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Single-Dose Pharmacokinetics of Metoclopramide

L. M. Ross-Lee, M. J. Eadie, W. D. Hooper, and F. Bochner

Department of Medicine, University of Queensland, Clinical Sciences Building, Royal Brisbane Hospital, Brisbane, Queensland, Australia

Summary. The time courses of plasma metoclopramide concentrations were followed in six subjects after oral and intravenous single dose administration. Plasma concentration-time data following i. v. administration in each subject were found to fit a two compartment model with a mean terminal half-life of 4.55 h ± 0.80 h and a mean distribution half-time of 0.35 h ± 0.09 h. Volumes of distribution were high (3.43 ± 1.18 l · kg^{-1}), and clearances (0.53 ± 0.19 l · kg^{-1}h^{-1}) approached liver plasma flow. This suggests that metoclopramide occurs at higher concentrations in tissues than in plasma, and that its clearance is probably limited by liver blood flow rather than liver metabolic capacity. The post-absorption decline in metoclopramide plasma levels after oral administration was also biexponential in each subject. The terminal half-life was 5.17 h ± 0.98 h. Mean volume of distribution and mean clearance were similar to intravenous values (after adjustment for bioavailability). Oral absorption was rapid with peak plasma concentrations being reached at a mean time of 0.93 h. A mean bioavailability of 0.77 was calculated for the six subjects, and it was postulated that this incomplete availability is due to a first-pass effect. The inter-individual variation in the degree of 'first-pass' was considerable (0.47–1.14).

Key words: metoclopramide; pharmacokinetics, bioavailability, first-pass effect

Metoclopramide (Maxolon) i. e. 4-amino-5-chloro-N-(2-diethyl-aminoethyl)-2-methoxybenzamide (Fig. 1) is a potent anti-emetic and alimentary antispasmodic agent, structurally related to procainamide. Though metoclopramide has been available for clinical use for over ten years, and many clinical trials have been conducted (Matts 1974; McCallum et al. 1977) very little work has been published on the pharmacokinetics of the drug in man.

Animal studies on metoclopramide have been carried out by means of spectrophotometric and thin layer chromatographic assays (Arita et al. 1970; Bakke and Segura 1976). However these analytical techniques suffer from a lack of sensitivity in the nanogram range required for human work, or from lack of specificity towards structurally related compounds.

To study the pharmacokinetics of metoclopramide in man, we developed an original electron-capture gas chromatographic assay for the drug in plasma (Ross-Lee et al. 1980). Concentrations over the range 0–200 μg · l^{-1} could be measured using 1.0 ml sampling volumes, and no interference from related drugs has been observed. This assay provided sufficient sensitivity and specificity for pharmacokinetic studies of metoclopramide.

Similar studies of the single dose pharmacokinetics of metoclopramide have been reported (Bateman et al. 1978, 1979; Graffner et al. 1979). Of particular interest to us however, was the low bioavailability of orally administered metoclopramide compared with an equivalent intravenous dose. We wished to establish if poor absorption, or a first-pass effect, or both, were responsible. The collection of blood samples at

