Linearity of metoclopramide kinetics at doses of 5–20 mg

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The disposition of metoclopramide was studied on a four-way crossover basis in six healthy non-smoking volunteers. The linearity of kinetic parameters and absolute bioavailability of metoclopramide were examined. In contrast to previous reports, metoclopramide obeyed linear kinetics over oral doses ranging from 5 to 20 mg. The absolute bioavailability of metoclopramide was 0.76 ± 0.38 (mean $\pm$ s.d.) from the oral dosage forms examined in this study.

Keywords metoclopramide absolute bioavailability dose-linearity pharmacokinetics

Introduction

Metoclopramide is commonly used in the treatment of nausea and vomiting of various aetiologies (Jones, 1968; Homesley *et al.*, 1982) and to reduce the incidence of the aspiration of gastric contents associated with general anaesthesia (Howard & Sharp, 1973). Despite its widespread use, uncertainty remains as to the dose-linearity of metoclopramide kinetics at low doses (5–20 mg), its absolute bioavailability and the extent of its first-pass metabolism.

There has been suggestion of dose-dependent elimination in man with i.v. and oral doses from 5–20 mg (Graffner *et al.*, 1979; Bateman *et al.*, 1980; Bateman, 1983). This finding has been widely reported and is included in common clinical references consulted by both physicians and pharmacists (USPDI, 1984). In contrast to the purported dose-dependency of metoclopramide after such low doses, the high doses (~ 1 – 2 mg kg⁻¹) used in the prophylaxis of emesis associated with cancer chemotherapy (Taylor *et al.*, 1984; Saller *et al.*, 1985; Bryson *et al.*, 1985) and doses from 20 to 100 mg (Wright *et al.*, 1984)

failed to elicit similar evidence of nonlinear elimination. Specifically, these latter investigations demonstrated an apparent proportional increase in AUC with increasing dose (Wright *et al.*, 1984) with no evidence of dose-dependent changes in either total clearance or elimination half-life (Wright *et al.*, 1984; Bryson *et al.*, 1985). The apparently conflicting evidence, that metoclopramide disposition displays dose-dependency in low doses, with no evidence of this occurring at much higher doses in man, required reevaluation. It appeared that there may have been several experimental reasons for the possibly erroneous conclusions drawn in the literature, pertaining to the claimed dose-dependent elimination and the precise extent of bioavailability of metoclopramide. More specifically, in many earlier studies the relatively insensitive assay procedures used allowed metoclopramide to be measured in plasma for only a relatively short period of time (6–8 h) (Bateman *et al.*, 1980; Graffner *et al.*, 1979). Truncation of the sampling interval in pharmacokinetic studies has long

been known to produce underestimates of the elimination half-life (Gibaldi & Weintraub, 1971). In the studies making claims for dose-dependent elimination of metoclopramide (Bateman *et al.*, 1980; Graffner *et al.*, 1979) the only evidence presented for dose-dependency was an apparent increase in terminal elimination half-life with increasing dose. It is quite possible that these apparent changes were, in fact, artifactual and created by the limited sensitivity of the assay methods used. Furthermore, many attempts to examine the bioavailability of metoclopramide (Block *et al.*, 1979; Schuppan *et al.*, 1979; Graffner *et al.*, 1979; Bateman *et al.*, 1980) used unequal intravenous and oral dosages of metoclopramide, which, in view of the uncertainty regarding the dose-linearity of kinetics seemed inappropriate. Finally, several groups had tried to approximate the relative bioavailability of metoclopramide using an oral tablet as the oral reference dosage form (Schuppan *et al.*, 1979; Graffner *et al.*, 1979; Bateman *et al.*, 1980; Ross-Lee *et al.*, 1981), which may have confused the interpretation of the extent of first-pass metabolism.

The objectives of this investigation, therefore, were: a) to examine the linearity of metoclopramide kinetics at low doses (5–20 mg) in normal healthy human subjects and, b) to establish the absolute bioavailability of metoclopramide.

