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THE INFLUENCE OF GASTRIC EMPTYING ON PLASMA CONCENTRATIONS OF THE ANALGESIC, MEPTAZINOL

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1 The influence of gastric emptying on the rate of absorption and peak plasma concentrations of meptazinol was studied in monkeys by comparison of the plasma concentrations of the drug achieved after intragastric and intraduodenal administration of the compound. Absorption was much more rapid and plasma concentrations were very much higher after intraduodenal than after intragastric dosage.

2 Determination of the 'normal' gastric emptying time in rats and monkeys showed that this was much longer in the monkey than in the rat. In addition, meptazinol was shown to have a pronounced retarding action on gastric emptying in the monkey, an effect which was not apparent in the rat.

3 The significance of these observations in relation to the species difference in oral potency of the drug is discussed.

Introduction

Meptazinol [*m*-(3-ethyl-1-methyl hexahydro-1H azepin-3-yl)phenol] hydrochloride is a potent new analgesic agent with an apparently low addiction liability. When given subcutaneously, the compound has been shown to be equipotent with pentazocine in both the rat tail flick and mouse acetylcholine writhing tests (Goode & White, 1971). In the monkey leg shock test the compound was almost 2.5 times more potent than pentazocine after intramuscular administration.

Although meptazinol was shown to have good analgesic activity after parenteral dosage, it was found to be considerably less potent after oral administration. For example, in the rat tail flick test the ED_{50} after oral dosage was 32 mg/kg compared to 8.7 mg/kg after subcutaneous administration (Goode, unpublished). In the monkey this difference was even more pronounced. After intramuscular injection the ED_{50} was 6.0 mg/kg but oral doses up to 10 times this failed to elicit a significant increase in shock threshold (Malis, unpublished).

This lower oral potency was reflected in lower plasma and tissue concentrations of the drug after oral compared with patenteral administration and was particularly marked in the monkey (Franklin & Aldridge, 1976). However these lower drug concentrations were not due to poor absorption since in both species over 70% of the radioactivity from an oral dose of the labelled compound was recovered in the urine.

Studies on the biotransformation of the compound indicated that it was extensively metabolized to the glucuronide conjugate in both species. However, a comparison of rat and monkey hepatic glucuronyl transferase showed that the enzyme activity in monkey liver was no greater than that in the rat (Franklin, 1975).

Closer inspection of the absorption data in the two species showed that the compound was more slowly absorbed in monkeys than in rats. This may have resulted in a flattening of the plasma concentration/time profile and in more extensive metabolism of the drug.

A major determinant of the rate of absorption of weakly basic drugs may be the rate of gastric emptying, since this determines the speed of passage of the drug to the site of absorption in the small intestine. This paper describes studies on the influence of gastric emptying on the rate of absorption of meptazinol. The consequent effect of this change in absorption rate on the magnitude of the plasma concentration is also described.

Methods

Radiochemicals

The random tritiation of meptazinol was carried out at the Radiochemical Centre, Amersham, Bucks. Labile tritium was removed by repeated dissolution in aqueous methanol and subsequent evaporation under reduced pressure. The further purification of the

compound was undertaken in these laboratories. The biological stability of the tritium label was demonstrated by the lack of significant quantities of tritiated water in the urine of animals dosed with the material. Radiochemical chemical purity was greater than 95% as shown by thin layer chromatography and the preparation had a specific activity of approximately 70 μCi/mg.

[^{14}C]-Polyethylene glycol (PEG) 4000 of specific activity 21.4 μCi/mg was used as an unabsorbable marker to determine the half-life of gastric emptying. This was obtained from the Radiochemical Centre, Amersham, Bucks.

Animals

Male rats, CD strain, descended from Sprague-Dawley were supplied by Charles River (U.K.) Ltd, Manston, Kent. They were maintained on a diet of Oxoid 41B pellets and weighed 250–350 g at the time of use.

Male Red Patas monkeys (*Erythrocebus patas*) weighing 3–5 kg were obtained from Shamrock Farms Ltd, Brighton, Sussex. They were maintained on an Oxoid 41B diet supplemented by fresh fruit.