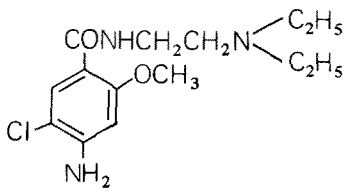

Fig. 1. The chemical structure of metoclopramide

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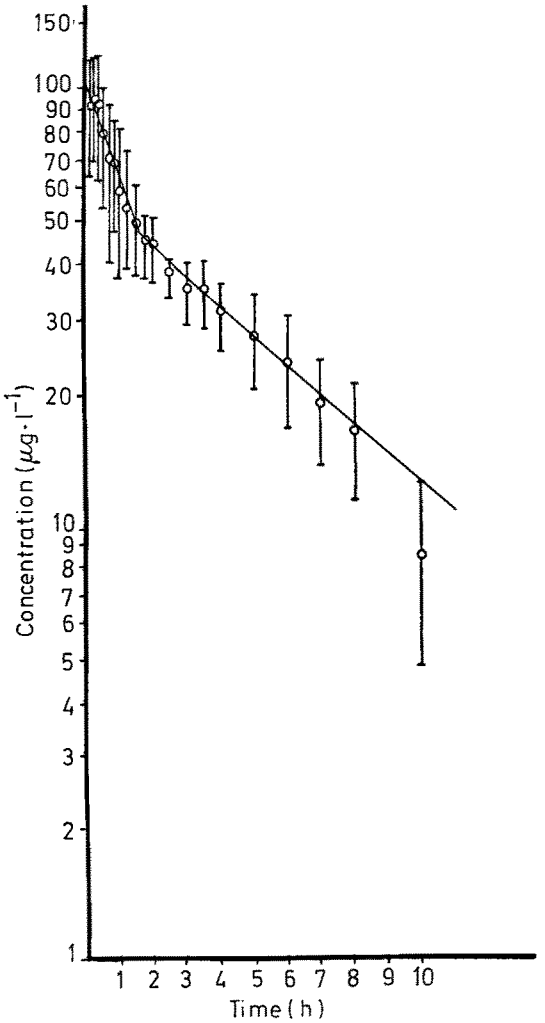

Fig. 2. Metoclopramide plasma concentration ($\mu g \cdot l^{-1}$) at various times after i. v. administration to six subjects
o = mean concentration (± SD)

frequent intervals, especially in the first hour after dosing, allowed us to calculate accurately, an absorption rate constant following oral administration and to determine the cause of the low oral bioavailability of metoclopramide.

Materials and Methods

Pharmacokinetic studies were carried out in six subjects. All were apparently healthy adult volunteers, ranging in age from 22 to 39 years. Four were female and two male. No subject was taking any drug therapy on a regular basis, or at the time of the metoclopramide studies.

Each subject was given a 10 mg dose of metoclopramide hydrochloride after an overnight fast, on one occasion as an oral, and on the other as an intravenous formulation (Maxolon – Beecham Research Laboratories). The order of administration of the preparations was randomised. An interval of at least one week separated the administration of the two dosage forms in each subject. An indwelling teflon cannula in an ante-cubital vein was used to collect 10 ml blood samples, the first prior to dosing, and the others taken at the following times after dosing: 0.08 h, 0.16 h, 0.33 h, 0.50 h, 0.67 h, 0.83 h, 1.00 h, 1.25 h, 1.50 h, 1.75 h, 2.00 h, 2.50 h, 3.00 h, 3.50 h, 4.00 h, 5.00 h, 6.00 h, 7.00 h, 8.00 h, 10.00 h, and 24.00 h. Samples were centrifuged immediately and the plasma removed and stored at −20 °C prior to analysis.

Plasma metoclopramide levels were measured by electron-capture gas chromatography (Ross-Lee et al. 1980). Plasma concentration data so obtained were adequately represented by the models:

$C_t = Ae^{-\alpha t} + Be^{-\beta t}$, after i. v. administration
and $C_t = Ae^{-\alpha(t-t1)} + Be^{-\beta(t-t1)} - Ce^{-\gamma(t-t1)}$
after oral administration, where

C_t = plasma concentration at time t
A, B, C = coefficients of the distribution, elimination and absorption terms respectively
α, β, γ = rate constants describing the rate of distribution, elimination and absorption respectively
and t1 = absorption lag time.

Estimates of the coefficients and exponents were obtained for each subject for both routes of administration:

(i) by visual observation (Gibaldi and Perrier 1975) then refinement of these estimates using the program MLAB (run on a PDP 10 computer);

(ii) using the iterative procedure C-STRIP (Sedman and Wagner 1976) run on a PDP11/34 computer. Once again estimates were further refined with MLAB. (Knott 1979)

The estimates of the former method resulted in a better data fit than did those of the latter (as evidenced by reduction in Root Mean Square [RMS] error). Hence they were used to calculate the following pharmacokinetic parameters (Gibaldi and Perrier 1975).

