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PHARMACOKINETIC AND CONCENTRATION-EFFECT STUDIES WITH INTRAVENOUS METOCLOPRAMIDE

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1 Pharmacokinetic and concentration-effect studies have been carried out following intravenous injection of 10 mg metoclopramide hydrochloride to seven normal male volunteers.

2 It is proposed that a two-compartment model adequately describes the disposition of the drug which is rapidly distributed ($T_{\frac{1}{2}}\alpha = 4.9 \pm 1.1$ min) and eliminated ($T_{\frac{1}{2}}\beta = 165.7 \pm 20.2$ min). Total body plasma clearance of the drug is high (10.9 ± 1.5 ml min^{-1} kg^{-1}) and approximates to liver plasma flow.

3 Metoclopramide i.v. increases gastric emptying as measured by an ethanol absorption test ($P < 0.005$). The duration of this effect is at least 3 h.

4 Ethanol given after i.v. metoclopramide administration produces significant sedation during the first hour and at 3 h ($P < 0.001$).

5 The effect of metoclopramide on gastric emptying, and the degree of sedation induced by ethanol would appear to be related to plasma metoclopramide concentration.

6 Metoclopramide increases serum prolactin to 59 ± 5.8 µg/l at 30 min after injection. There is a linear relationship ($r = 0.809$) between serum prolactin increase and plasma metoclopramide concentration.

Introduction

Metoclopramide (4-amino-5-chloro-2-methoxy-N-(2-diethyl amino ethyl benzamide) has been in clinical use for over 10 years but there have been no studies of plasma concentration-effect relationships in man. There is evidence from human studies (Eisner, 1971; Johnson, 1973; Kreel, Trott & Howells, 1972) that the drug increases gastric motility and gastric emptying rates. Studies in animals suggest a direct action on the chemoreceptor trigger zone (Robinson, 1973a) but the relative importance of each of these properties in the therapeutic action is not understood. Extrapyramidal side effects occur in man (Robinson, 1973b) and there are experimental data in animals demonstrating dopamine antagonist activity (Dougan, Mearrick & Wade, 1974; Ahtee, 1975; Donaldson, Jenner, Marsden, Miller & Peringer, 1976). The studies described here were designed to investigate the kinetics of metoclopramide after intravenous administration in normal male volunteers, and to determine whether a relationship exists between plasma concentration of the drug and its pharmacological effects in man.

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Method

Seven normal male volunteers (age 26-36 years) participated in the study after fully informed consent had been obtained. They attended the laboratory fasting on the morning of each of the two study days, having refrained from alcohol for at least 36 h beforehand. A forearm vein was cannulated for blood sample withdrawal. An intravenous injection of either saline or metoclopramide hydrochloride 10 mg (equivalent 8.93 mg free base) was given into the opposite arm in a blind randomised order.

On each day studies of gastrointestinal and sedative effects were performed for two 1 h periods. These were (a) immediately after the i.v. injection (Study 1) and (b) 3 h later (Study 2). Blood samples were drawn for metroclopramide analysis at 0, 5, 10, 15, 30, 60, 90, 120, 180, 240, 360 and 480 min, and for prolactin estimation at 0, 30, 60, 90, 180, 240, 360 and 480 min. Gastric emptying was assessed by measuring the plasma concentration profile of ethanol after a drink of 500 ml of warm (37°C) orange cordial containing ethanol (70 mg/kg body weight), sampling at 0, 5, 7.5, 10, 12.5, 15, 20, 25, 30 and 40 min after the drink. Sedative effects during the ethanol absorption studies were assessed by a self-scored visual analogue scale. This consists of a 100 mm line which is marked 'wide awake' and 'nearly asleep' at opposite poles. Subjects were invited to indicate their degree of