Methods

Six normal, healthy (as judged by physical and biochemical/haematological examinations) non-smoking males, well matched for age and weight participated in this study after giving written informed consent. The protocol received the approval of the Human Ethics Committee of the University of British Columbia. All subjects were fasted for 12 h prior to drug administration and were not allowed food for a period of 4 h following drug administration. None was taking other medications and alcohol consumption was prohibited for 48 h prior to and during the study.

The study was conducted on a four-way cross-over basis with all patients receiving a 10 mg intravenous (i.v.) dose (Reglan Injectable®, A. H. Robins Canada, Inc., Montreal, Quebec, Canada) and a 5 and 20 mg dose of an oral solution of metoclopramide (Reglan®, A. H. Robins). Three patients received a 10 mg dose of the metoclopramide oral solution while the other three patients received a 10 mg oral dose of metoclopramide in tablet form (Reglan®, A. H. Robins). All drug administrations were

separated by a period of at least 1 week to allow for complete drug washout. On each study day, an indwelling cannula (Butterfly®-19 INT, Venisystems, Abbott Ireland Ltd) was placed in a forearm vein prior to drug administration to facilitate blood sampling. A blank blood sample was taken and the patency of the cannula was maintained throughout the experiment using heparinized (50 u ml⁻¹) saline (~1 ml).

On the day of i.v. drug administration, a cannula was placed in the forearm vein contralateral to the arm containing the sampling cannula to allow drug administration. Blood samples (5 ml) were taken at 2, 4, 6, 10, 20, 40, and 60 min, and 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 48, and 72 h following i.v. dosing. Oral drug administration was accompanied by ~200 ml of water. Following oral drug administration, 5 ml blood samples were taken at 15, 30, 45, and 60 min, and 1.5, 2, 3, 5, 6, 8, 10, 12, 14, 16, 24, 48, and 72 h. Blood was drawn from the cannula into 10 ml glass Vacutainer® tubes containing lithium heparin (Vacutainer®, Vacutainer Systems, Rutherford N.J.). The plasma was separated by centrifugation, placed in fresh glass tubes (Pyrex®) with screw-on PTFE-lined caps, and frozen until analysis. Urine was collected, at hourly intervals for the first 12 h, and then up to 72 h. Collection of urine was made in plastic Whirl-pak® bags (Can-Lab, Richmond, B. C.), the volume and pH were measured immediately, and an aliquot of urine stored frozen until analysis. All samples were analysed by the gas-chromatographic assay method of Riggs *et al.* (1983) developed in our laboratory. The limit of detection of this assay method is about 2 ng ml⁻¹ from a 200 µl plasma sample, with a coefficient of variation <10% over the concentration range analyzed.

Initial estimates of the pharmacokinetic parameters of metoclopramide were obtained from plots of the plasma concentration vs time data. The concentration vs time data were then fitted by AUTOAN (Sedman & Wagner, 1976) to obtain estimates of the kinetic parameters and to permit assignment of a kinetic model. These initial estimates were then used by the computer program NONLIN (Metzler *et al.*, 1974) to yield final estimates of the kinetic parameters. Area under the plasma drug concentration vs time curve (AUC) values were estimated by the method of trapezoidal approximation. All kinetic calculations were based on the NONLIN generated parameters and the determined AUC values.

Statistical evaluations were performed using ANOVA analysis to compare mean values between groups (significance of $P < 0.05$, two-tailed).

The pharmacokinetic values of clearance, volume of distribution and bioavailability were based upon calculations described by Gibaldi & Perrier (1982).

Results

The kinetic data derived from the plasma and urine of the normal, healthy volunteers are

shown in Table 1. A representative set of plasma curves from a single volunteer, at all four dose levels, is given in Figure 1. The AUC increased linearly with an increase in dose (Table 1). The average bioavailability of metoclopramide, as determined from the urine and plasma data, was 0.76 ± 0.38 (mean $\pm$ s.d.) and showed no statistically significant change with changes in dose. The average total body clearance was $0.370 \pm 0.077 \text{ l h}^{-1} \text{ kg}^{-1}$ and was independent of dose.

