082
4	Meperidine	16.8	210	0.008	0.047
5	Control	31.1	20	0.049	0.171
5	Meperidine	24.1	40	0.015	0.118
6	Control	17.5	25	0.035	0.153
7	Control	17.7	20	0.046	0.218
7	Meperidine	7.7	120	0.014	0.256
7	Pentazocine	11.2	180	0.009	0.210
7	Pentazocine/naloxone	12.7	25	0.027	0.173
8	Control	15.7	25	0.038	0.050
	Mean				0.139
	Standard deviation				0.073

*Based on model of Schema 1.
†Based on model of Schema 2.
‡Conventional analysis of these data was inappropriate.

50	*60*	*75*	*90*	*120*	*150*	*180*	*210*	*240*	*360*	*480*
15.0	15.1	14.2	12.0	10.3	—	7.4	—	5.1	2.7	1.4
2.7	4.0	3.3	2.9	3.1	—	2.2	—	1.7	1.5	0.7
8.2	10.0	12.3	13.8	14.3	12.1	11.5	11.4	9.8	5.1	2.6
8.5	7.3	8.8	7.8	4.9	3.4	4.2	5.1	3.4	2.0	1.3
4.6	5.5	7.0	8.8	10.0	10.3	10.7	—	7.4	4.4	2.8
4.2	5.0	3.4	2.1	1.7	0.7	1.3	—	1.6	1.4	1.3
11.0	11.2	10.9	10.7	9.4	—	6.9	—	5.3	2.7	1.6
3.1	3.3	2.7	2.9	2.3	—	1.9	—	1.4	0.8	0.7

acetaminophen is the rate of gastric emptying (Tables I to III, Table V).

Fig. 3 shows the observed and calculated plasma concentrations and the observed gastric emptying pattern (Type 1) in Subject 2. Meperidine delayed the onset of emptying in this subject by about 35 min, and the quiescent period was reflected in a delay before the plasma concentrations rose. The data suggest that a small amount of solution had emptied from the stomach in the quiescent period, and this is seen as a small rise in plasma concentrations.

Fig. 4 shows the plasma concentration–time profile and gastric emptying pattern for Type 2 gastric emptying in subject 6. About one-third of the dose left the stomach rapidly and the plasma concentration rose correspondingly. In the subsequent exponential phase, gastric emptying was rapid (K_G equal to 0.050 min^{-1}). Since K_A* was even larger (0.153 min^{-1}), the quantity of acetaminophen in the small intestine fell rapidly.

The measured plasma concentrations of acetaminophen in one subject showed two peaks. The gastric emptying pattern indicated that there were two exponential portions separated by an interval of about 20 min during which there was no emptying. Using an analog computer program with the times of start (t_1) and end (t_2) of the quiescent interval, and the rate constants $K_{G(1)}$ and $K_{G(2)}$ for the first and second exponential emptying periods, respectively, the calculated plasma concentration–time curve agreed remarkably well with the observed points (Fig. 5).

In a process with two consecutive steps, estimation of the rate constant for the faster step is subject to some error. Successive increases in K_A*,with K_G held constant and of similar magnitude to K_A*, make substantial changes in the predicted curve (Fig. 6). However, if $K_A^* >> K_G$, the rate constant for the overall process of transfer from stomach to systemic circulation is approximately equal to K_G, and the predicted plasma concentration–time curve is influenced only slightly by small changes in K_A*.

Discussion

Gastric emptying patterns in the 19 studies showed considerable variation but could be conveniently classified into three types. Departures of emptying from the simple monoexponential pattern are well recognized in the litera-