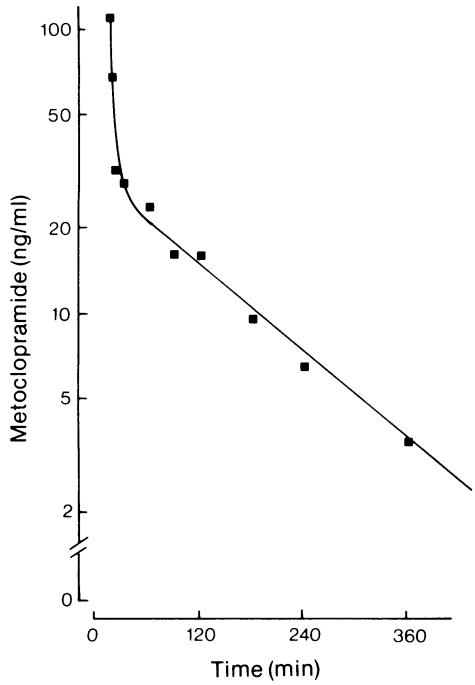

Figure 1 Plasma concentration profile of metoclopramide (=8.93 mg free base) given intravenously to Subject 2.

sedation every 5 min during the hour after ethanol administration. Spontaneous subjective complaints were also noted. Subjects were not allowed access to food for the first 4 h of the experiment. They were seated during the studies of sedation and gastric emptying but were otherwise freely mobile in the laboratory.

In five of the subjects measurements of gastric antral contraction rates were made by ultrasound pulse-echo scanning during the first 45 min of each ethanol absorption study. This technique has been described in full elsewhere (Bateman, Leeman, Metreweli & Willson, 1977).

In three subjects urinary collections were made over a 36 h period to estimate urinary excretion of the free drug and conjugated metabolites.

Metoclopramide was measured by a specific assay based on stable isotope dilution utilizing gas chromatography-mass spectrometry (GC-MS) with selected ion monitoring (Davies *et al.*, to be published). Blood samples were taken into bottles containing lithium heparin. Plasma was separated immediately and spiked with deuterated metoclopramide in a concentration of 5 μg/ml. Samples were stored deep frozen prior to analysis. Urine volume and pH was recorded and 20 ml aliquots stored deep frozen.

Metoclopramide in urine was measured after d_3-metoclopramide had been added at 15 μg/ml. For measurement of total (free and conjugated) metoclopramide, urines were hydrolysed by addition of an equal volume of 11.4M HCl and heating at 40°C for 1 h.

Plasma and urine samples were made alkaline and extracted with ether. Combined GC-MS was carried out using a Finnigan 3200 Quadrupole mass spectrometer combined with a Finnigan 6100 interactive data system. A 1 m × 2 mm i.d. pyrex glass column was packed with 3% OV-17 on Gas Chrom Q (100-120 mesh) for chromatography. Selected ion monitoring was carried out at m/e 184 for metoclopramide and m/e 189 for d_3–metoclopramide and peak height ratios calculated using the data system used to quantify metoclopramide from previously prepared calibration curves. The limit of sensitivity of this assay is 5 μg/ml with a coefficient of variation of 9% at this level and of 5% at 15 ng/ml.

Serum prolactin was measured by a double antibody radiommunoassay as μg/l (hPRL VLS l) using [I^{125}]-human prolactin (hPRL V,S 3) and rabbit antiserum to human prolactin (anti-VLS 3). The normal range for males is 5-15 μg/l.

Plasma ethanol concentration was measured by gas-liquid chromatography (Hewlett-Packard 5750-G Instrument, column packing Poropak Q 80-100 mesh, oven temperature 160°, carrier (helium) flow 20 ml/min). Propan-1-ol diluted in water to 20 mg/100 ml was used as internal standard. The propanol solution was mixed with plasma (1:1) and injected directly onto the chromatograph. A pre-column packed with glass wool was fitted to prevent soiling of the chromatography column with plasma debris.

Analysis of data

Statistical analysis was performed by three-way analysis of variance on plasma ethanol measurements and sedation scores. Results are expressed as mean ± s.e. mean. Arc sine transformation was performed on the visual analogue scale measurements of sedation prior to analysis to normalize the data.

Gastric emptying was assessed by comparing the plasma ethanol profiles of each subject during the study periods. The time taken for each individual to reach the measured peak plasma ethanol level was used as an index of gastric emptying. Measurements of gastric motility were taken as a mean intercontraction interval for each 5 min of the 45 min monitoring period.

Pharmacokinetic analysis was performed by fitting the plasma metoclopramide concentration-time data to a bi-exponential equation using a digital computer

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p is the plasma concentration at time t after the intravenous injection of metoclopramide, and α and β are the first order hybrid rate constants for the

fast and slow disposition processes respectively. A and B are the ordinate intercepts of the exponential terms at t = 0. There was no significant difference between observed and calculated values of plasma concentrations in a test of 'goodness of fit' for data from all the subjects. Figure 1 illustrates the plasma concentration profile in one subject.

