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PHARMACOKINETICS OF METOCLOPRAMIDE INTRAVENOUSLY AND ORALLY DETERMINED BY LIQUID CHROMATOGRAPHY

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1 A rapid and sensitive method, based on liquid chromatography, has been developed for determination of metoclopramide concentrations in plasma and urine samples. Concentrations down to 15 nmol/l (5 ng/ml) of plasma and 100 nmol/l (30 ng/ml) of urine could be determined with a relative standard deviation of $\leq 10\%$. The method was used to study disposition of metoclopramide in healthy volunteers following single doses intravenously and orally as aqueous solution and a slow release tablet.

2 The initial distribution after intravenous administration was very rapid. The elimination half-life postdistribution was 4.9 h. The apparent volume of distribution, V_d, was 3.0 l/kg body weight. On average 19% was excreted unchanged after intravenous administration of 5 and 10 mg (15 and 30 μmol) of drug. The rate of absorption of metoclopramide was delayed after administration of a slow release tablet and the maximum plasma concentration was about 50% lower than after a solution. The extent of bioavailability was the same following the two different formulations suggesting a first-pass elimination of 25–40%.

Introduction

Metoclopramide, structurally related to procainamide, has been in clinical use for about 10 years. The drug is mainly used as an anti-emetic.

Recently some pharmacokinetic data on metoclopramide based on drug concentrations in plasma and urine samples, have been reported (Bateman, Davies, Kahn & Mashiter, 1977; Bateman, Kahn, Mashiter & Davies, 1978; Teng, Bruce & Dunning, 1977). The biological half-life of the drug has been estimated to be 3–4 h, which might explain the short duration of action of the agent (Cohen, Morris, Schoen & di Marino, *et al.*, 1976). Thus, the drug has to be administered frequently in order to maintain effective concentrations throughout the day. Frequent administration, however, is inconvenient for the patient and the risk of decreased compliance in high. A slow-release tablet that makes twice daily administration of metoclopramide possible might therefore be an advantageous dosage form.

The aim of the present study was firstly to investigate the disposition of metoclopramide after intravenous infusion of short duration and oral administration in a rapidly available dosage form, and secondly to examine the influence of a slow-release tablet formulation on the rate and extent of bioavailability of metoclopramide.

A rapid and sensitive method, based on liquid chromatography (LC), was developed for determination of metoclopramide concentrations in biological samples. Only a few methods have been described for the analysis of metoclopramide in plasma and urine, thin-layer chromatography-colorimetry (Bakke & Segura, 1976) after relatively large doses of metoclopramide and LC (Teng *et al.*, 1977). These methods are rather tedious and also require larger sample volumes. A recently published method (Bateman *et al.*, 1978) has a similar sensitivity to ours but requires GC-MS equipment.

Methods

Principle

Metoclopramide was extracted as base into methylene chloride. (The partition constant $K_{D(A)}=490$). An aliquot of the extract was injected into an LC-column and metoclopramide was isolated by liquid-solid chromatography using UV-detection at 267 nm and quantitated from the chromatogram by peak height measurement and standard curves. If neces-

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sary, the sensitivity for analysis of plasma samples could be increased 3 times, as outlined for procainamide (Graffner, Jansson, Lagerström & Persson, 1977).

Chromatographic system

The liquid chromatograph consisted of a Milton Roy mini pump with a pulse dampener (LDC 711–47), a precision-bore stainless steel column as separation column (length 150 mm, i.d. 4.5 mm and o.d. 6.35 mm), a Cecil 212 UV-spectrophotometer with an 8μl flow cell and a Valco injection valve with 150- and 250-μl loops. The separation column was packed with microporous silica particles (Partisil 5, Whatman) and the mobile phase consisted of diethylamine 1 mol/l (in methanol) + methanol + dichloromethane (1 + 10 + 89, v/v).

Analytical procedure

A. Plasma samples

1. Plasma (2 ml), in a centrifuge tube, is made alkaline with 100 μl NaOH 2 mol/l and extracted with 1 ml methylene chloride by shaking for 10 min.
2. After centrifugation, the aqueous phase is sucked off and 250 μl of the organic phase is injected into the LC-column.