Table 1 Metoclopramide kinetic parameters obtained from urine and plasma of healthy volunteers

Dose	5 mg solution	10 mg solution	10 mg tablet	20 mg solution	10 mg intravenous	
<i>n</i>	6	3	3	6	6	Mean $\pm$ sd
k_a (h^{-1})	3.21 ± 1.68	3.28 ± 2.71	2.78 ± 0.51	3.64 ± 1.93	—	3.29 ± 1.71
λ_1 (h^{-1})	0.6 ± 0.3	0.2	0.7	0.8 ± 0.3	7.3 ± 5.3	—*
λ_2 (h^{-1})	0.14 ± 0.06	0.14 ± 0.05	0.13 ± 0.04	0.14 ± 0.05	0.14 ± 0.06	0.14 ± 0.04
AUC ($\mu\text{g l}^{-1} \text{ h}$)	155.7 ± 111	427.9 ± 226	255.2 ± 41	608.0 ± 383	362.1 ± 66	—
CL^a ($\text{l h}^{-1} \text{ kg}^{-1}$)	0.37 ± 0.08	0.36 ± 0.12	0.38 ± 0.05	0.37 ± 0.08	0.37 ± 0.08	0.37 ± 0.08
V_{area} (l kg^{-1})	3.51 ± 1.49	3.87 ± 2.04	3.42 ± 0.75	3.29 ± 0.93	3.06 ± 1.58	3.38 ± 1.30
% dose excreted intact	16.4 ± 5.5	20.6 ± 0.4	11.7 ± 0.2	19.5 ± 4.7	29.7 ± 12.3	20.4 ± 9.3
CL_R^b ($\text{l h}^{-1} \text{ kg}^{-1}$)	0.11 ± 0.10	0.07 ± 0.03	0.06 ± 0.01	0.10 ± 0.03	0.11 ± 0.05	0.10 ± 0.06
<i>F</i>	0.73 ± 0.42	0.90 ± 0.28	0.73 ± 0.19	0.75 ± 0.39	—	0.76 ± 0.38

* Determined for those volunteers whose data were fitted by a biexponential function

a. CL is the total body clearance.

b. CL_R is the renal clearance.

Figure 1 Metoclopramide plasma concentration vs time profiles in a single healthy volunteer, 5 mg oral solution (○—○), 10 ml oral solution (□—□), 10 mg i.v. bolus (●—●), 20 mg oral solution (■—■).

Furthermore, the average value of the terminal elimination rate constant was $0.14 \pm 0.05 \text{ h}^{-1}$, as determined from the urine and plasma data. Calculation of the oral clearance (Dose/AUC) shows that this is larger than the total body clearance determined from an intravenous dose suggesting incomplete availability of the oral doses. The mean volume of distribution, as determined by the area method, was $3.38 \pm 1.30 \text{ l kg}^{-1}$ and appeared to be dose-independent. An average of $25 \pm 12\%$ of the oral dose of metoclopramide was excreted unchanged in the urine and the average renal clearance was $0.10 \pm 0.06 \text{ l h}^{-1} \text{ kg}^{-1}$, both of which remained constant with changing dose. The absorption rate constant, k_a , and λ_1 , the distribution rate constant, were estimated and were found to be highly variable but showed no evidence of dose-dependency.

There was no evidence of major side effects, including akathisia or dystonia, in any of the normal, healthy volunteers. Some volunteers did experience transient drowsiness and mild irritability shortly after intravenous drug administration.

Discussion

The results of this study indicate that, in normal subjects, metoclopramide shows dose-independent kinetics over the dose range studied (5–20 mg). Thus, there were no dose-dependent changes in metoclopramide total body clearance, terminal elimination half-life, volume of distribution or urinary recovery (see Table 1).