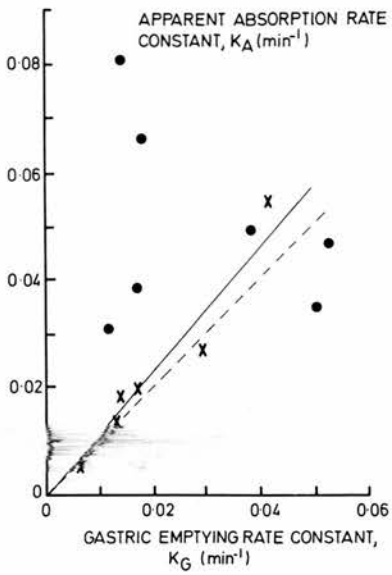


Fig. 2. Apparent absorption rate constant (K_A) plotted against gastric emptying rate constant (K_G) in studies showing Type 1 (X) and Type 2 (•) gastric emptying patterns. ----, Line of identity; ——, regression line for Type 1 emptying.

ture.[6] Inspection of the emptying pattern and plasma acetaminophen concentration–time curve for each experiment showed that the two were closely related. In particular, where the start of gastric emptying was delayed there was a corresponding "lag" period during which the plasma concentration did not rise or rose only very slightly and slow gastric emptying was associated with a slow rise in plasma concentration. Conversely, the most rapid increases in acetaminophen concentrations were found with Type 2 gastric emptying, particularly when a substantial proportion of the dose emptied in the initial "squirt." This obvious relationship between gastric emptying and the initial rise in plasma concentration strongly suggest that gastric emptying was the rate-limiting step in the absorption of acetaminophen.

Overall, the values obtained for K_A using conventional pharmacokinetic analysis did not correspond to the observed values of K_G, but these two values were in excellent agreement when there was Type 1 gastric emptying. This is to be expected since emptying is then a single exponential process which limits absorption. There was no significant correlation between K_G and K_A with Types 2 and 3 gastric emptying patterns and Schema 2 was developed to take these patterns into account. Using this model there was good agreement between calculated and actual plasma concentrations in all cases. Even when gastric emptying was interrupted by a quiescent period and the plasma concentration–time curve had two peaks, satisfactory agreement was found using the model (Fig. 5). The occurrence of two peaks early in the plasma concentration–time curve observed here and in other studies is seen to be due to an interruption in gastric emptying. The first rapid decline in plasma concentration starts at the time when emptying from the stomach temporarily ceases.

As expected, the true absorption rate constant K_A* (Schema 2) exceeded the apparent absorption rate constant K_A (Table V). Since there was no significant correlation between K_A* and K_A, the true absorption rate constant cannot be predicted from K_A obtained by conventional pharmacokinetic analysis. The absolute bioavailability was not determined in this investigation. Since Rawlins, Henderson, and Hijab[14] found that the mean bioavailability of acetaminophen from two 500-mg tablets was 89%, the apparent absorption rate constants (Table V) should be corrected for incomplete bioavailability, but this does not alter the conclusions drawn. The concurrent administration of narcotic analgesics does not influence the total urinary excretion of acetaminophen and its major metabolites.[9]

The value of K_A* was greater than K_G in all experiments and confirms that gastric emptying is the rate-limiting step in the absorption of acetaminophen given orally in solution. Absorption from the small intestine is rapid, and the estimated mean t½ for absorption is 6.8 ± 0.9 min (SE). The results of our study confirm that absorption of acetaminophen was highly dependent on the kinetics of gastric emptying.

Body position has recently been shown to alter the absorption of acetaminophen from tablets taken by mouth,[10] presumably by influencing gastric emptying. Our work demonstrates that even under carefully controlled conditions there is considerable individual variation in gastric emptying and acetaminophen absorption from a solution.

