CONCENTRATION EFFECT STUDIES WITH ORAL METOCLOPRAMIDE

D.N. BATEMAN*, C. KAHN & D.S. DAVIES

Department of Clinical Pharmacology, Royal Postgraduate Medical School,
Ducane Road, London W12 0HS

- 1 The effects of single oral doses of 10 mg and 20 mg metoclopramide have been compared to placebo in six normal male volunteers.
- 2 The drug did not significantly increase the rate of gastric emptying as measured by ethanol absorption.
- 3 Sedation during the absorption of ethanol was only observed 1 h after the 20 mg oral dose of metoclopramide ($P < 0.05$).
- 4 Akathisia, a central nervous system side effect of metoclopramide, occurred only in subjects who had peak plasma concentrations above 100 ng/ml.
- 5 It has not been possible to define a concentration-effect relationship for the action of metoclopramide on the stomach and comparison with previous results after intravenous dosing suggests that the route of administration is of major importance in determining the action of this drug.

Introduction

Metoclopramide (4-amino-5-chloro-2-methoxy-N-2-diethylaminoethyl benzamide) is a widely used anti-emetic drug. There are conflicting reports of the effect of metoclopramide on gastric emptying in normal subjects. Hancock and colleagues (Hancock, Bowen-Jones, Dixon, Dymock & Cowley, 1974) reported no effect whilst Kreel (Kreel, Trott & Howells, 1972) found an increased rate of emptying. Ramsbottom & Hunt (1970) could demonstrate an effect of the drug only after the administration of apomorphine. In these studies techniques for the measurement of gastric emptying have differed, and both the dose and route of administration of the drug have varied. We have previously reported on the relationship between plasma concentrations of metoclopramide and effects on gastric emptying after intravenous administration (Bateman, Kahn, Mashiter & Davies, 1978). We now report a similar study with oral metoclopramide.

Methods

The protocol for these studies was submitted to, and approved by, the Ethics Committee of the Royal Postgraduate Medical School. All subjects gave their written informed consent to participate in the studies.

*Present address: Wolfson Unit of Clinical Pharmacology, The University, Newcastle-upon-Tyne.

Subjects

The subjects were all members of the Department of Clinical Pharmacology, were male and aged between 26 and 36 years. Five of the subjects were non-smokers.

The doses

For each of the three studies the subjects received two tablets which consisted of:

1. Two $\times$ 10 mg metoclopramide hydrochloride (Maxolon, Beecham Pharmaceuticals).
2. One tablet of 10 mg metoclopramide hydrochloride + one matching placebo.
3. Two matching placebo tablets.

The three different doses were given in a randomized fashion with both the subjects and the experimenter blind.

Plan of study

The subjects were requested to refrain from drinking alcohol for 36 h before each experimental day. At 08.30 h on the day of the study the subjects came to the Clinical Laboratory and an indwelling cannula was inserted into a forearm vein. The two tablets (placebo, 10 or 20 mg metoclopramide) were taken with 100 ml water. Blood samples (10 ml) for the

measurement of plasma metoclopramide were withdrawn into a lithium heparin tube and were obtained at zero and at 15, 30, 45, 60, 90, 120, 180, 270, 330, 480 and 540 min after dosing.

Gastric emptying was assessed by examination of the plasma concentration-time profile of ethanol after a standard dose of ethanol (70 mg/kg body weight) in orange cordial (500 ml) heated to 37°C. This was administered at 1, 4.5 and 8 h after dosing. Blood samples (1 ml into a fluoride oxalate tube) for the measurement of plasma ethanol concentrations were obtained at 0, 5, 7.5, 10, 12.5, 15, 20, 25, 30 and 40 min after each dose of ethanol. The subjects were allowed to drink 250 ml of milk after each study of gastric emptying but were not allowed any food or other beverages during the 9 h of the study.

Central nervous system effects of the drug were monitored as follows:

1. Sedation during ethanol absorption was assessed using a self scored visual analogue scale. The analogue scale consisted of a 100 mm line marked 'wide-awake' and 'nearly asleep' at the opposite poles. Subjects were invited to assess their degree of sedation by placing a mark between the two poles. This was done every 5 min for 1 h after each dose of ethanol. Sedation was measured in mm from the 'wide awake' axis.
2. Akathisia, a feeling of restlessness and unease, by spontaneous reporting.

Analytical procedures

Metoclopramide concentrations in plasma were measured by a sensitive and specific method based on stable isotope dilution and gas chromatography-mass spectrometry as previously described (Bateman *et al.*, 1978). Ethanol was measured by gas liquid chromatography (Bateman *et al.*, 1978).

Statistical analysis

Plasma concentrations of ethanol and sedation scores were subjected to three way analysis of variance.

Results

In this study gastric emptying time, as assessed by the alcohol absorption test, was not significantly changed by oral doses of 10 or 20 mg of metoclopramide. At 1 h after the 20 mg dose the mean time to peak ethanol concentration was 13.8 ± 1.7 min compared with 18.3 ± 1.7 min for placebo but the difference was not significant ($P > 0.1$). Eight hours after the 20 mg dose gastric emptying was significantly prolonged being 20.8 ± 1.5 min compared with 17.5 ± 2.0 min for placebo ($P < 0.05$). All measurements of gastric emptying time are shown in Table 1 and compared with results we have previously obtained with intravenous metoclopramide (Bateman *et al.*, 1978).