Administration of meptazinol and collection of blood samples

Monkeys were fasted overnight before drug administation but were allowed free access to water. Food was withheld for 2 h after dosage. The drug was administered orally by gastric intubation and intraduodenally by injection through a rubber septum attached to the proximal end of a duodenal cannula. In both cases the drug was given as a solution of the hydrochloride salt in isotonic saline. The dose was 25 mg/kg and the vehicle volume 5 ml/kg.

At various times up to 7 h dosage, samples (2 ml) were taken from a femoral vein and immediately transferred to heparinized containers.

Measurement of radioactivity

Radioactivity was determined by liquid scintillation counting in a Packard Tricarb spectrometer, model 3380, equipped with automatic external standardization. The method of sample preparation and the scintillants employed were the same as those previously described by Franklin & Aldridge (1976).

Permanent cannulation of the monkey duodenum

This was performed by Dr B. Alps of the Pharmacology Dept., Wyeth Institute of Medical Research. Two female Patas monkeys were anaesthetized with halothane and a midline abdominal incision made to expose the gastrointenstinal tract. Taking care to minimize disruption of the vasculature, one end of a small plastic cannula (Portex manometer line type 200/490/100) was inserted through a small incision made in the duodenum. This was secured by a circular purse string suture and then anchored by stitching to the lower region of the stomach. The other end of the cannula was exteriorized through the peritoneum, capped with a small rubber septum and pushed beneath a fold of skin near the animals groin. The main incision was closed and the animal allowed to recover. The implantation of the cannula did not appear to affect the animals in any obvious way. Food consumption, body weight and general behaviour seemed normal. There was no evidence of altered gastro-intestinal motility since the animals did not suffer from constipation or diarrhoea.

Measurement of gastric emptying

The rate of gastric emptying was determined by measurement of the disappearance of [^{14}C]-PEG 4000, from the stomach. The utility of this material as an unabsorbable marker to measure gastrointestinal motility was described by Miller & Schedl (1970).

Rats. Groups of eight male rats were fasted overnight and 1 h before dosing, access to water was withdrawn. Each animal was given, by gastric intubation, 3 ml of isotonic saline containing 1 μCi [^{14}C]-PEG 4000. Groups were killed at 10, 20 and 30 min after dosing, by injection of ethanol directly into the brain (Pfeiffer & Muller, 1967). The abdomen of each animal was opened and the stomach clamped at either end as quickly as possible after death. The stomach was then removed and the contents were washed out with saline, and aliquots subjected to liquid scintillation counting. Since gastric emptying of a liquid appears to be a first order process the speed of emptying could be conveniently expressed in terms of a half-life, determined from a plot of $\log_{10}$ dose remaining in stomach against time.

After establishing the half-life of gastric emptying under these conditions, the influence of meptazinol on the process was investigated. Thus, unlabelled meptazinol (8 mg≡dose of 25 mg/kg) was added to each 3 ml portion of isotonic saline containing the [^{14}C]-PEG 4000 and the half-life of gastric emptying re-determined.

Monkeys. A group of four male monkeys were fasted overnight. The following morning each animal was given, by gastric intubation, 15 ml isotonic saline, containing 5 μCi [^{14}C]-PEG 4000. Thirty minutes later the animals were restrained and their stomachs washed out with 3 x 50 ml isotonic saline. The amount of radiolabelled marker present was subsequently determined by liquid scintillation counting. Assuming disappearance from the stomach to proceed in an

exponential fashion, the half-life of emptying was calculated from the expression

$$T_{\frac{1}{2}} = \frac{0.301 \times t}{\log_{10}(x_0)(x_t)}$$

where t = time after dosing (in this case 30 min); x_0 = % remaining in stomach at time zero (=100%); x_t = % remaining in stomach at time t.

After establishing the half-life gastric emptying under these conditions, the influence of meptazinol on the process was investigated. Thus, unlabelled meptazinol (75 mg ≡ dose of 25 mg/kg) was added to each 15 ml portion of isotonic saline containing the [^{14}C]-PEG 4000 and the half-life of gastric emptying re-determined.