$t_{1/2}\beta = 0.693/\beta$ (1)
$t_{1/2}\alpha = 0.693/\alpha$ (2)
$t_{1/2}\gamma = 0.693/\gamma$ (3)
Area Under Curve $(AUC)_0^{\infty} = AUC_0^{t} + AUC_t^{\infty}$
where AUC_0^{t} was calculated by trapezoidal rule integration (HP1018A desk calculator)
and $AUC_t^{\infty} = c_t/\beta$ (Gibaldi and Perrier 1975) (4)
F = bioavailabilty

$$= \frac{AUC_0^{\infty}\ \text{ORAL}}{AUC_0^{\infty}\ \text{i.v.}} \text{ in the same subject} \quad (5)$$

Vd = apparent volume of distribution

$$= \frac{\text{dose}}{\beta \cdot AUC_0^{\infty}} \text{ for i. v. administration} \quad (6A)$$

$$\text{or } = \frac{F \cdot \text{dose}}{\beta \cdot AUC_0^{\infty}} \text{ for oral administration,} \quad (6B)$$

Cl_p = plasma clearance

$$= \beta \cdot Vd \quad (7)$$

Pharmacokinetic parameters so obtained were analysed statistically using Student's t-test (comparison of two means).

Results

Semilogarithmic plots of metoclopramide plasma concentrations against time in the six volunteers are shown in Fig. 2 (i. v. administration) and Fig. 3 (oral administration). Pharmacokinetic parameters related to both i. v. and oral administration are set out in Tables 1 und 2 respectively.

Following intravenous administration, metoclopramide concentrations of 72.4 $\mu g \cdot l^{-1}$ to 126 $\mu g \cdot l^{-1}$ were measured 5 min after dosing. The subsequent decline in plasma concentration was biexponential in all subjects. The initial distribution (α) phase was reasonably rapid ($t_{1/2}$ = 0.35 h ± 0.09 h) while the terminal part of the plasma level curve had a half-life of 4.55 h ± 0.80 h. No metoclopramide could be detected in plasma 24 h after dosage. The apparent volume of distribution was high (3.43 $l \cdot kg^{-1}$ ± 1.18 $l \cdot kg^{-1}$) as was the clearance (0.53 ± 0.19 $l \cdot kg^{-1}h^{-1}$). AUC_0^{∞} ranged from 196 to 455 $\mu g \cdot l^{-1} \cdot h$. A large interindividual variation in parameters was observed over the six subjects. This is reflected in the magnitude of the SD's around the means in the plasma concentration versus time plot, and in the pharmacokinetic parameters.

The time courses of plasma concentrations of metoclopramide after oral administration in six subjects are shown in Fig. 3. The drug was detected in plasma within five minutes of dosing and reached peak concentrations between 0.5 h and 1.25 h.

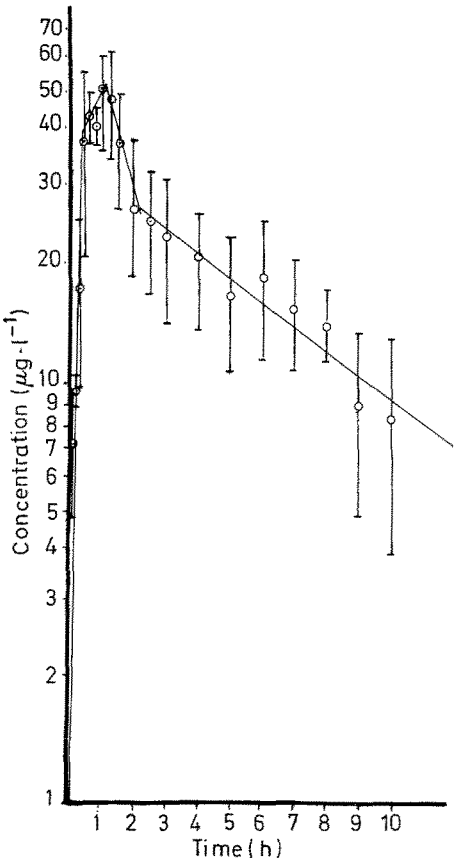

Fig. 3. Metoclopramide plasma concentration ($\mu g \cdot l^{-1}$) at various times after oral administration to six subjects
○ = mean concentration (± SD)

Table 1. Summary of pharmacokinetic parameters following 10 mg intravenous dose of metoclopramide in six subjects