The computer programme produces estimates of the pharmacokinetic parameters of a two compartment open model from A, B, α, β as previously described (Davies, Wing, Reid, Neill, Tipett & Dollery, 1977).

Results

Gastric emptying as assessed by ethanol absorption was increased by metoclopramide both immediately after injection (Study 1) and 3 h after injection (Study 2) when compared to placebo (Figures 2 and 3). The curves as analysed by three-way analysis of variance are significantly different at each study time (Study 1: $P < 0.05$, Study 2: $P < 0.005$).

There was a significant decrease in the time to peak ethanol concentration after metoclopramide during Study 1 and Study 2 (Table 1). The time to peak ethanol concentration after metoclopramide was longer in Study 2 as compared to Study 1, but this did not reach statistical significance. There were no significant differences in the peak plasma ethanol concentrations which were 12.69 ± 3.37 mg% after metoclopramide and 10.43 ± 2.39 mg% after placebo in Study 1 and 11.31 ± 3.56 mg% after metoclopramide and 8.91 ± 1.60 mg% after placebo in Study 2.

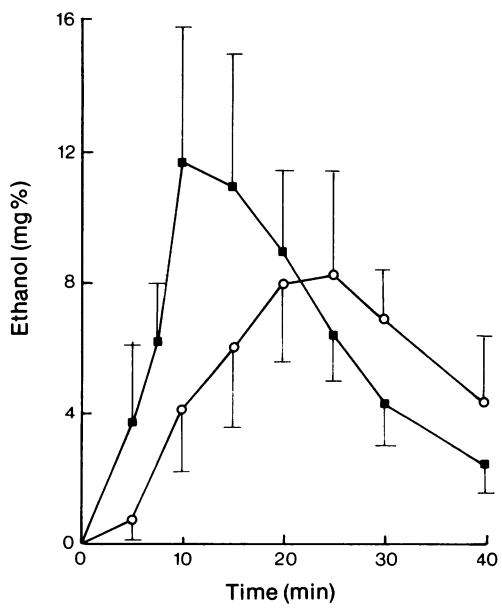

Figure 2 Study 1: Plasma ethanol-time plot (mean ± s.e. mean, $n = 7$) ○ placebo; ■ metoclopramide.

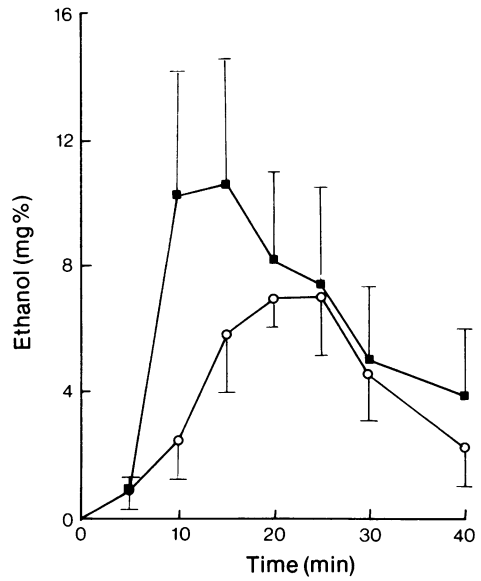

Figure 3 Study 2: Plasma ethanol-time plot (mean ± s.e. mean, $n = 7$) ○ placebo; ■ metoclopramide.

Side effects of metoclopramide which are thought to be centrally mediated were apparent in most of the subjects. Firstly, six of the subjects experienced akathisia (a feeling of restlessness and unease) within the first 15 min after the intravenous dose of metoclopramide. This was moderately severe in one subject who had an intense desire to move and remove his i.v. cannula. The akathisia was terminated by the onset of sedation.

Sedation scores after metoclopramide were not significantly different from those after placebo at the beginning and end of both Study 1 and Study 2 (Figures 4 and 5). However significant sedation occurred during both the ethanol absorption studies after metoclopramide ($P < 0.001$). There was significantly less sedation during Study 2 than Study 1 (P 0.05 > 0.01). The time taken for individuals to reach their peak sedation score did not correlate with the

Table 1 Gastric emptying—time to peak ethanol concentration (Mean ± s.e. mean, $n = 7$)

	Metoclopramide	*Placebo*
	Time to peak ethanol concentration (min)	
Study 1	11.79 ± 1.79*	20.71 ± 2.30
Study 2	13.04 ± 1.81**	20.71 ± 1.80

Significant differences from placebo: * $P = < 0.005$; ** $P = < 0.001$.