Sedation after the standard dose of ethanol was only significantly different from placebo at 1 h after the 20 mg dose (Figure 1). Akathisia was reported by one subject after 10 mg and by three subjects after 20 mg metoclopramide. No subject experienced akathisia with placebo. Peak plasma concentrations of metoclopramide showed considerable inter-individual differences (Table 2) suggesting variable 'first-pass' metabolism since early studies with radio-labelled drug show that it is well absorbed. It is of interest to note that subjects 2, 3 and 4 who reported akathisia all achieved peak plasma concentration in excess of 100 ng/ml (Table 2). Plasma concentrations of metoclopramide at the beginning of each measurement of gastric emptying are shown in Table 3 and compared with those found in a previous study with intravenous metoclopramide.

Table 1 Gastric emptying measured as time (min, mean $\pm$ s.e. mean for six subjects) to peak ethanol concentration. Also shown are data obtained in a previous study with intravenous metoclopramide 10 mg

Oral	Time after dosing (h)		
	1	4.5	8
Placebo	18.3 ± 1.7	18.3 ± 3.4	17.5 ± 2.0
10 mg metoclopramide	17.5 ± 2.7	15.4 ± 2.9	17.9 ± 1.4
20 mg metoclopramide	13.8 ± 1.7	15.8 ± 2.5	$20.8 \pm 1.5^*$
<i>Immediately after injection</i>			
i.v.			3
Placebo	20.7 ± 2.3		20.7 ± 2.3
10 mg metoclopramide	$11.8 \pm 1.8^{**}$		$13.0 \pm 1.8^*$

* $P < 0.05$, ** $P < 0.005$ compared to placebo.

Figure 1 Sedation scores are plotted against time (min) after a standard dose of ethanol. The dose of ethanol was administered 1 h after placebo (●), 10 mg (◆) or 20 mg (□) of metoclopramide.

Discussion

In these studies we have failed to demonstrate an effect of 10 or 20 mg metoclopramide on gastric emptying as measured by the alcohol absorption test although there was a tendency to more rapid emptying 1 h after the 20 mg dose. This contrasts to our previous studies (Bateman *et al.*, 1978) in which an intravenous dose of 10 mg significantly increased the rate of gastric emptying both immediately after the injection and 3 h later (Table 1). The present results are surprising in that at 1, 4.5 and 8 h after the 20 mg and at 1 h after the 10 mg dose plasma concentrations of metoclopramide were considerably

greater than the 21 ng/ml found at 3 h after an i.v. dose (Table 3), when there was a significant effect on gastric emptying (Table 1).

It has recently been suggested that under certain circumstances ethanol absorption may not be a suitable tool for investigating gastric emptying (Mattila, Linnoila, Seppälä & Koskinen, 1978). In our hands, however, using a low dose of ethanol (70 mg/kg body weight) in a 500 ml drink, at 37°C to avoid direct inhibiting effects of ethanol (Barboriak & Meade, 1970) or cold fluid (Bateman *et al.*, 1978) on the stomach, this technique has proved reproducible.

With this low dose of ethanol plasma concentrations fall off rapidly after the peak concentration has occurred, presumably because ethanol metabolism is still first order at the low concentrations obtained (Kalant, 1971).

We do not have an explanation for the failure of the oral doses of metoclopramide to significantly change gastric emptying. It is possible that rapid delivery of high concentrations of the drug to the brain as is obtained after i.v. dosing is required to produce an effect on the stomach. Subsequent decline of drug effect may then be unrelated to the plasma concentration. This is supported by the results of our previous intravenous study (Bateman *et al.*, 1978) in which a similar effect on gastric emptying was seen immediately and 3 h after dosing despite a five-fold fall in plasma concentration. Similar considerations apply to the almost total absence of a sedative interaction between alcohol and metoclopramide in this study. As five of the six subjects had taken part in the earlier intravenous experiment inter-subject difference in response to metoclopramide would not account for the findings.

It is of interest to note that the akathisia which was experienced by six of the seven subjects following the i.v. dose of 10 mg was only reported by three subjects in the present study and they were the ones whose peak plasma concentration exceeded 100 ng/ml (Table 2).

Table 2 Peak plasma metoclopramide concentration (ng/ml) after orally administered drug at two dose levels (10 mg and 20 mg)

Subject	Peak plasma metoclopramide (ng/ml)	
	10 mg orally	20 mg orally
1	14.5	70
2	54	120*
3	42	138*
4	140*	131*
5	28.5	88
6	17	40

* Denotes presence of akathisia.

Table 3 Mean ($\pm$ s.e. mean) plasma metoclopramide concentration (ng/ml) at the beginning of each study of gastric emptying. Also shown is the plasma concentration found during studies on the effects of intravenously administered metoclopramide. (Drug was injected over 30 s and the alcohol absorption test was started immediately after the injection)

Dose and route	Plasma metoclopramide (ng/ml) at:		
	1 h	4.5 h	8 h
10 mg p.o.	37 $\pm$ 10.9	14.7 $\pm$ 3.9	7.3 $\pm$ 2.9
20 mg p.o.	82.3 $\pm$ 13.9	42.2 $\pm$ 7.1	26.8 $\pm$ 4.6
Immediately after injection			
10 mg i.v.	> 100 ng/ml*		21 $\pm$ 2.5

*As calculated by extrapolation of the plasma concentration time curve.

The almost ten-fold inter-individual variability in peak plasma concentration of metoclopramide following oral dosing is due to differences in the degree of 'first-pass' metabolism (Bateman, Kahn & Davies, unpublished observations) and makes the drug difficult to use. Our findings of little or no effect following oral doses of 10 and 20 mg suggest that the drug is best given intravenously and this will also

greatly reduce inter-individual difference in pharmacokinetic parameters.

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