Results

Comparison of plasma concentrations of meptazinol achieved after intragastric or intraduodenal dosage of the drug to monkeys

Intraduodenal dosage of meptazinol resulted in very much more rapid absorption of the drug than occurred after intragastric dosing (Table 1). Peak plasma concentrations of the unchanged drug were achieved after only 15–30 min compared to 3.5 h after oral administration and were at least five times higher than when the same dose was given intragastrically (Table 1). Peak plasma concentrations of free meptazinol after intraduodenal administration ranged from 300 to 470 ng/ml compared to only 9 to 67 ng/ml after the same dose was given orally. Elimination of the drug from the plasma of the intraduodenally dosed animals proceeded with a half-life of 1.18 hours. In the orally dosed animals elimination was also rapid but the plasma concentrations were too low to enable accurate calculation of the half-life.

Effect of meptazinol on gastric emptying time in the rat and monkey

The half-life of gastric emptying in the rat under the conditions used in these experiments was found to be 6.29 ± 1.01 min which is in close agreement with that found by Bridges, Dent & Johnson (1976). The addition of meptazinol to the marker solution used to measure emptying rate resulted in a slight but not statistically significant effect on the half-life, increasing it to 8.08 ± 1.03 (see Table 2).

The 'normal' half-life of gastric emptying in the monkey was found to be considerably longer than in the rat, being approximately 30 minutes. This agrees well with that observed in Rhesus monkeys by Jacoby & Brodie (1967). The addition of meptazinol to the marker solution resulted in the half-life of emptying being increased to 64 min (see Table 3). This difference was statistically significant (P=0.05–0.02).

Discussion

Recently, several workers have drawn attention to the importance of gastric emptying in determining the rate

Table 1 Plasma levels of total radioactivity and radioactivity due to unchanged meptazinol found in two female monkeys following intragastric or intraduodenal administration of ^{3}H labelled drug at 25 mg/kg

Time after dosing (h)	Monkey 1				Monkey 2			
	Intragastric		Intraduodenal		Intragastric		Intraduodenal	
	Total radioact.	Unchanged drug	Total radioact.	Unchanged drug	Total radioact.	Unchanged drug	Total radioact.	Unchanged drug
0.25	—	—					54.47	0.472
0.50	0.11	<0.010	45.08	0.297	0.92	<0.006	53.62	0.470
1.00	0.70	<0.010	37.09	0.204	0.92	<0.006	38.05	0.315
1.50	1.32	<0.010	28.08	0.145	0.85	<0.006	22.54	0.151
2.00	5.64	0.014	20.77	0.107	1.85	<0.006	17.10	0.148
2.50	11.98	0.025	13.25	0.073	3.64	<0.006	13.14	0.096
3.00	15.96	0.034	10.48	0.057	—	—	—	—
3.50	28.65	0.067	8.66	0.048	—	—	—	—
3.75	—	—	—	—	9.64	0.009	—	—
4.00	—	—	—	—	—	—	5.43	0.036
5.00	24.44	0.037	4.85	0.032	4.58	0.008	3.41	0.019
6.00	15.07	0.026	3.91	0.028	4.78	0.007	2.95	0.014
7.00	9.69	0.019	3.68	0.026	4.00	<0.006	2.67	0.011
8.00	7.27	0.018	3.41	0.027	—			

All results expressed as μg equivalents meptazinol/ml plasma.

of drug absorption and the consequential effect on the magnitude of the plasma concentration. Goto, Tsuzuki & Iguchi (1971), found increased plasma levels of aminopyrine in rabbits when the drug was given in combination with barbitone. This was due to the action of barbitone reducing the inhibitory effect of aminopyrine on gastric emptying (Goto, Tsuzuki & Iguchi, 1972). In studies with paracetamol, Heading, Nimmo, Prescott & Tothill (1973) found a good correlation between gastric emptying rate and the magnitude of the peak plasma levels of the drug in humans.