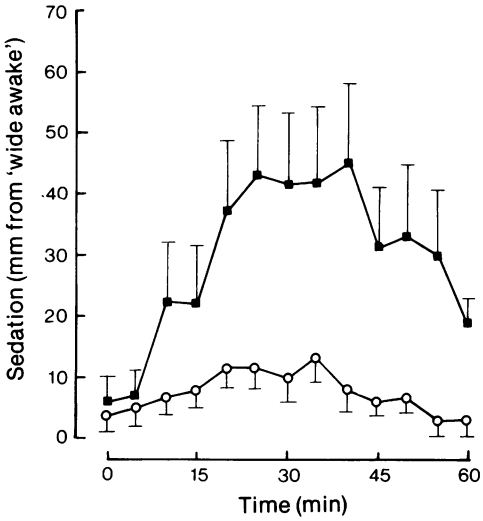

Figure 4 Study 1: Sedation (mean ± s.e. mean, n = 7) ○ placebo; ■ metoclopramide.

time taken to reach peak ethanol concentration, or the individual peak ethanol measurement. Individual peak sedation times were 33 ± 3.74 min in Study 1 and 24 ± 5.79 min in Study 2. These values were both significantly longer than times to peak ethanol concentration ($P < 0.005$).

Serum prolactin increased following the administration of metoclopramide to a mean peak at 30 min of 59 ± 5.8 μg/l. After placebo prolactin remained relatively constant between 5 and 10 μg/l. A plot of increase in serum prolactin from mean placebo concentration against plasma metoclopramide concentration revealed a linear relationship (Figure 6) r = 0.806.

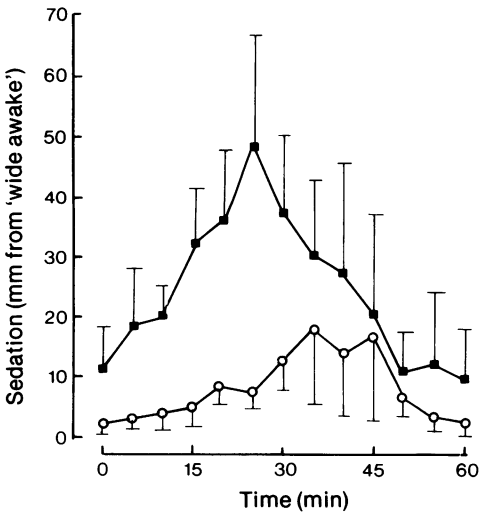

Figure 5 Study 2: Sedation (mean ± s.e. mean, n = 7) ○ placebo; ■ metoclopramide.

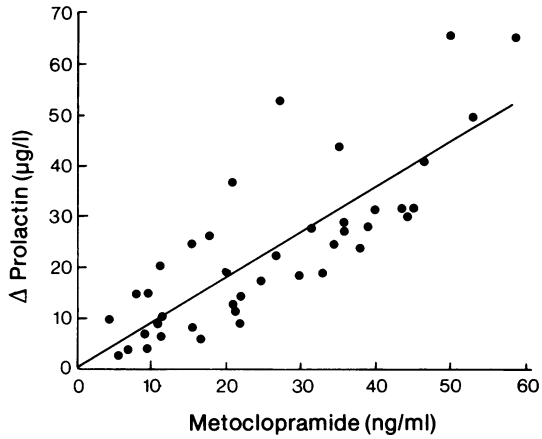

Figure 6 Relationship between plasma metoclopramide and increase in serum prolactin concentration. $n = 6$, $r = 0.806$, $y = 0.8943x + 0.345$.

There was no apparent drug effect on gastric intercontraction interval during Study 1. In Study 2 there was a small but significant decrease in gastric intercontraction intervals ($P < 0.05$) after metoclopramide. The overall pattern of response of gastric contractions to the liquid meal did not appear to be altered by metoclopramide (Figure 7).