Subject	Weight [kg]	Dose [$\mu g \cdot kg^{-1}$]	β [h^{-1}]	$t_{1/2\beta}$ [h]	$t_{1/2\alpha}$ [h]	AUC [$\mu g l^{-1} \cdot h$]	Vd [$l \cdot kg^{-1}$]	Cl [$l \cdot kg^{-1}h^{-1}$]
1	60.0	166.7	0.187	3.71	0.18	284.9	3.13	0.585
2	49.5	202.0	0.161	4.30	0.35	340.7	3.68	0.593
3	60.0	166.7	0.151	4.59	0.40	196.2	5.63	0.850
4	69.0	144.9	0.163	4.25	0.40	385.5	2.31	0.376
5	58.5	170.9	0.158	4.39	0.37	418.3	2.59	0.409
6	60.0	166.7	0.114	6.08	0.40	455.5	3.21	0.366
Mean	59.5	169.7	0.156	4.55	0.35	346.9	3.43	0.530
SD	6.2	18.4	0.024	0.80	0.09	94.8	1.18	0.187

Table 2. Summary of pharmacokinetic parameters following 10 mg oral dose of metoclopramide in six subjects

Subject	Weight [kg]	Dose [$\mu g \cdot kg^{-1}$]	β [h^{-1}]	$t_{½\beta}$ [h]	$t_{½\alpha}$ [h]	$t_{½\gamma}$ [h]	AUC [$\mu g l^{-1} h$]	Vd [$l \cdot kg^{-1}$]	Cl [$l \cdot kg^{-1} h^{-1}$]	C_{max} [$\mu g l^{-1}$]	t_{max} [h]	Bioavailability
1	60.0	166.7	0.168	4.13	0.76	0.40	160.1	3.48	0.585	45.1	1.00	0.56
2	49.5	202.0	0.108	6.42	0.40	–[a]	158.7	5.49	0.593	63.3	0.50	0.47
3	60.0	166.7	0.125	5.54	1.00	0.40	223.3	6.80	0.850	42.2	1.07	1.14
4	69.0	144.9	0.122	5.68	0.80	0.40	334.9	3.08	0.376	51.1	0.72	0.87
5	58.5	170.9	0.180	3.85	0.40	0.35	354.7	2.27	0.409	60.9	1.03	0.85
6	60.0	166.7	0.128	5.41	0.43	0.25	343.7	2.86	0.366	62.9	1.25	0.76
Mean	59.5	169.7	0.139	5.17	0.63	0.36	262.6	4.00	0.530	54.3	0.93	0.77
SD	6.2	18.4	0.029	0.98	0.26	0.07	92.9	1.76	0.187	9.4	0.27	0.24

[a] Insufficient data prior to C_{max}

Table 3. Comparison of observed and calculated bioavailability in six subjects

Subject	F_{obs}	F_{calc}[a]
1	0.562	0.779
2	0.466	0.806
3	1.138	0.714
4	0.869	0.824
5	0.848	0.835
6	0.755	0.846
Mean	0.773	0.801
SD	0.240	0.049

[a] Refer equations (8) and (9)

Absorption half-times ranged from 0.25 h to 0.40 h (mean 0.36 h ± 0.07 h); hence absorption was virtually complete within 1.5 h. The mean peak plasma concentration was 54.3 $\mu g \cdot l^{-1}$ (± 9.4 $\mu g \cdot l^{-1}$) at about one hour. After peak concentrations were reached, the disappearance of the drug was biexponential in each subject. After ten hours, a mean concentration of 8.3 $\mu g \cdot l^{-1}$ was measured in plasma; after 24 h, no drug could be detected. The mean distribution half-time was 0.63 h ± 0.26 h while the mean elimination half-life was 5.17 h ± 0.98 h. The apparent volume of distribution ranged from 2.7 to 11.8 $l \cdot kg^{-1}$ (mean 5.7 ± 3.3 $l \cdot kg^{-1}$) and clearance from 0.43 to 1.27 $l \cdot kg^{-1} \cdot h^{-1}$ (mean 0.74 ± 0.35 $l \cdot kg^{-1}\ h^{-1}$). Mean bioavailability calculated from the oral and intravenous AUC_0^∞ ratios was 0.77. After adjustment for bioavailability, volumes of distribution were still slightly higher by the oral route (4.00 $l \cdot kg^{-1}$) than by the intravenous, though the difference was not statistically significant ($P > 0.2$). Area Under Curve (extrapolated to infinity) was 262.6 ± 92.9 $\mu g \cdot l^{-1} h$. Once again, large inter-individual variations were seen between the six subjects.