Most control studies showed Type 2 gastric

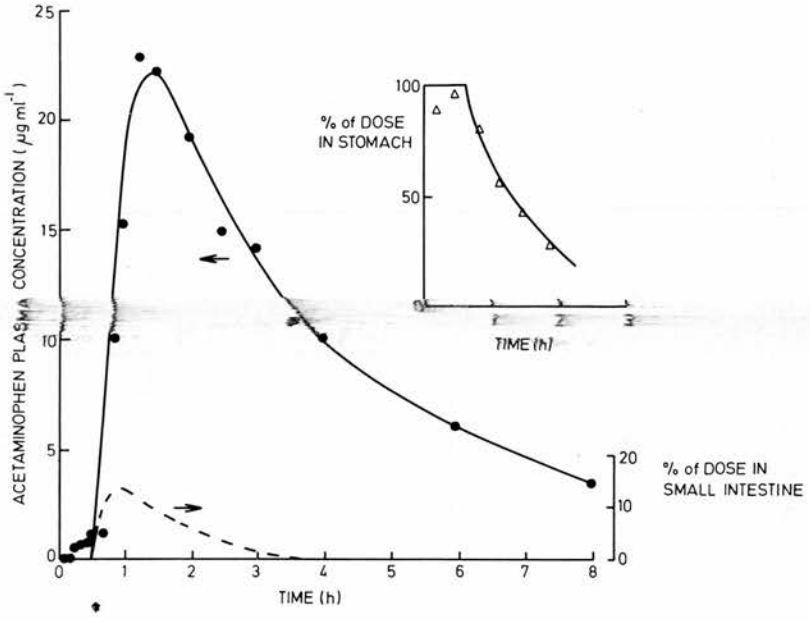


Fig. 3. Plasma acetaminophen concentration plotted against time for Type 1 emptying with a lag period (Subject 2, meperidine). • Data points; ——, calculated curve; ----, predicted percentage of dose in small intestine. *Inset,* Gastric emptying pattern. △, Data points; ——, calculated curve.

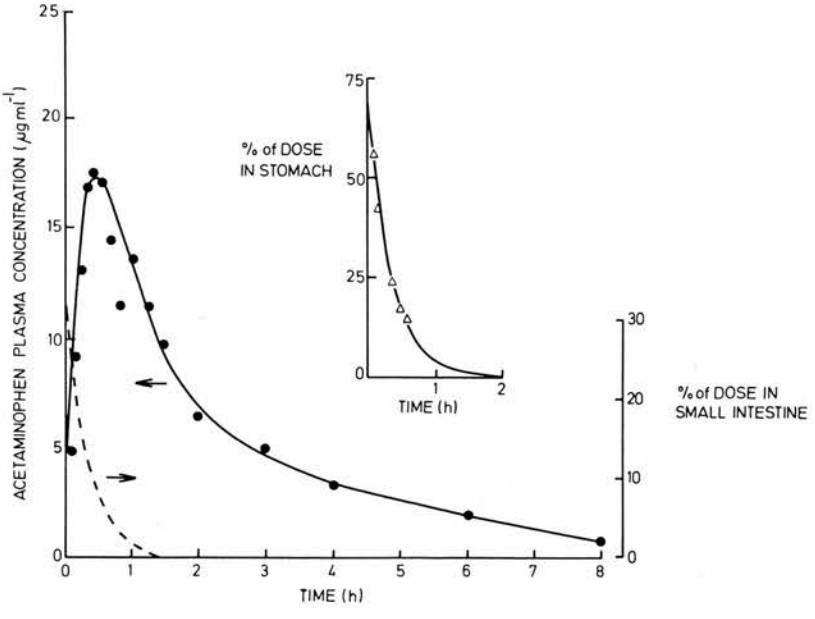


Fig. 4. Plasma acetaminophen concentration plotted against time for Type 2 gastric emptying (Subject 6, control). •, Data points; ——, calculated curve; ----, predicted percentage of dose in small intestine. *Inset,* Gastric emptying pattern. △, Data points; ——, calculated curve.