The results of the pharmacokinetic analyses are shown in Table 2. The mean half-life of the distribution phase ($T_{\frac{1}{2}}\alpha$) was 4.9 ± 1.11 min. The mean half-life of the elimination phase ($T_{\frac{1}{2}}\beta$) was 165.7 ± 20.15 min. Mean total body plasma clearance was 10.89 ± 1.46 ml min^{-1} kg^{-1}. Free and conjugated metoclopramide excretion in urine was measured over 36 h. The total of free and conjugated metoclopramide excreted accounts for a mean of 43% of the dose (Table 3).

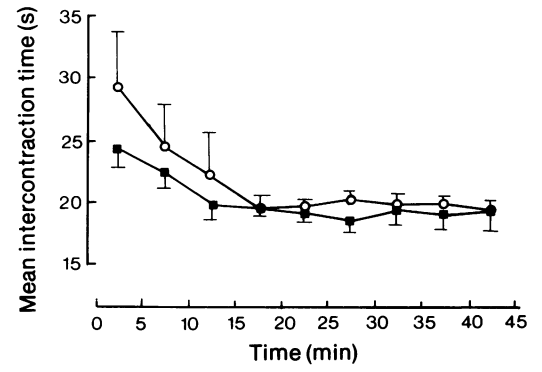

Figure 7 Study 2: Gastric intercontraction times (mean ± s.e. mean, n = 5) ○ placebo; ■ metoclopramide.

Table 2 Two compartment disposition constants for metoclopramide following intravenous administration

Subject	α (min^{-1})	$T_{\frac{1}{2}}\alpha$ (min)	β (min^{-1})	$T_{\frac{1}{2}}\beta$ (min)	K_{12} (min^{-1})	K_{21} (min^{-1})	K_{10} (min^{-1})	V_1 (ml/kg)	V_dss (ml/kg)	Cl (ml min^{-1} kg^{-1})
1	0.596	1.2	0.0058	120.2	0.469	0.098	0.035	493.2	2849.3	17.28
2	0.176	3.9	0.0056	123.4	0.102	0.015	0.065	223.1	1707.7	14.40
3	0.190	3.7	0.0051	136.6	0.119	0.060	0.016	583.0	1736.2	9.35
4	0.163	4.3	0.0047	148.9	0.092	0.064	0.012	1019.0	2498.9	12.17
5	0.075	9.3	0.0027	260.5	0.042	0.028	0.007	1025.2	2587.6	7.32
6	0.081	8.6	0.0046	151.2	0.035	0.041	0.009	950.8	1765.2	8.56
7	0.197	3.5	0.003	219.2	0.135	0.054	0.012	611.4	2159.2	7.13
Mean	0.211	4.9	0.0045	165.7	0.142	0.051	0.022	700.8	2186.3	10.89
s.e. mean	0.067	1.11	0.0005	20.15	0.056	0.01	0.008	115.69	176.48	1.46

Discussion

The pharmacokinetic data (Table 2) are derived assuming a two compartment open pharmacokinetic model. There is an initial rapid fall in plasma concentration ($T_{\frac{1}{2}}\alpha$ – 4.9 min) showing that metoclopramide is rapidly distributed in the body as would be expected with a lipid soluble, basic drug. The high mean volume of distribution at steady state (V_dss = 2186.3 ml kg) indicates extensive extravascular dis tribution of the drug.

The terminal half-life is relatively short ($T_{\frac{1}{2}}\beta$ = 165.7 min) and the value of the total body plasma clearance (Cl = 10.89 ml min^{-1} kg^{-1}) is high, being similar to liver plasma flow. If the drug is largely cleared by metabolism in the liver, one would expect to see an extensive 'first pass' effect and a reduced systemic bioavailability of motoclopramide given orally. We are investigating this aspect further.

In the three subjects in whom urinary excretion was measured, it was possible to account for less than half the dose as free and conjugated motoclopramide (Table 3), less than 20% of the dose was excreted unchanged. Metoclopramide therefore probably undergoes metabolism other than conjugation in man as has been described in laboratory animals (Bakke & Segura, 1976; Cowan, Huizing & Beckett, 1976).