B. Urine samples

1. Urine (500 μl), in a centrifuge tube, is made alkaline with 100 μl NaOH 1 mol/l and extracted with 1 ml methylene chloride by shaking for 10 min.
2. After centrifugation, the aqueous phase is sucked off and 150 μl of the organic phase is injected into the LC-column.

Quantitation

Standard curves are constructed by analysing plasma and urine samples with known amounts of metoclopramide.

The recovery from samples spiked with metoclopramide was ≥ 95% (theoretical recovery ≥ 99%). The relative standard deviation ($n = 10$) was determined at two levels in plasma (600 nmol/l − 1.5% s.d., 40 nmol/l − 8%) and in urine (600 nmol/l − 2.3%). By the procedures described, about 15 nmol/l of plasma and 100 nmol/l of urine could be determined with a relative standard deviation of ≤ 10%. A chromatogram from an authentic plasma sample is shown in Figure 1.

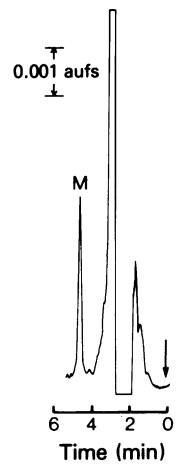

Figure 1 Isolation of metoclopramide (M) in plasma: Packing material: Partisil 5. Mobile phase: Diethylamine 1 mol/l (in methanol) + methanol + dichloromethane 1 + 10 + 89 (by volume). Mobile phase speed: 1 ml/min. Wavelength: 267 nm. Sample: 250 μl of an extract containing 100 nmol/l of metoclopramide.

Study

Design of the study The study was scrutinized and approved by the Ethical Committee of the University of Göteborg.

Five male volunteers (age 21–28 years, and weight 64–83 kg) participated. They were judged healthy as determined from medical history, physical examination and routine laboratory tests. After explaining the procedures and potential hazards of the study, the consent of each volunteer was obtained.

Each subject was given an acute dose of metoclopramide on four different occasions. An interval of at least 1 week was allowed between each administration. An intravenous infusion corresponding to 5 and 10 mg of drug and an oral mixture containing 20 mg of drug were given in random order, while a slow-release tablet containing 20 mg metoclopramide was always given on the fourth occasion. The subjects were fasting since midnight. Each dose was given after about 0.5 h rest in the laboratory. The oral doses were ingested together with about 150 ml water and the subjects remained sitting for 2 h. When given intravenously the drug was infused over a 5 min period under continuous supervision of ECG (oscilloscope) and heart rate. In all experiments the subjects got a light breakfast 3 h after drug administration and a standardized lunch 2 h later. Drugs, alcohol and smoking were not permitted during sampling periods.

Before drug administration, blood and urine specimens were obtained for background control of

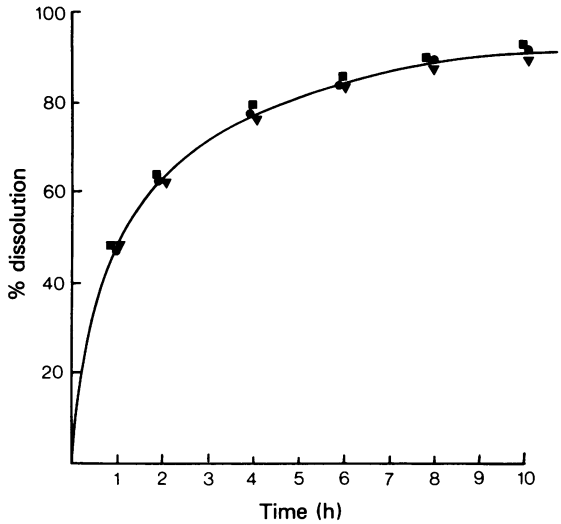

Figure 2 Dissolution *in vitro* of slow-release metoclopramide tablets. Dissolution liquids: ● water, ▼ simulated gastric juice, ■ simulated intestinal juice.

sample assays. Blood samples were drawn from a cubital vein at standardized intervals (see Figures 3 and 4). When metoclopramide was given as an infusion or as an aqueous solution samples were taken over an 8 h period. After tablet administration samples were also collected at 10 h and 24 h. The samples were collected in heparinized tubes. The plasma was immediately separated by centrifugation and frozen until assayed. Hourly urine samples were collected for 8 h and as a total portion from 8 to 24 h after drug administration. About 50 ml of each sample was stored frozen until analysed.