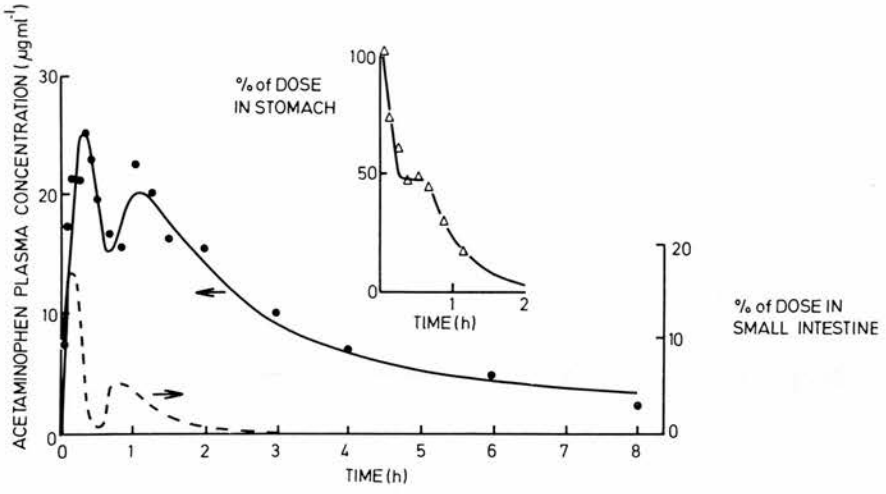


Fig. 5. Plasma acetaminophen concentration plotted against time for Type 3 gastric emptying (Subject 2, control). •, Data points; ——, calculated curve; ----, predicted percentage of dose in small intestine. *Inset*, Gastric emptying pattern. △, Data points; ——, calculated curve.

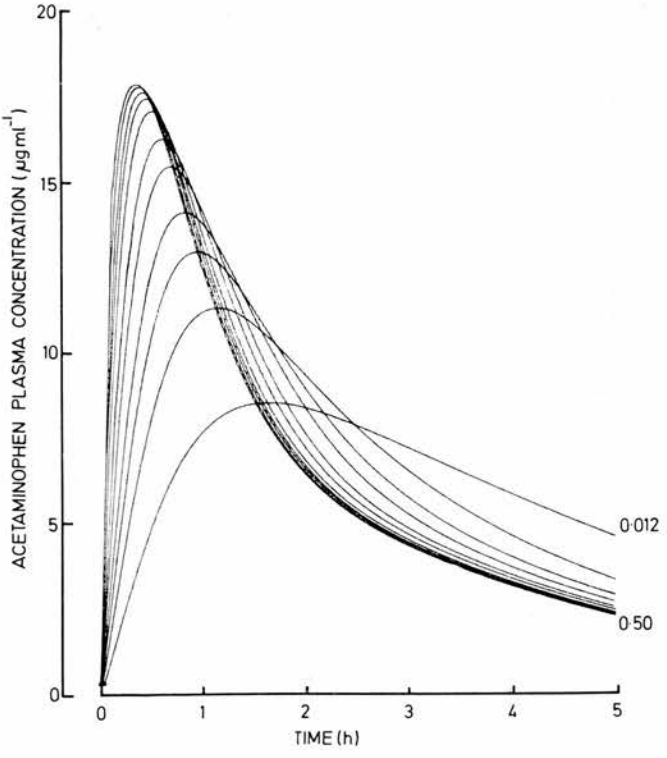


Fig. 6. Predicted plasma concentration–time curves showing the effects of change in K_A^*. (Subject 6, control study. Type 2 gastric emptying: $f_1 = 34\%$, $f_2 = 66\%$; $K_G = 0.050$; $K_{12} = 0.016$; $K_{21} = 0.011$; $K_{el} = 0.010$ min^{-1}). Values of K_A^* for successive curves are: 0.012, 0.025, 0.038, 0.05, 0.075, 0.10, 0.15, 0.20, 0.25, 0.35, and 0.50 min^{-1}.

emptying but the percentage of the dose emptied as an initial bolus varied from 9% to 65%. When a large proportion of the dose rapidly entered the small intestine, plasma acetaminophen concentration rose rapidly and the apparent absorption rate constant (K_A) approached that for the true absorption rate constant (K_A*). However, when only a small amount was released from the stomach in the first bolus, K_A* was 3 to 5 times as great as K_A.

Premedication with a narcotic analgesic abolished the initial bolus in seven out of eight studies and emptying was arrested or greatly reduced. Plasma concentrations remained at or close to zero for about 30 to 40 min. In some cases a very slow rise was observed to concentrations of about 5% to 10% of the peak values (Fig. 3); this may be due to a small amount of solution passing through the pylorus (since the emptying measurements did show a small loss of solution from the stomach), or to a small amount of acetaminophen that may have been absorbed from the stomach.