The duration of action of metoclopramide is in doubt, and has been variously reported as less than 10 min (Eisner, 1971) and between 12 and 24 h (Klein, Militello & Ballinger, 1968) depending on route of administration and effect studied. In addition, the effect of the drug on gastric emptying is not apparent under some test conditions in normals (Ramsbottom & Hunt, 1970) but clear in others (Kreel *et al.*, 1972).

Table 3 Total urinary excretion of free and conjugated metoclopramide to 36 h

Subject	*Metoclopramide (mg)* *Free*	*Conjugated*	*Total*
1	1.035	2.989	4.024
2	1.408	2.229	3.637
3	1.156	2.799	3.955

The measurement of drug (Heading, Nimmo, Prescott & Tothill, 1973) or ethanol (Finch, Kendall & Mitchard, 1974; Gibbons & Lant, 1975) absorption is an index of gastric emptying rate. We have used ethanol absorption as a method of measuring gastric emptying. This appears to be reproducible, mean time to peak being 20.71 min in both placebo studies (Table 1). This is more rapid than in other reported studies (Finch *et al.*, 1974). It may reflect the effect of a warm fluid (Bateman *et al.*, 1977) or the low dose of ethanol used. Ethanol has a direct inhibitory action on gastric motility (Barboriak & Meade, 1970).

The time to peak ethanol concentration was significantly reduced by metoclopramide to 11.79 min immediately and 13.04 min at 3 h after an intravenous dose (Table 1). The plasma metoclopramide concentrations at these times were in excess of 100 ng/ml and 21 ± 2.47 ng/ml respectively. These results are suggestive of a relationship between plasma concentration of metoclopramide and an effect on gastric emptying.

The mechanism of the action of metoclopramide in increasing gastric emptying is in doubt. It has been suggested that the amplitude and rate (Eisner, 1971; Johnson, 1973) of contractions in the stomach may be altered by the drug. In addition, it is claimed that synchronization of gastric antral and duodenal contraction waves may occur (Johnson, 1973).

The rate of contraction of the gastric antrum was monitored by means of ultrasound pulse-echo scanning during each alcohol absorption study. A warm fluid meal produces a biphasic gastric response with initial less frequent contractions and then a gradual increase until at about 10 min regular gastric contractions are seen approximately every 20 sec (Bateman *et al.*, 1977).

There was no change in gastric contraction frequency during the first absorption study. However, at 3 h there was a small but statistically significant increase in gastric frequency, particularly during the early phase of the meal (Figure 7). As gastric empty-

ing rate, as measured by ethanol absorption, was slower than during Study 1, this suggests that the frequency of gastric contraction is of little importance in the rate of emptying of liquid from the stomach.

Metoclopramide and ethanol have not been reported as synergistic in producing sedation. The sedation we observed is surprising considering the low dose of ethanol given and the fact that peak plasma concentrations of ethanol were low (Study 1 = 12.69 ± 3.37 mg% Study 2 = 11.31 ± 3.56 mg%). Sedation has been reported following ethanol and chlorpromazine (Zirkle, King, McAtee & van Dyke, 1959), which also blocks dopamine receptors. The mode of interaction with ethanol is not clear. Our results demonstrate such an interaction for metoclopramide which appears to be related to the plasma concentration of the drug, sedation being more marked during Study 1 ($P0.05 > 0.01$) and mean peak ethanol concentrations being not statistically different between the two study periods.

Metoclopramide stimulates release of prolactin (McNeilly, Thomas, Volans & Besser, 1974) probably by blocking the normal prolactin inhibiting factor (PIF) which is known to be dopamine, and indeed the action of metoclopramide on this system is blocked by levodopa (Judd, Lazarus & Smythe, 1976; McCallum, Sowers, Hershman & Sturdevant, 1976). Our results relating decline in plasma metoclopramide to the level of prolactin suggests that the drugs effect on prolactin release by the pituitary is related to plasma concentration. However this needs to be confirmed using graded doses of metoclopramide.

Conclusions

We have measured the plasma concentration of metoclopramide after i.v. dosing and assessed the pharmacological activity of the drug in man. It would appear that there is a relationship between the plasma concentration of the drug and the increase in serum prolactin it produces. In addition, the effect of the drug on gastric emptying and the interaction between ethanol and metoclopramide in producing sedation would also appear to be related to the plasma metoclopramide level.

The plasma concentration-time curve for the drug is compatible with a two compartment pharmacokinetic model and appropriate rate constants have been calculated.

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