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Pharmacokinetics of metoclopramide in patients with liver cirrhosis

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The pharmacokinetics of metoclopramide were investigated after intravenous and oral administration in eight patients with severe alcoholic cirrhosis and in eight healthy volunteers. As a consequence of a 50% lower clearance (0.16 ± 0.07 *vs* 0.34 ± 0.09 l h^{-1} kg^{-1}, plasma drug concentrations and the half-life of metoclopramide were greater in patients following both routes of drug administration. Volume of distribution (3.1 ± 0.8 *vs* 3.4 ± 1.2 l kg^{-1}) and absolute bioavailability (79 ± 19 *vs* 84 ± 15%) were similar in the two groups. The adverse effects of metoclopramide observed in patients with marked hepatic impairment are likely to result from increased accumulation of the drug as a result of impaired clearance. Consequently a reduction in dose of 50% is recommended in patients with severe liver cirrhosis.

Keywords metoclopramide pharmacokinetics bioavailability liver cirrhosis

Introduction

Metoclopramide is widely used as an antiemetic and in the treatment of a variety of gastrointestinal disorders (Harrington *et al.*, 1983). Good results have been achieved in the treatment of nausea in patients with liver cirrhosis (Uribe *et al.*, 1985). However, these patients often develop side-effects such as extrapyramidal reactions (Bernardi *et al.*, 1986), aldosterone mediated sodium retention (D'Arienzo *et al.*, 1985) and have a high risk of developing encephalopathy (Wedlund & Branch, 1983). Previous single dose pharmacokinetic studies have shown that the elimination of metoclopramide occurs mainly through hepatic biotransformation (Bateman, 1983). Therefore to determine whether the increased risk of side-effects in patients with cirrhosis could be related to impaired metoclopramide pharmacokinetics, this study was performed in both patients with severe cirrhosis and in healthy volunteers.

Methods

Eight patients (five males, and three females) with histologically proved alcoholic cirrhosis were studied. They were 40 to 65 years old (mean 54 ± 9 years) and their weights ranged from 46 to 80 kg (mean 63 ± 11 kg).

The severity of the liver disease was assessed according to Pugh's modification of Child's classification (Howden *et al.*, 1989). All patients had severe cirrhosis with ascites and were grade C on the scale with a score of 11 to 13; serum bilirubin concentration ranged from 78 to 462 μmol l^{-1}, plasma albumin ranged from 23 to 32 g l^{-1} and prothrombin time ranged from 29 to 47%. The patients had normal renal function as indicated by plasma creatinine concentrations which ranged from 48 to 110 μmol l^{-1} (73 ± 22 μmol l^{-1}). Seven patients were treated with other drugs which included lactulose, vitamins, paracetamol and antiulcer drugs such as ranitidine and antacids. Intake of the latter was delayed on the day of the study. The patients had not been receiving any drugs known to induce or inhibit drug metabolism.

Results were compared with those obtained in eight healthy volunteers (three males, five females) aged 24 to 37 years (mean 30 ± 5) and weighing 52 to 88 kg (mean 64 ± 14 kg). Their clinical chemistry tests did not show any abnormalities.

All subjects gave written informed consent to the study which was approved by the ethics committee of the University of Paris-Sud.

Study design

All subjects were given metoclopramide intravenously (dihydrochloride salt – two 10 mg ampoules – 7.7 mg metoclopramide base) and orally (hydrochloride salt – two 10 mg tablets – 8.5 mg base) on separate occasions, in randomized order and after an overnight fast. The two administrations were separated by a period of at least 4 days to allow for complete drug wash-out.

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Blood samples were drawn at 5, 10, 15, 30, 45 min, 1, 2, 4, 8, 12, 24, 36 and 48 h after i.v. administration and at 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 h after oral administration.

Plasma samples were stored at −30° C until analyzed.

Assay method

Metoclopramide was assayed by h.p.l.c. using a modification of a method developed for sulpiride (Nicolas *et al.*, 1986). The column was a Lichrospher 100 RP C8 (Merck®). The mobile phase was a mixture of an aqueous solution of sodium heptane sulphonate ($2.5 \cdot 10^{-3}$ M), acetonitrile and diethylamine (78/22/1, v/v/v) and the pH was adjusted to 3.5 with orthophosphoric acid; the flow rate was 1.4 ml min^{-1}. A spectrofluorimeter was used for detection with excitation and emission wavelengths set at 310 and 367 nm, respectively. Metoclopramide was extracted from plasma as follows: 0.5 ml of plasma to which 10 ng of alizapride (internal standard) was added, was made alkaline with 0.5 ml of tris buffer pH 8.1 and extracted with 7 ml of a mixture of chloroform/ethyl acetate (3/1–v/v). After centrifugation the organic layer was evaporated under a stream of nitrogen until dry, the residue was dissolved in 150 µl of the mobile phase and 50 µl was injected. The limit of assay was 5 ng ml^{-1}. The within day coefficient of variation was 5% at a concentration of 80 ng ml^{-1}. All concentrations were expressed in terms of metoclopramide base.

Pharmacokinetic analysis

Data were analyzed using standard compartmental model independent methods (Rowland & Tozer, 1989).

Statistical analysis

All results are expressed as means ± s.d. Relationships between pharmacokinetic parameters and chemical data were assessed using regression analysis.

The kinetic parameters in patients with cirrhosis and normal subjects were compared using Student's *t*-tests.