Using these results, the cause of the low bioavailability of orally administered metoclopramide was determined. Assuming that: (1) a 10 mg oral dose of metoclopramide is completely absorbed from the gastrointestinal tract; (2) approximately 20% of the i. v. dose is excreted unchanged (Graffner et al. 1979); and (3) the ratio of drug in plasma to drug in erythrocytes is approximately 1.00 over the range of plasma concentrations encountered in this study (Ross-Lee, unpublished observation), then the fraction of the dose metabolized during the first passage through the liver, f_m, can be predicted by the equation (Chiou 1975):

$$f_m = \frac{(F_m)\,\text{dose}}{\text{dose} + (\text{HFR})\,(AUC_0^\infty)} \tag{8}$$

where

F_m = fraction of the administered dose metabolized at infinite time (here, 0.8)

HFR = hepatic blood flow rate (taken as 1.53 $l \cdot min^{-1}$)

and

AUC_0^∞ = total area under the plasma concentration-time curve after i. v. administration

Hence $F_{calc} = 1 - f_m$ (9)

where

F_{calc} = 'expected' bioavailability.

This calculation was performed for each of the six subjects. The results are set out in Table 3, together with the observed availability for each subject. The mean observed value was 0.77 ± 0.24 (SD) while the expected value of F (F_{calc}) was 0.80 ± 0.05 (SD).

There is no significant difference between these results ($P > 0.35$) which supports the hypothesis that a first-pass effect is operative when metoclopramide is administered orally.

All subjects experienced unwanted effects, though in varying degrees. All six volunteers felt drowsy at about 1 h after i. v. dosing, and two complained of restlessness and irritability over the period of i. v. infusion. Three subjects were still mildly sedated at 3 to 4 h post administration. Correlating these side effects with plasma concentrations, sedation was evident at a mean plasma concentration of 60 $\mu g \cdot l^{-1}$, and restlessness at concentrations in excess of 90 $\mu g \cdot l^{-1}$. Both these effects occurred during the distribution phase of the drug. Three subjects also felt drowsy 1–2 h after oral administration. This drowsiness occurred at the times of peak plasma levels in each subject (range 45.1 $\mu g \cdot l^{-1}$ to 63.3 $\mu g \cdot l^{-1}$).

The shapes of both the oral and intravenous plasma concentration-time profiles were characterized by minor 'peaks' in the post distribution phase. After oral dosing, a smaller peak prior to C_{max} also was evident in two of the subjects. Consequently, the fitting of the data to a biexponential or triexponential model using an iterative procedure (C-STRIP) was not ideal. As mentioned earlier, a better fit was obtained using visually determined estimates and refining these using M-LAB. An indication of the goodness of fit of this procedure is given in Fig. 4 which illustrates the deviation of plasma concentration (calculated) from plasma concentration (observed) in one subject after both oral and intravenous administration.

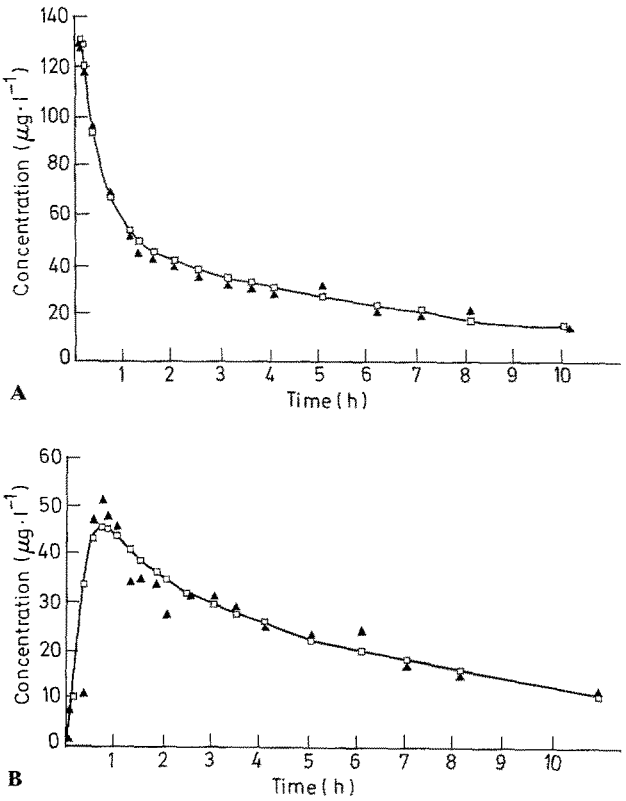

Fig. 4 A and B. Metoclopramide plasma levels in one subject at various times after **A** 10 mg i. v. and **B** 10 mg orally
▲ = measured values □ = computer adaptation

Discussion

This study proposed to investigate the pharmacokinetics of metoclopramide in man after single dose administration of the drug orally and intravenously. Of particular interest to us was the cause of the low oral bioavailability of the drug.