This contrasts with previous reports of dose-dependency over the same dose range (Bateman, 1983; Graffner *et al.*, 1979). However, in these studies relatively short (6–8 h) sampling periods were used. The relatively short sampling periods employed in these studies may have contributed to an underestimation of the elimination half-life at the lower doses examined (Gibaldi & Weintraub, 1971) and, hence, to inappropriate claims of dose-dependent elimination. Furthermore, no statistical evidence for dose-dependency was provided (Graffner *et al.*, 1979) so claims of dose-dependent elimination in this

study were made on the basis of apparent, observed changes in elimination half-life. Unfortunately, this proposed half-life change could be explained on the basis of the short sampling period employed and a resulting miss-estimate of this parameter. Our observation, in man, that metoclopramide does not undergo dose-dependent kinetics also contrasts with our findings in the rat (Tam *et al.*, 1981; Kapil *et al.*, 1984) where metoclopramide was noted to undergo non-linear kinetics. However, studies in cancer chemotherapy at doses greater than 0.5 mg kg^{-1} (Taylor *et al.*, 1984; Bryson *et al.*, 1985) and 20–100 mg (Wright *et al.*, 1984) are consistent with linear kinetics.

In the present investigation, we estimated both the absolute bioavailability ($F_{\text{absolute}} = 0.76 \pm 0.38$) and the relative availability ($F_{\text{relative}} = 1.2 \pm 0.25$) of metoclopramide. Although we cannot conclude with certainty, due to a small sample size, the relative bioavailability of metoclopramide, our results do appear to agree with that of Wright & Pitts (1984) where a relative bioavailability of ~ 1 was reported.

The renal clearance of metoclopramide accounts for about 25% of total body clearance, as pointed out previously (Bateman *et al.*, 1980; Graffner *et al.*, 1979). As noted earlier (Bateman, 1983), the volume of distribution of this drug appears to be relatively large ($V_{\text{area}} = 3.38 \pm 1.30 \text{ l kg}^{-1}$) suggesting extensive drug distribution outside the well-perfused body regions.

In summary, it can be stated that metoclopramide obeys linear kinetics at doses between 5 and 20 mg. Furthermore, there appears to be significant first-pass metabolism but the bioavailability of both the tablet and oral solution dosage forms would appear to be equal.

The authors are grateful to the Medical Research Council of Canada (MRC), The Kidney Foundation of Canada and the Vancouver Foundation for their support of this research. The authors also wish to thank the MRC for the MRC Studentship Award to Mr M. R. Wright. Thanks are offered to A. H. Robins Canada, Inc. and Nordic Laboratories, Inc. for the supply of authentic metoclopramide reference standards and the clinical supplies used in this study.

References

- Bateman, D. N. (1983). Clinical pharmacokinetics of metoclopramide. *Clin. Pharmacokin.*, **8**, 523–529.
- Bateman, D. N., Kahn, C. & Davies, D. S. (1980). The pharmacokinetics of metoclopramide in man with observations in the dog. *Br. J. clin. Pharmac.*, **9**, 371–377.
- Block, W., Pingoud, A., Khan, M. & Kjellerup, P. (1981). The pharmacokinetics, bioequivalence and bioavailability of different formulations of metoclopramide in man. *Arzneim. Forsch.*, **31**, 1041–1045.
- Bryson, S. M., McGovern, E. M., Kelman, A. W.,