In one study (Subject 5, post-meperidine) an initial bolus of 30% of the dose entered the small intestine. The plasma concentration rose immediately after ingestion of the solution. Subsequent gastric emptying was much slower than in the control and the peak plasma concentration was lower. The reason for the reduced or delayed effect of meperidine on this subject is not known.

Measurements of gastric emptying have confirmed that it is not usually a simple monoexponential process in supine individuals. Type 2 gastric emptying is more common, and when a large proportion of the dose passes through the pylorus, absorption is very rapid. Using a model in which separate compartments represent the stomach and the small intestine, it is possible to calculate plasma concentrations arising from several patterns of gastric emptying and to estimate the true absorption rate constant (K_A*) for absorption from the small intestine. Although simpler models such as that of Schema 1 may be consistent with experimental data, the proposed model seems to be more appropriate for the description of drug absorption from orally administered solutions if gastric emptying is to be taken into account.

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PLETHYSMOGRAPHIC STUDY WITH FRUSEMIDE AND PIRETANIDE IN HEALTHY VOLUNTEERS

Biamino, Wessel, Schüren, Ramdohr, Nöring & Schröder (1974) made extensive studies of the effect of frusemide on venous compliance in normal subjects. The compliance increased, which might explain the observed fall in the forward load on the left ventricle (Dikshit, Vyden, Forrester, Chaterjee, Prakash & Swan, 1973; Schenk, Biamino & Schröder 1975). Frusemide was therefore compared with piretanide, a new highly effective diuretic (Merkel, Bormann, Mania, Muschaweck & Hropot, 1976) in a plethysmographic study.

A double-blind cross over experiment was made in five healthy male volunteers. Their mean ± s.e. mean age was 24.6 ± 1.36 years and their mean weight 65.8 ± 5.9 kg. Intravenous bolus doses of frusemide (40 mg) and piretanide (12 mg) were given at intervals of 1 week. Venous pressure was measured using a thin cannula passed into a forearm vein and connected to a Statham transducer. Changes of forearm volume were recorded using a mercury in rubber strain gauge. Measurements were made at the following times:

10.5 min and immediately before each bolus, and 3, 5 and 10 min after each bolus. Each measurement was repeated three times.

Venous compliance was calculated as the ratio between the slopes of the curve for volume change and the curve for pressure change plotted against time, i. e. compliance $= \Delta v/\Delta p$.

Venous compliance was found to increase before the tenth minute. The mean increase was 16.8% for frusemide which is consistent with the data of Biamino *et al.* (1974) and Dikshit *et al.* (1973). With piretanide the mean increase was 19.9%. There was a significant difference between initial compliance, and that measured at the fifth minute ($P = 0.01$) and at the tenth minute ($P = 0.05$) with piretanide. These significances were found using the Dunnett test. Both drugs evoked comparable diureses during the first hour after injection.

The data show that piretanide has an effect on venous compliance like that of frusemide. Results were similarly found in another randomly allocated experiment in patients with heart failure.

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Received February 21, 1978

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PARACETAMOL AND ASPIRIN ABSORPTION FROM SAFAPRYN AND SAFAPRYN-CO.

Bajorek, Widdop & Volans (1978) demonstrated that oral codeine phosphate (15–30 mg) does not delay the absorption of paracetamol (1.5 g) when given 30 min previously. This may seem surprising since other narcotic analgesics can delay gastric emptying and greatly slow the rate of paracetamol absorption (Nimmo, Wilson & Prescott, 1975; Nimmo, Heading, Wilson, Tothill & Prescott, 1975). However, Crone & Ardran (1957) found that intravenous morphine in subtherapeutic doses increased the amplitude of gastric peristalsis and 'propulsive power' of the stomach for approximately 30 min in healthy volunteers; this 'augmented activity' being followed by a longer phase of inhibition of peristalsis. This could conceivably explain the failure of inhibition of paracetamol absorption by codeine in the studies of Bajorek *et al.* (1978) and it may be that low doses of narcotics initially have a stimulating effect on gastric emptying.