Early studies on metoclopramide kinetics were carried out in animals, using spectrophotometric and thin-layer chromatographic assays. Bakke and Segura (1976) found that there was little interspecies variation in pharmacokinetic parameters following intravenous administration of metoclopramide in the rat, rabbit and dog. The elimination was first-order with a half-life of 20–30 min. Orally, however, high doses of metoclopramide gave rise to a significant interspecies variation in the parameters.

Tam and Axelson (1978) studied the kinetics of metoclopramide in the rat using an electron capture-gas chromatographic technique, and found distinct distribution and elimination phases ($t_{½}$ = 50 min for the terminal elimination phase).

In this study the pharmacokinetics of a 10 mg dose of metoclopramide administered by either route is adequately described by a two-compartment model. The mean volume of distribution was high, and clearances approached liver plasma flow. Absorption by the oral route was rapid.

The route of administration appears to affect the disposition kinetics of metoclopramide. A change from intravenous to oral administration is associated with changes in several pharmacokinetic parameters. The elimination half-time was slightly longer (4.55 h to 5.17 h) after oral administration, as was the distribution half-time (0.35 h to 0.63 h). Area Under Curve (AUC) is reduced by roughly 30% following an oral dose of metoclopramide; as well, volumes of distribution and clearance were higher by this route, until adjusted for bioavailability.

The findings are in reasonable agreement with the results of other workers. Davies and Dollery (personal communication 1977) developed a mass fragmentographic assay to study metoclopramide kinetics in man; they reported an average elimination half-life of 4–6 h and a high volume of distribution (2.4 $l \cdot kg^{-1}$) after intravenous single dose adminis-

tration. Teng et al. (1977), using a UV-HPLC method, confirmed the short elimination half-time reported by Davies and Dollery (1977). Graffner et al. (1979) used a HPLC technique to quantitate plasma metoclopramide levels after i. v. and oral dosing, and found a rapid distribution value (6.3 min) and short elimination half-life (4. 9 h) and a mean volume of distribution of $3.0\,l \cdot kg^{-1}$. Bateman et al. (1978, 1979) obtained similar results. In the present study, however, the distribution half-time of the drug was higher than reported previously [0.35 h for i. v. administration as opposed to approximately 5 min reported by Bateman et al. (1979) and Graffner et al. (1979)]. Also, a mean value for absorption half time (0.36 h ± 0.07 h) was calculated in this study. This parameter has not been reported previously.

The reduced amount of metoclopramide available to the systemic circulation following oral administration has been reported by other workers (Graffner et al. 1979; Bateman et al. 1979) and is believed to be due to 'first-pass' metabolism rather than poor absorption in view of the comparatively high intravenous clearance value. This low oral bioavailability has been shown in this study to be caused by a first-pass effect, which reduces the amount of drug available to the systemic circulation by up to 53%. The added complication of a high interindividual variation in the degree of 'first-pass' makes metoclopramide difficult to use orally.

Two of the subjects (1 and 2) exhibited a much lower bioavailability than expected. In their cases, absorption may not have been complete. It is possible that the enhancement of gastric motility by metoclopramide may have been sufficiently large in these two subjects to actually limit the amount of drug available for absorption, that is, the gastrointestinal action of metoclopramide may have a limiting effect on the amount of drug absorbed in certain subjects.