The results of the present study have implicated gastric emptying as a major determinant of the rate of absorption and magnitude of the plasma concentrations of meptazinol, since intraduodenal dosage to monkeys resulted in much more rapid absorption and higher plasma concentrations than when the drug was given intragastrically. These higher plasma concentrations were not considered to be the result of a greater chemical stability of the drug in the duodenum since the compound is known to be stable in acidic and basic environments. More probably this effect was the result of a change in the rate of absorption leading to saturation of the glucuronide conjugation mechanism. Indeed the proportion of unchanged drug to metabolites in the plasma was greater following intraduodenal dosage lending support to this hypothesis. Recently other workers have demonstrated that the glucuronide conjugation mechanism is saturable within the therapeutic dose range for a number of drugs including salicylamide and aspirin (Levy, 1971). Furthermore, Cohen, Bakke & Davies (1974) in studying the first pass metabolism of paracetamol by the isolated perfused liver of the rat showed that the hepatic extraction ratio decreased with increasing concentration of the drug in the perfusion fluid. They suggested that gastric emptying, by controlling the concentration of drug in the portal vein, would influence the amount of first pass metabolism and presumably therefore, the peak plasma levels of the compound.

The influence of gastric emptying on the extent of the first pass effect may also explain the previously observed species difference in plasma levels of meptazinol (Franklin & Aldridge, 1976). In the rat where plasma drug levels were much higher than in the monkey, gastric emptying was shown to be intrinsically more rapid and was not retarded by the action of the drug. This would be expected to lead to faster absorption, a prediction borne out experimentally since peak plasma levels were shown to

Table 2 Influence of meptazinol on gastric emptying in female rats

Time after dosing (min)	*Undosed control groups %[^{14}C]-PEG remaining in stomach*	*Dosed groups* %[^{14}C]-PEG remaining in stomach*
10	37.85 ± 3.72	40.85 ± 3.60
20	24.39 ± 3.86	30.93 ± 3.62
30	6.90 ± 2.45	8.90 ± 2.11
$T_{\frac{1}{2}}$ (min)	6.29 ± 1.01	8.08 ± 1.03

Results are means ± s.e. mean for groups of 8 rats. Half-lives calculated from regression analysis of all individual (not mean) data points.

* [^{14}C]-polyethylene glycol ([^{14}C]-PEG) marker solution contained meptazinol at a dose equivalent to 25 mg/kg.

Table 3 Influence of meptazinol on gastric emptying in female monkeys

Monkey No.	*Undosed control group %[^{14}C]-PEG remaining in stomach after 30 min*	$T_{\frac{1}{2}}$ *(min)*	*Dosed group* %[^{14}C]-PEG remaining in stomach after 30 min*	$T_{\frac{1}{2}}$ *(min)*
284	56.17	37.78	64.30	49.42
285	42.76	23.64	67.39	65.44
286	53.70	33.97	79.00	88.62
287	46.88	28.17	67.76	53.72
	Mean ± s.e. mean =	30.89 ± 3.12	Mean ± s.e. mean =	64.32 ± 8.77

* [^{14}C]-polyethylene glycol ([^{14}C]-PEG) marker solution contained meptazinol at a dose equivalent to 25 mg/kg.

Note Each value is the mean of two separate experiments.

occur by 0.66 h in the rat but not until 2.5 h in the monkey (Franklin & Aldridge, 1976). As a consequence of this more rapid absorption, saturation of the conjugation mechanism may well have occurred resulting in the observed higher plasma concentrations of the drug.

The mechanism by which meptazinol retards gastric emptying in the monkey is presently unknown. Since the drug possessed no cholinolytic activity in the rat or guinea-pig, as determined by its effects on the acetylcholine-stimulated isolated ileum (Goode, unpublished), it seems unlikely that it would do so in the monkey. However, this possibility has not been entirely excluded. It is perhaps more likely that the retarded gastric emptying was due to the local anaesthetic activity of the drug. The inhibitory action of chloroquine on gastric emptying has previously been ascribed to its local anaesthetic properties (Varga, 1966). Although meptazinol was only weakly active in this respect (equivalent to 1/10th lignocaine in the guinea-pig weal test) the relatively high concentrations of the drug in the stomach and the intrinsically slower gastric emptying in the monkey, favouring penetration of the drug to the receptor site(s), may facilitate such an action.