Little is known of the absorption of paracetamol

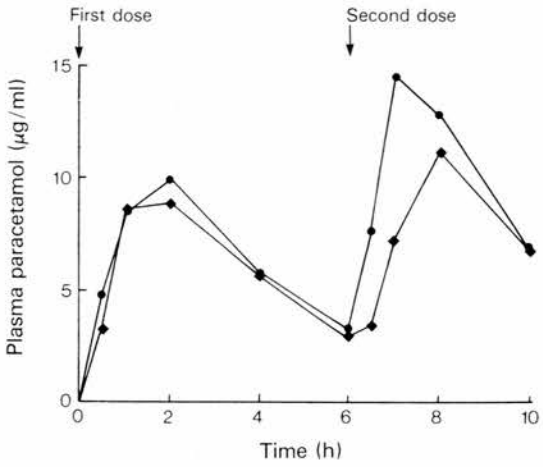

Figure 1 Mean plasma paracetamol concentrations following Safapryn (◆) and Safapryn-Co (●). Four tablets were administered at time 0 and 6 h. Each tablet contains 250 mg paracetamol.

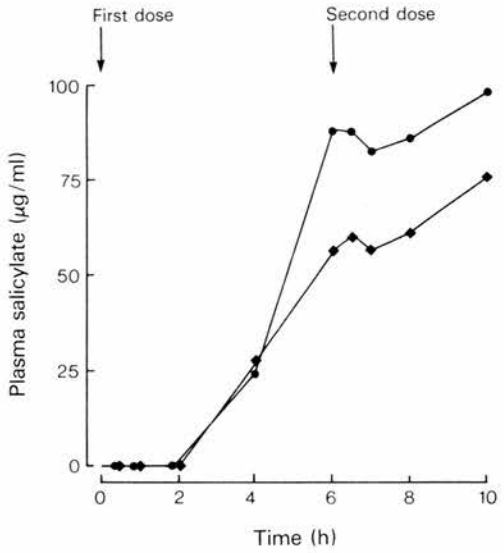

Figure 2 Mean plasma salicylate concentrations following Safapryn (◆) and Safapryn-Co (●). Four tablets were administered at time 0 and 6 h. Each tablet contains 300 mg aspirin as an enteric coated core.

and aspirin from codeine-containing compound analgesics after single or repeated doses. We have compared the absorption of aspirin from two doses of Safapryn (aspirin 300 mg as enteric coated core surrounded by an outer layer of paracetamol 250 mg) and Safapryn-Co (aspirin and paracetamol as in Safapryn plus 8 mg codeine phosphate).

Four healthy male volunteers with a mean ± s.d. age of 29 ± 2.1 years and a mean ± s.d. weight of 68.2 ± 3.2 kg were studied twice. On one occasion, the fasting subjects received four tablets of Safapryn with 200 ml water at 09.00 h followed by a further four tablets in the same way at 15.00 h. A light lunch was taken at 12.00 h. No tobacco was allowed and the subjects were ambulant throughout the study. Not less than 1 week later, the study was repeated with Safapryn-Co. Blood was taken at intervals for 10 h and plasma was separated for estimation of unchanged paracetamol and salicylate by gas liquid chromatography (Prescott, 1971) and fluorimetry (Schachter & Manis, 1958) respectively.

The results are shown in Figures 1 and 2. Following the first dose of Safapryn and Safapryn-Co, plasma paracetamol concentrations were the same. Absorption was rather slow with peak concentrations occurring at 2 h. However, paracetamol concentrations in all four subjects were greater following Safapryn-Co 30 min and 60 min after the second dose. The mean ± SD concentrations at 30 min were 7.6 ± 3.9 μg/ml and 3.3 ± 1.3 μg/ml after Safapryn-Co and Safapryn respectively and at 60 min the values were 14.5 ± 6.8 μg/ml and 7.2 ± 3.6 μg/ml ($P < 0.05$; paired *t*-test). Plasma salicylate concentrations were greater in three of the four subjects following the second dose of Safapryn-Co compared with Safapryn but the differences did not reach statistical significance.

