Bioavailability of intranasal metoclopramide

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After intranasal administration of metoclopramide, (5 mg in 0.5 ml sterile water) the maximum plasma concentration of 13.5 ± 7.3 (mean $\pm$ s.d.) ng ml⁻¹ was achieved. Absolute bioavailability was $50.5 \pm 29.5\%$, 110 $\pm$ 41 min later. We conclude that the intranasal route does not allow rapid absorption of the drug and is not associated with greater bioavailability than the oral route.

Keywords metoclopramide bioavailability intranasal

Introduction

Metoclopramide is a widely used antiemetic but its use by the oral route is limited by delayed or impaired absorption which occurs in the very situations (e.g. vomiting) in which its therapeutic effect would be beneficial. Even in normal individuals its bioavailability is incomplete and variable (Bateman *et al.*, 1980; Ross-Lee *et al.*, 1981; Block *et al.*, 1981) because of presystemic metabolism in the gut or liver.

The nasal mucosa is rich in blood vessels and we postulated that intranasal administration of metoclopramide might result in faster and (because it might avoid presystemic metabolism) more complete absorption than after the oral route.

Methods

Six healthy drug-free subjects (five males) aged between 21 and 34 years participated in the study after giving fully informed written consent. The study was approved by the local Ethics Committee. After an overnight fast, they received metoclopramide 5 mg intravenously or 5 mg intranasally (freshly dissolved in 0.5 ml sterile water) on two separate occasions in random order and at least 1 week apart.

The intravenous dose was administered into an antecubital vein over 5 min and the intranasal solution was administered using a rhinyle calibrated thin bore plastic tube (Ferring,

Middlesex), the solution being blown into the nose by the subject.

Blood was sampled from an indwelling cannula in the opposite arm at 0, 15, 30, 45, 60 min, 2, 3, 4, 5, 6 and 8 h after drug administration. Samples were immediately centrifuged and the plasma stored at -20° C prior to analysis. Metoclopramide was measured by a high performance liquid chromatographic method. Briefly, samples were alkalised and extracted into acetonitrile, back-extracted into hydrochloric acid and injected into an h.p.l.c. using a spherisorb column, a mobile phase of 0.02 M KH₂PO₄ pH 3 acetonitrile (60:40) at a flow rate of 2 ml min⁻¹ and u.v. absorbance detection at 275 nm. Quinidine was used as an internal standard. Intra-assay variation was 6% at 500 ng ml⁻¹, and inter-assay variation 3% at the same concentration. The limit of sensitivity of the assay was 3 ng ml⁻¹ (Buss *et al.*, 1989). Area under the plasma concentration-time curve was measured using the model-independent linear trapezoidal method. Comparisons were made using Student's paired *t*-test and *P* < 0.05 was taken as the minimum level of statistical significance.

Results

The pharmacokinetic variables for the individual patients are shown in Table 1 and the mean

Table 1 Pharmacokinetic variables after administration of 5 mg metoclopramide by intravenous and intranasal routes (mean $\pm$ s.d.)

	5 mg intravenous (i.v.)	5 mg intranasal (i.n.)	Comparison of i.n. and i.v.
AUC (ng ml ⁻¹ min)	13204 $\pm$ 4074	6408 $\pm$ 4121	$P < 0.05$
$C_{\max}$ (ng ml ⁻¹)	—	13.5 $\pm$ 7.3	—
$t_{\max}$ (min)	—	110 $\pm$ 41	—
$t_{1/2}$ (min)	356 $\pm$ 153	275 $\pm$ 34	NS
Bioavailability $F(\%)$	—	50.5 $\pm$ 29.5	—

concentrations for each time point in Figure 1. The mean time to peak concentration after intranasal administration ($t_{\max}$) was 110 $\pm$ 41 min. The bioavailability of the drug administered intranasally was 50.5% $\pm$ 29.5%. The half-life of elimination was not significantly different between intravenous (356 $\pm$ 153 min) and intranasal (275 $\pm$ 34 min) administration.

Discussion

The time to peak concentration after the intranasal route in this study is similar to those reported by others after oral administration of metoclopramide. Graffner *et al.* (1979) observed a $t_{\max}$ of 1.05 $\pm$ 0.83 h after oral administration of an aqueous solution. The absolute bioavailability after the intranasal route was lower than reported for oral aqueous solution (73% $\pm$ 25%) by Graffner *et al.* (1979), however, and varied markedly between individuals.

A recent study has examined the pharmacokinetics of metoclopramide after intranasal administration of a gel formulation (Citron *et al.*, 1987). $t_{\max}$ after a 5 mg and 10 mg dose was 80.6 and 131.3 min respectively and bioavailability relative to a 5 mg intramuscular dose was 40% and 51% respectively. Intravenous drug was not given by Citron & co-workers (1987) so absolute bioavailability could not be calculated. The relative bioavailability of a 10 mg oral tablet was 48% in the same study. The results of our own study and that of Citron *et al.* (1987) suggest either that the absorption of drug from the nose is slow and incomplete or that the greater part of the drug is swallowed and absorbed from the gut in the normal way. If the latter is true, intranasal

Figure 1 Mean plasma metoclopramide concentration after intravenous (●) and intranasal (○) administration.

administration is unlikely to avoid the problems of absorption associated with metoclopramide in situations where oral absorption of the drug is poor or unreliable (e.g. migraine or during opiate administration).

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References

- 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. (1980). The pharmacokinetics, bioequivalence and bioavailability of different formulations of metoclopramide in man. *Arzneimittel-Forschung*, **31**, 1041–1045.
- Buss, D. P., Hutchings, A. D., Scott, S. & Routledge, P. A. (1989). Liquid chromatographic analysis of metoclopramide in human plasma. *Ther. Drug Monitoring*, (in press).
- Citron, M. L., Reynolds, J. R., Kalra, J., Kay, B. G., Natham, K. A., Jaffe, N. D. & Miller, F. R. (1987). Pharmacokinetic comparison of intranasal, oral and intramuscular metoclopramide in healthy volunteers. *Cancer Treat. Rep.*, **71**, 317–319.
- Graffner, C., Lagerstrom, P. O., Lundborg, P. & Ronn, A. (1979). Pharmacokinetics of metoclopramide intravenously and orally determined by liquid chromatography. *Br. J. clin. Pharmac.*, **8**, 469–474.
- 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.

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