These observations suggest that gastric emptying may play an important role in determining the oral potency of drugs subject to extensive first pass metabolism and that drugs which retard gastric emptying are likely to exacerbate the extent of this first pass effect. Amongst the other major analgesics, morphine and pentazocine both delay gastric emptying (Crone & Ardran, 1957; Danhof, 1967), and both are subject to extensive first pass metabolism (Beckett, Taylor & Kourounakis, 1970; Brunk & Delle, 1974). It is noteworthy, in this respect that these drugs too, are much less potent after oral than after parenteral administration (Beecher, Keats, Mosteller & Lasagna, 1953; Beaver, 1968).

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References

BEAVER, W.T. (1968). Comparison of the analgesic effects of oral and intramuscular pentazocine in patients with cancer. *Fedn Proc.*, **27**, 653.

BEECHER, H.K., KEATS, A.S., MOSTELLER, F. & LASAGNA, L. (1953). The effectiveness of oral analgesics (morphine, codeine, acetyl salicylic acid) and the problem of placebo 'reactors' and 'non-reactors'. *J. Pharmac. exp. Ther.*, **109**, 393–400.

BECKETT, A.H., TAYLOR, J.F. & KOUROUNAKIS, P. (1970). The absorption, distribution and excretion of pentazocine in man after oral and intravenous administration. *J. Pharm. Pharmac.*, **22**, 123–128.

BRIDGES, J.W., DENT, J.G. & JOHNSON, P. (1976). The effects of some pharmacologically active amines on the rate of gastric emptying in rats. *Life Sci.*, **18**, 97–107.

BRUNK, S.F. & DELLE, M. (1974). Morphine metabolism in man. *Clin. Pharmac. & Ther.*, **16**, 51–57.

COHEN, G.M., BAKKE, O.M. & DAVIES, D.A. (1974). 'First-pass' metabolism of paracetamol in rat liver. *J. Pharm. Pharmac.*, **26**, 348–351.

CRONE, R.S. & ANDRAN, G.M. (1957). The effect of morphine sulphate on gastric motility. Some radiologic observations in man. *Gastroenterology*, **32**, 88–95.

DANHOF, I.E. (1967). Pentazocine effects on gastrointestinal motor functions in man. *Am. J. Gastroenterol.*, **48**, 295–309.

FRANKLIN, R.A. (1975). The application of drug metabolism studies to the development of a new analgesic. Ph.D. thesis, University of Surrey.

FRANKLIN, R.A. & ALDRIDGE, A. (1976). Studies on the pharmacokinetics and metabolism of the new analgesic meptazinol in rats and patas monkeys. *Xenobiotica*, **6**, 499–508.

GOODE, P.G. & WHITE, A.C. (1971). Some properties of Wy 22811, a new analgesic compound. *Br. J. Pharmac.*, **43**, 462–463P.

GOTO, S., TSUZUKI, O. & IGUCHI, S. (1971). Effect of combination of pharmaceuticals on gastrointestinal absorption. III. Combination of aminopyrine and barbital (1). *Chem. Pharm. Bull.*, **19**, 944–953.

GOTO, S., TSUZUKI, O. & IGUCHI, S. (1972). Relationship between enhancement of plasma level of aminopyrine in barbital and stomach emptying. *J. Pharm. Sci.*, **61**, 945–947.

HEADING, R.C., NIMMO, J., PRESCOTT, L.F. & TOTHILL, P. (1973). The dependence of paracetomol absorption on the rate of gastric emptying. *Br. J. Pharmac.*, **47**, 415–421.

JACOBY, M.I. & BRODIE, D.A. (1967). Gastrointestinal actions of metoclopramide. An experimental study. *Gastroenterology*, **52**, 676–684.

LEVY, G. (1971). Saturation of glucuronide formation in man and its clinical implications. *Chem. Biol. Interactions*, **3**, 291.

MILLER, D.I. & SCHEDL, H.P. (1970). Total recovery studies of nonabsorbable indicators in the rat small intestine. *Gastroenterology*, **58**, 40–46.

PEIFFER, C.J. & MULLER, P.J. (1967). Physiologic correlates dependent upon mode of death. *Toxic appl. Pharmac.*, **10**, 253–260.

VARGA, F. (1966). Intestinal absorption of chloroquine in rats. *Archs int. Pharmacodyn. Thér.*, **163**, 38–46.

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