Dosage forms The sterile solution of metoclopramide HCl, issued in Sweden as Primperan®, Lundbeck, (5 mg/ml corresponding to 15 μmol/ml) was diluted to 10 ml with 0.9% sodium chloride solution and infused at a constant rate for 5 min.

An oral mixture of metoclopramide HCl, (20 ml) issued in Sweden as Primperan®, Lundbeck, (1 mg/ml corresponding to 3 μmol/ml) was ingested and the drinking cup was rinsed with water that was immediately swallowed.

Slow-release tablets containing 20 mg metoclopramide HCl (corresponding to 60 μmol) were prepared using the inert matrix principle (Sjögren, 1971). The *in vitro* drug release rate was determined using a beaker method and a propeller speed of 40 rev/min. Five tablets were tested in 500 ml of different dissolution liquids at 37°C. The release of metoclopramide is shown in Figure 2.

Calculations

The symbols used in this paper are taken from the terminology of Gibaldi & Perrier (1975).

The individual sets of plasma concentration of metoclopramide *v* time after intravenous infusion were analyzed using a computer program, CSTRIP (Sedman & Wagner, 1976). The parameters calculated were used as initial estimates in a nonlinear regression analysis of the biexponential equation

$$C = R \cdot e^{-\alpha t'} + S \cdot e^{-\beta t'} \quad (1)$$

Inverted concentration was used as weighting factor.

C is the sum of free and protein-bound plasma concentration of metoclopramide, t′ corresponds to postinfusion time, R, S are intercepts related to the zero time intercepts, A and B, according to Loo & Riegelman (1970).

The area under the plasma concentration *v* time curve from zero to infinite time, $\int_0^\infty C dt$, was calculated by means of the trapezoidal rule. The remaining area after the last observation was calculated according to Wagner (1971).

The apparent volume of distribution, V_d, was calculated from the equation

$$V_d = \frac{\text{Dose}}{\beta \cdot \int_0^\infty C dt} \quad (2)$$

Total body clearance, Q_B, was calculated from the equation

$$Q_B = V_d \cdot \beta \quad (3)$$

Uncorrected renal clearance, Q, was calculated by regression analysis of linear correlations according to the equation

$$Q = \frac{dX_u/dt}{C} \quad (4)$$

where dX_u/dt is rate of renal excretion of metoclopramide, and C is the plasma concentration of metoclopramide at the midpoint of each urine collection period.

Results and Discussion

Pharmacokinetics after intravenous administration

Semilogarithmic plots of the mean metoclopramide concentration in plasma versus time after a single intravenous infusion of 5 and 10 mg are shown in Figure 3. The plasma concentration after the higher intravenous dose was also determined 24 h after administration in three of the subjects. The

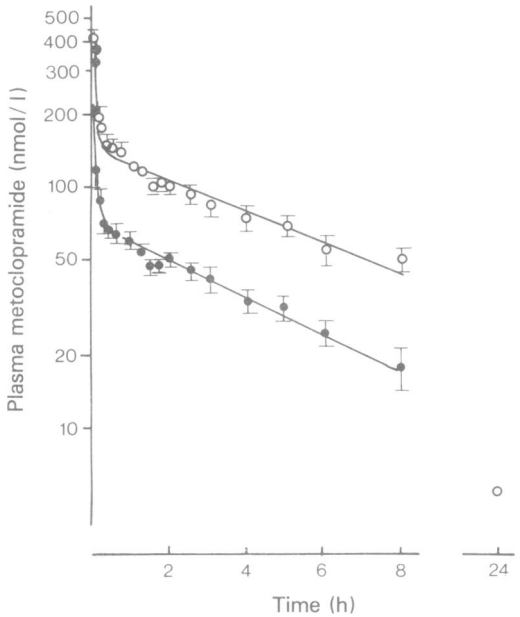

Figure 3 Semilogarithmic plot of metoclopramide concentration in plasma *v* time (mean ± s.e. mean, $n=5$) after 5 (●) and 10 mg (○) intravenously, (100 nmol/l = 30 ng/ml).