Codeine phosphate, in a dose of 32 mg, seems unlikely to inhibit the absorption of aspirin and paracetamol from compound analgesic preparations. If anything, absorption after the second dose of Safapryn-Co was more rapid than from Safapryn and this is consistent with a time- and dose-dependent effect of narcotic analgesics on gastric emptying.

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Received October 27, 1978

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Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone

Narcotic analgesics inhibit gastric emptying and consequently delay the absorption of orally administered drugs such as paracetamol.[1-3] This increases the risk of aspiration of gastric contents during induction of anaesthesia in women in labour after narcotic analgesics and is not reversed by metoclopramide.[1] We have investigated the effect of the specific narcotic antagonist naloxone on narcotic-induced delay in gastric emptying.

Subjects, methods, and results

Gastric emptying and paracetamol absorption (20 mg/kg) were measured simultaneously in four fasting healthy volunteers aged 26-39 years, as described.[2] Each subject was studied "blind" on three occasions in random order at least seven days apart, once after placebo injections, once 30 minutes after pentazocine 60 mg intramuscularly, and once 30 minutes after pentazocine and immediately after naloxone 1·2 mg intravenously.

Gastric emptying and paracetamol absorption were rapid in all the control studies (see table). The mean time to empty half of the ingested dose was 13 minutes and the mean peak plasma paracetamol concentration 23·8 mg/l 22·5 minutes after ingestion. After pentazocine, however, gastric emptying and paracetamol absorption were greatly delayed in all subjects. Fifty per cent gastric emptying occurred at 97.3 minutes ($P<0·02$; paired t test). The mean peak plasma paracetamol concentration was only 10·8 mg/l, which occurred 160 minutes after ingestion ($P<0·05$ and $P<0·01$ respectively). This inhibition was largely reversed by naloxone. The gastric-emptying measurements and mean time to peak plasma paracetamol concentration after pentazocine and naloxone did not differ significantly from control values (27·8 minutes and 25 minutes respectively). Nevertheless, the mean peak paracetamol concentration was only 15·0 mg/l, which was significantly lower than control values ($P<0·05$). This may reflect the short duration of action of naloxone compared with pentazocine. The total amount of paracetamol absorbed was not influenced by pentazocine administered alone or with naloxone. Recovery of the administered dose in the urine in 24 hours in the control studies following pentazocine and pentazocine and naloxone was 75%, 79%, and 74% respectively.

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BMJ/415/79

Effect of pentazocine and pentazocine/naloxone on gastric emptying and paracetamol absorption

	Mean (±SE) time to 50% gastric emptying (minutes)	Mean (±SE) peak plasma paracetamol concentration (μg/ml)	Mean (±SE) time to peak concentration (minutes)
Control	13·0±3·5	23·8±1·9	22·5±1·3
Pentazocine	97·3±17·6	10·8±0·6	160·0±16·3
Pentazocine/naloxone ..	27·8±7·6	15·0±1·8	25·0±1·8

Comment

Gastric emptying and paracetamol absorption are severely inhibited by narcotic analgesics, and the delay in gastric emptying observed in women during labour is almost certainly attributable to narcotic analgesics. Metoclopramide does not reverse this delay.[1] In this study naloxone largely reversed the effect of pentazocine on gastric emptying, though its effect was probably shorter. Larger doses of naloxone may produce a greater reversal of pentazocine's effects, and naloxone may more effectively reverse the effects of a pure narcotic agonist such as pethidine. When reversal of the effects of narcotic analgesics on gastric emptying is desirable—for example, immediately before anaesthesia during labour or in recurrent vomiting—intravenous naloxone reverses the delay in gastric emptying as well as the other effects of narcotics.

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(*Accepted 23 August 1979*)

Printed in Great Britain by Qualitex Printing Limited, Cardiff