- White, K., Addis, G. J. & Whiting, B. (1985). The pharmacokinetics of high dose metoclopramide in patients with neoplastic disease. *Br. J. clin. Pharmac.*, **19**, 757–766.
- Gibaldi, M. & Perrier, D. (1982). *Pharmacokinetics*, 2nd Edition, pp 83–84. New York: Marcel Dekker Inc.
- Gibaldi, M. & Weintraub, H. (1971). Some considerations as to the determination and significance of biologic half-life. *J. Pharm. Sci.*, **60**, 625–626.
- Graffner, C., Lagerstrom, P. & Ronn, O. (1979). Pharmacokinetics of metoclopramide intravenously and orally determined by liquid chromatography. *Br. J. clin. Pharmac.*, **8**, 469–474.
- Homesley, H. D., Gainey, J. M., Jobson, V. W., Welander, C. E., Muss, H. B. & Wells, H. B. (1982). Metoclopramide as an antiemetic in chemotherapy. *New Engl. J. Med.*, **307**, 250.
- Howard, F. A. & Sharp, D. S. (1973). Effect of metoclopramide on gastric emptying during labour. *Br. med. J.*, **1**, 446.
- Jones, C. T. (1968). Metoclopramide in the treatment of nausea. A double blind trial. *N.Z. Med. J.*, **68**, 388–393.
- Kapil, R. P., Axelson, J. E., Ongley, R. & Price, J. D. E. (1984). Nonlinear bioavailability of metoclopramide in the rat: Evidence for saturable first-pass metabolism. *J. pharm. Sci.*, **73**, 215–218.
- Metzler, C. M., Elfring, G. L. & McEwen, A. J. (1974). A package of computer programs for pharmacokinetic modelling. *Biometrics*, **30**, 562–563.
- Riggs, K. W., Axelson, J. E., Rurak, D. W., Hasman, D. A., McErlane, B., Bylsma-Howell, M., McMorland, G. H. & Price, J. D. E. (1983). Electron-capture determination of metoclopramide in biological fluids using fused silica capillary columns: Application to placental transport studies in sheep and humans. *J. Chromatogr.*, **276**, 319–328.
- Ross-Lee, L. M., Eadie, M. J., Hooper, W. D. & Bochner, F. (1981). Single-dose pharmacokinetics of metoclopramide. *Eur. J. clin. Pharmac.*, **20**, 465–471.
- Saller, R., Hellenbrecht, D., Briemann, L., Hellstern, A., Hess, H., Mitrou, P., Hodgson, M., Achtert, G., Brockmann, P. & Hausleiter, H. J. (1985). Metoclopramide kinetics at high-dose infusion rates for prevention of cisplatin-induced emesis. *Clin. Pharmac. Ther.*, **37**, 43–47.
- Schuppan, D., Schmidt, I. & Heller, M. (1979). Preliminary pharmacokinetics of metoclopramide in humans—Plasma levels following single oral and intravenous dose. *Arzneim. Forsch.*, **29**, 151–154.
- Sedman, A. & Wagner, J. G. (1976). *Autoan. A decision-making pharmacokinetic computer program*. Publication distribution service. Ann Arbor, Michigan.
- Tam, Y. K., Axelson, J. E., McErlane, B., Ongley, R. & Price, J. D. E. (1981). Dose-dependent pharmacokinetics of metoclopramide in the rat: An effect of hemoperfusion? *J. Pharmac. exp. Ther.*, **217**, 764–769.
- Taylor, W. B., Proctor, S. J. & Bateman, D. N. (1984). Pharmacokinetics and efficacy of high-dose metoclopramide given by continuous infusion for the control of cytotoxic drug-induced vomiting. *Br. J. clin. Pharmac.*, **18**, 679–684.
- United States Pharmacopeial Convention 1980–1985 (National Consensus) (1984). In *Drug information for the health care provider* (Vol. 1) p. 711. Rockville MD The United States Pharmacopeial Convention Inc.
- Wright, G. J., Melikian, A. P. & Crowe, J. T. (1984). Dose proportionality of metoclopramide. *Clin. Pharmac. Ther.*, **35**, 284.
- Wright, G. J. & Pitts, J. E. (1984). Bioavailability of metoclopramide from tablet and liquid dosage forms relative to intravenous injection. *Clin. Pharmac. Ther.*, **35**, 284.

(Received 14 January 1988,
accepted 14 June 1988)