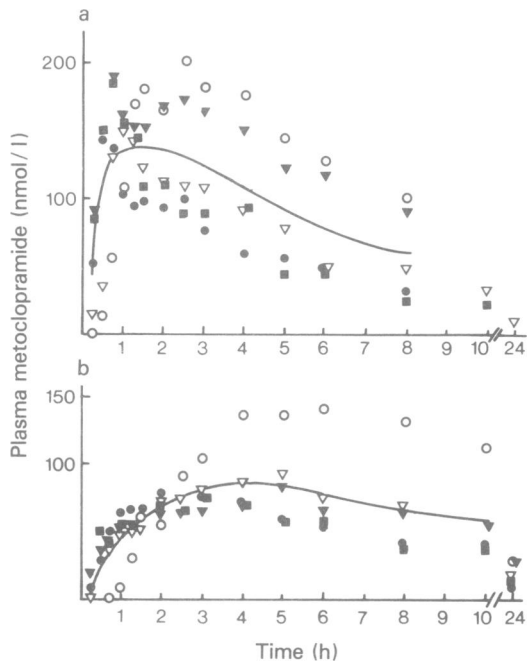

Figure 4 Individual plasma concentrations of metoclopramide *v* time after a single oral dose in an aqueous solution (a) and a slow-release tablet (b). The solid lines correspond to the calculated mean concentrations. (100 nmol/l = 30 ng/ml).

concentration was below 15 nmol/l in all cases. From Figure 3 and Table I it is evident that the initial distribution of metoclopramide was very rapid corresponding to a plasma half-life of about 4 min. This means that a distribution equilibrium will be achieved within 15 min after administration. The elimination half-life postdistribution was on average 4.9 h. The mean apparent volume of distribution of the drug in the body, V_d, was 3.0 l/kg body weight. The data were consistent to those reported after an acute i.v. dose of 10 mg (Bateman *et al.*, 1978).

Doubling of the dose from 5 to 10 mg of metoclopramide produced a twofold increase in the plasma levels during 6–8 h after the infusion. Peak concentrations 2 min after termination of infusion were within the range of 152–313 nmol/l (mean 204 nmol/l) after 5 mg and 305–464 nmol/l (mean 414 nmol/l) after 10 mg. The doubled dose resulted in an increase in the area under the curve from zero to infinite times of about 150%. A similar increase was found in urine after administration of the two i.v. doses and on average 16% and 21% of the dose given was recovered in unchanged form after 5 and 10 mg respectively. The results are indicating that the time course of elimination of metoclopramide is dependent on dose. Similar observations were recently reported by Bateman *et al.* (1979).

Table 1 Pharmacokinetic data for metoclopramide after i.v. infusion of 5 and 10 mg to five healthy subjects (mean ± s.d.)

Dose (mg/kg)	0.07 ± 0.01	0.14 ± 0.02
A(μmol l^{-1})	0.49 ± 0.24	2..8 ± 2.5
B(nmol l^{-1})	66.4 ± 5.4	129.5 ± 23.5
$T_{\frac{1}{2}}\alpha$ (min)	2.9 ± 1.8	6.3 ± 11.0
$T_{\frac{1}{2}}\beta$ (h)	4.4 ± 1.2	5.4 ± 1.8
V_d (l/kg)	3.0 ± 0.5	2.9 ± 0.7
$\int_0^\infty$Cdt (nmol l^{-1} h)	445 ± 114	1108 ± 286
Q_B (ml/min)	589 ± 143	477 ± 125
Q (ml/min)	108 ± 58	121 ± 57
% of dose excreted unchanged in 0–24 h urine	16 ± 4	21 ± 7

The uncorrected renal clearance of metoclopramide was found to be about 115 ml/min after both i.v. doses given.

Oral administration

The individual plasma concentrations and the mean curve of metoclopramide after oral administration in a solution and as a slow-release tablet are shown in Figure 4.