Even though 80% of a metoclopramide dose is metabolized, relatively few workers have set out to establish a metabolic pathway for the drug. Arita et al. (1970), working with rabbits, found evidence of metoclopramide conjugates (principally N^4-glucuronide and N^4-sulphonate) as well as unchanged metoclopramide in the urine. As well, minor amounts of oxidative and dealkylated products were present. Bakke and Segura (1976) found that, as in man, the liver played an important role in reducing the systemic availability of metoclopramide in the rat, rabbit and dog. Once again, the major routes of metabolism appeared to be N-dealkylation and conjugation. Beckett and Huizing (1975) studied the metabolism of metoclopramide using in vitro incubation techniques and found eight transformation products, two of which were positively identified as the mono- and di-dealkylated derivatives. Teng et al. (1977) investigated the urinary excretion products of metoclopramide in rats, dogs and man, and found eight metabolites in all. N-de-ethylation proved a major pathway for metoclopramide in the lower animals but could not be detected in humans. They concluded that metoclopramide is excreted mainly unchanged, or as conjugates of the otherwise intact molecule, in man.

The first-pass effect following oral administration of metoclopramide may contribute to the large interindividual variation observed in certain pharmacokinetic parameters. The scatter around the mean values of these parameters was larger when metoclopramide was administered orally, than when given intravenously (Tables 1 and 2). This also tends to mask any significant difference in metoclopramide kinetics between the two routes of administration.

Secondary peaks were observed in the post-distribution phase in all subjects given metoclopramide orally. These peaks roughly correlate with the time of food intake following dosing. Increased blood supply to the gut wall at this time may have temporarily enhanced absorption (of the tablet) and resulted in these minor peaks.

Clinically the findings of this study imply that an oral metoclopramide dosage of 10 mg may be less reliable and less effective than the same dose given intravenously. This lessened efficiency of oral dosage is most likely due to first-pass metabolism among individuals. This causes an incomplete and variable bioavailability. The steady state kinetics of the drug after oral dosing have not been studied yet and may yield further insights into the human body's handling of metoclopramide.

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References

Arita T, Hori R, Ito K, Ichikawa K, Uesugi T (1970) Transformation and excretion of drugs in biological systems. II. Transformation of metoclopramide in rabbits. Chem Pharm Bull 18: 1663–1669

Bakke OM, Segura J (1976) The absorption and elimination of metoclopramide in three animal species. J Pharm Pharmacol 28: 32–39

Bateman DN, Kahn C, Mashiter K, Davies DS (1978) Pharmacokinetics and concentration effect studies with intravenous metoclopramide. Br J Clin Pharmacol 6: 401–407

Bateman DN, Kahn C, Davies DS (1979) Concentration effect studies with oral metoclopramide. Br J Clin Pharmacol 8: 179–182

Beckett AH, Huizing G (1975) In vitro metabolism of metoclopramide. J Pharm Pharmacol 27: (Suppl) 42P

Chiou WL (1975) Estimation of hepatic first-pass effect of acetaminophen in humans after oral administration. J Pharm Sci 64: 1734–1735

Gibaldi M, Perrier D (1975) Pharmacokinetics. Marcel Dekker, New York

Graffner C, Lagerstrom P, Lundborg P (1979) Pharmacokinetics of metoclopramide intravenously and orally determined by liquid chromatography. Br J Clin Pharmacol 8: 469–474

Knott GD (1979) MLAB – a mathematical modelling tool. Comput Programs Biomed, 10: 271–280

Matts SG (1974) Metoclopramide in the treatment of migraine. Practitioner 212: 887–890

McCallum RW, Ippoliti AF, Cooney C, Sturdevant RAL (1977) A double-blind trial of metoclopramide in symptomatic gastrooesophageal reflux. Gastroenterology 70: 354–357

Ross-Lee LM, Eadie MJ, Bochner F, Hooper WD, Tyrer JH (1980) Electron capture gas chromatographic assay for metoclopramide in plasma. J Chromatogr 183: 175–184

Sedman AJ, Wagner JG (1976) C-STRIP, a Fortran IV computer program for obtaining initial polyexponential parameter estimates. J Pharm Sci 65: 1006–1010

Tam YK, Axelson R (1978) Sensitive electron-capture GLC determination of metoclopramide in biological fluids. J Pharm Sci 67: 1073–1077

Teng L, Bruce R, Dunning L (1977) Metoclopramide metabolism, and determination by high pressure liquid chromatography. J Pharm Sci 66: 1615–1618

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Mrs. L. Ross-Lee
Department of Medicine
University of Queensland
Clinical Sciences Building
Royal Brisbane Hospital
Brisbane, Queensland
Australia, 4029