Results

Irrespective of the route of administration, plasma concentrations of metoclopramide were higher in patients with cirrhosis than in healthy volunteers (Figure 1). Mean pharmacokinetic parameters are listed in Table 1. In patients, systemic clearance of metoclopramide was decreased by two fold whereas the volume of distribution remained unchanged. Consequently values of half-life and MDRT were doubled in patients when compared with volunteers. However, the differences were statistically significant following i.v. administration only. After oral administration, the maximum plasma metoclopramide concentration was higher in patients than in control subjects, whereas absolute bioavailability was unaffected by hepatic cirrhosis (79 ± 19 *vs* 84 ± 15%). Values of MRT calculated after oral administration were similar to MDRT values, indicating a rapid rate of drug absorption.

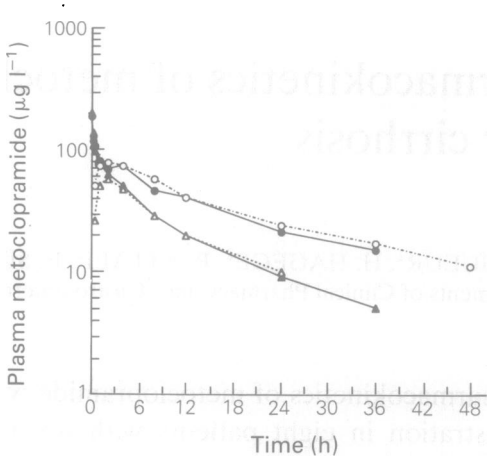

Figure 1 Plasma concentrations of metoclopramide in patients with cirrhosis (n = 8) and in normal subjects (n = 8) after intravenous and oral administration. ▲ volunteers i.v., △ volunteers oral, ● cirrhosis i.v., ○ cirrhosis oral.

Table 1 Mean pharmacokinetic parameters (± s.d.) of metoclopramide

	Controls	*Cirrhosis*	
i.v. route			
AUC (ng ml^{-1} h)	749 ± 291	1689 ± 749	$P < 0.05$
CL (ml min^{-1})	370 ± 144	172 ± 76	$P < 0.005$
CL (l h^{-1} kg^{-1})	0.34 ± 0.09	0.16 ± 0.07	$P < 0.05$
V (l kg^{-1})	3.4 ± 1.2	3.1 ± 0.8	NS
$t_{½}$ (h)	7.2 ± 2.4	15.4 ± 5.0	$P < 0.05$
MRDT (h)	9.5 ± 3.1	20.8 ± 7.1	$P < 0.05$
oral route			
C_{max} (ng ml^{-1})	63 ± 19	101 ± 37	$P < 0.05$
t_{max} (h)	1.9 ± 1.0	2.4 ± 2.5	NS
AUC (ng ml^{-1} h)	689 ± 260	1559 ± 905	$P < 0.05$
$t_{½}$ (h)	8.6 ± 3.8	12.3 ± 4.0	NS
MRT (h)	12.4 ± 4.2	17.5 ± 6.7	NS
F (%)	84.5 ± 15.3 (range 61–109)	79.0 ± 18.8 (range 49–103)	NS

No relationships could be found between pharmacokinetic parameters and clinical data.

Discussion

The pharmacokinetics of metoclopramide are well-documented in normal subjects and in cancer patients receiving high doses (Bateman, 1983; McGovern *et al.*, 1986; Taylor & Bateman, 1986; Wright *et al.*, 1988).

The present data in volunteers are consistent with those reported previously.

Assuming that 20 to 30% of the dose is excreted unchanged in urine (Bateman, 1983; Wright *et al.*, 1988), that the ratio of drug in plasma and erythrocytes is approximately 1.00 (Ross-Lee *et al.*, 1981) and that biotransformation occurs mainly in the liver, our clearance data indicate a mean hepatic extraction of 0.2, which is consistent with the observed bioavailability of 80%. In spite of large interindividual variation, the extent of the metoclopramide first pass effect is rather low and in accordance with previous estimates (Taylor & Bateman, 1986; Wright *et al.*, 1988).

Our findings indicate significant impairment of metoclopramide clearance in patients with severe liver cirrhosis. However, it should be noted that the cirrhotic patients were generally older than the normal controls. To our knowledge there are no data on metoclopramide disposition in elderly subjects. Although some impairment of hepatic drug metabolism may occur on ageing (Dawling & Crome, 1989), it is unlikely that increasing age alone would explain the large reduction in clearance seen. The plasma binding of metoclopramide is relatively low (40% – Webb *et al.*, 1986) and levels of α_1-acid glycoprotein, the major binding protein, are stable in cirrhosis (Kremer *et al.*, 1988). Therefore, changes in metoclopramide binding are also unlikely to explain our observations. It has been shown that the major metabolite of metoclopramide in man is the *N*-4 sulphate, the urinary excretion of which accounts for 32% of an intravenous dose (Bateman, 1983). A 50% decrease in clearance is therefore surprising as it is commonly thought that phase II pathways of metabolism are unaffected in liver dysfunction. However, in contrast to other enzymes involved in drug biotransformation, such as monooxygenases and to a lesser extent glucuronosyltransferases, little is known about the factors influencing sulphotransferase activity. The total pool of sulphate is usually quite limited (Mandel, 1971). Whether it is less in patients with poor nutritional status, such as those with severe liver cirrhosis remains to be established.

It should be mentioned that our results do not agree with those of Bernardi *et al.* (1987) who showed that after oral administration the kinetics of metoclopramide were not impaired in patients with cirrhosis with or without ascitis. However the degree of liver impairment was not mentioned by these authors.

Metoclopramide kinetics are impaired in patients with renal failure as a consequence of a decrease in non-renal clearance (Bateman *et al.*, 1981; Lehman *et al.*, 1985). An alteration in enterohepatic circulation in uraemic patients has been suggested and this cannot be excluded in patients with cirrhosis.

In conclusion, the adverse effects of metoclopramide observed in marked hepatic impairment are likely to be due to accumulation of the drug as a result of lowered clearance. Consequently a reduction in dose of 50% is recommended in patients with severe liver cirrhosis.

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