Absorption of the drug was rapid after administration in aqueous solution, and the mean plasma peak concentration was 180 ± 33 nmol/l within about 1 h (see Table 2). One of the subjects seemed to have a delayed absorption and no drug was detected in plasma until 30 min after drug administration. The mean elimination half-life after completed absorption was calculated to 4.7 h, which was very close to that after intravenous administration.

After administration of metoclopramide in slow-release tablets very flat plasma concentrations curves were obtained. Unfortunately, the plasma concentration of metoclopramide after the two oral formulations was compared up to 24 h only in two subjects. However, in both subjects the concentration in plasma 10 h after administration was about 75% higher after slow-release tablet than after the solution. The results thus suggest that metoclopramide is absorbed from a large portion of the gastrointestinal canal. The peak plasma concentration obtained after the tablets was reduced to a mean value of 95 ± 27 nmol/l at about 4 h after administration (Table 2). The plasma curves suggested a lag of at least 15 min before absorption in three of the subjects. Owing to too infrequent plasma sampling in the postabsorptive phase, it was not possible to calculate an absorption rate constant after the tablets.

The average ratio of the areas under the plasma curves of metoclopramide, given as a solution and a slow-release tablet, was found to be 1.1, (Table 2). A similar ratio was observed between the amount excreted in urine after the two formulations, suggesting the same extent of absorption from the slow-release tablet and the solution.

The extent of bioavailability of metoclopramide was estimated by comparing the area under the plasma curves and the urinary excretion of unchanged drug after oral administration and intravenous infusion. An average value of 0.73 ± 0.21 and 0.58 ± 0.11 was obtained on comparison with the 5 and 10 mg dose, respectively. The results are

Table 2 Metoclopramide data (mean ± s.d.) after a single oral dose of 20 mg in aqueous solution (S) and a slow release tablet (SR) to five healthy subjects

Preparation	*S*	*SR*
$K\ (h^{-1})$	0.16 ± 0.04	—
$T_{\frac{1}{2}}$ (h)	4.7 ± 1.2	—
C_p^{max} (nmol/1)	180 ± 33	95 ± 27
T^{max} (min)	63 ± 50	252 ± 99
$\int_0^\infty$ Cdt (nmol l^{-1} h)	1298 ± 568	1358 ± 554
% of dose excreted unchanged in 0–24 h urine	12 ± 3	11 ± 5
$\frac{1/4 \int_0^\infty \text{Cdt, orally}}{\int_0^\infty \text{Cdt, 5 mg i.v.}}$	0.73 ± 0.25	0.78 ± 0.33
$\frac{1/4 \int_0^\infty \text{Cdt, orally}}{\int_0^\infty \text{Cdt, 10 mg i.v.}}$	0.57 ± 0.14	0.61 ± 0.15
$\frac{X^{urine}\text{, orally}}{X^{urine}\text{, 5 mg i.v.}}$	0.73 ± 0.11	0.67 ± 0.14
$\frac{X^{urine}\text{, orally}}{X^{urine}\text{, 10 mg i.v.}}$	0.59 ± 0.14	0.56 ± 0.08

indicating a first-pass elimination of 25–40%. No significant difference was observed between the mixture and the slow-release tablets (see Table 2).

Side effects

Adverse effects, mainly restlessness, lasting for up to 90 min, were observed in three out of five subjects after intravenous administration of the 10 mg dose. These symptoms can probably be ascribed to central nervous system (CNS) effects of the drug, presumably an interference with central dopamine receptors (Pinder, Brogden & Sawyer, 1976).

Since metoclopramide has been found to be a very potent inhibitor of central dopamine receptors, preferentially in the striatal region, extrapyramidal reactions can be expected to occur during treatment with this drug. If such effects can be correlated to plasma levels exceeding those necessary for the therapeutic effects of metoclopramide a slow release preparation of the compound should provide therapeutic advantages. If, on the other hand, unwanted CNS effects appear even at plasma levels necessary for the therapeutic effects, the use of a slow-release preparation might prolong the time of exposure of the CNS to the drug, thereby increasing the risk of unwanted effects. It should be pointed out that a serious extrapyramidal effect, tardive dyskinesia, has recently been associated with long-term treatment with high doses of metoclopramide (Lavy, Melamed & Penchas, 1978).

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