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Bioavailability and Pharmacokinetics of Cimetidine

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Summary. The bioavailability and pharmacokinetics of cimetidine have been studied in healthy volunteers after administration of single intravenous (100 mg) and oral doses (100, 400 and 800 mg). After i. v. administration, the kinetics of cimetidine could be described by a linear, two compartment open model. Substantial variation in half-life was observed between subjects, with a mean value of 2.1 h (range 0.9–4.7). Cimetidine had a low hepatic extraction ratio and a high total plasma clearance, due to extensive urinary excretion of unchanged drug. After oral administration, the plasma concentration vs time curves in most subjects exhibited two marked peaks, an observation that seemed to be constant within individuals and was independent of dose. Bioavailability, estimated as the area under the plasma concentration vs time curves (AUC), after oral doses as compared to the intravenous dose, in most cases exceeded 100%. There was no correlation between bioavailability estimated as AUC and as urinary excretion of unchanged drug. These observations may indicate an enterohepatic circulatory mechanism, predominantly after oral administration. Both unchanged drug and its sulphoxide metabolite appear to be excreted in bile. The latter was shown in vitro to be reduced to cimetidine by fecal bacteria.

Key words: cimetidine; enterohepatic circulation, irregular absorption, bioavailability, pharmacokinetics, volunteers

Cimetidine has rapidly gained widespread use in the treatment of duodenal and gastric ulcer (Binder et al., 1978; Burland and Simkins, 1977; Frost et al., 1977). The compound has been subjected to many clinical trials and discussions about its efficacy and safety (Editorial, 1978; Fortrand, 1978). Few studies, however, have focused on the basic pharmacokinetics of the drug (Bodemar et al., 1977; 1979; Burland et al., 1975; Griffiths et al., 1977; Spence et al., 1976; Walkenstein et al., 1978). The present study deals with certain pharmacokinetic properties of cimetidine after single intravenous and oral doses given to healthy volunteers.

Material and Methods

Ten healthy volunteers, five men and five women, aged between 22 and 25 years, and weighing 54–76 kg, gave their informed written consent to the study, which was approved by an ethics committe.

All subjects underwent medical examination, including blood pressure measurement, ECG and the following laboratory tests: Hb, S-bilirubin, S-alkaline phosphates, S-ALAT, S-creatinine. Urine was examined for deposits, ketones, protein and glucose. Two female subjects were using oral contraceptives. Six of the participants regularly used tobacco, three smoked cigarettes and three took oral snuff. All female subjects were tested for pregnancy (Pregnancy Tube Test, Roche, Switzerland), before each trial. The subjects received cimetidine (Tagamet®) in single oral doses, as the commercially available tablets (100 mg, n = 3; 400 mg, n = 10; and 800 mg, n = 4), or as an i. v. solution for injection over 5 min (100 mg, n = 10). The 100 mg oral dose was given as half of a 200 mg tablet. The latter tablets were weighed before and after being divided, in order to check the dose. A dissolution rate test showed no difference in dissolution rate due to breaking the tablet film coat.

The drug was given after fasting overnight, and no food or fluid was allowed until two hours after

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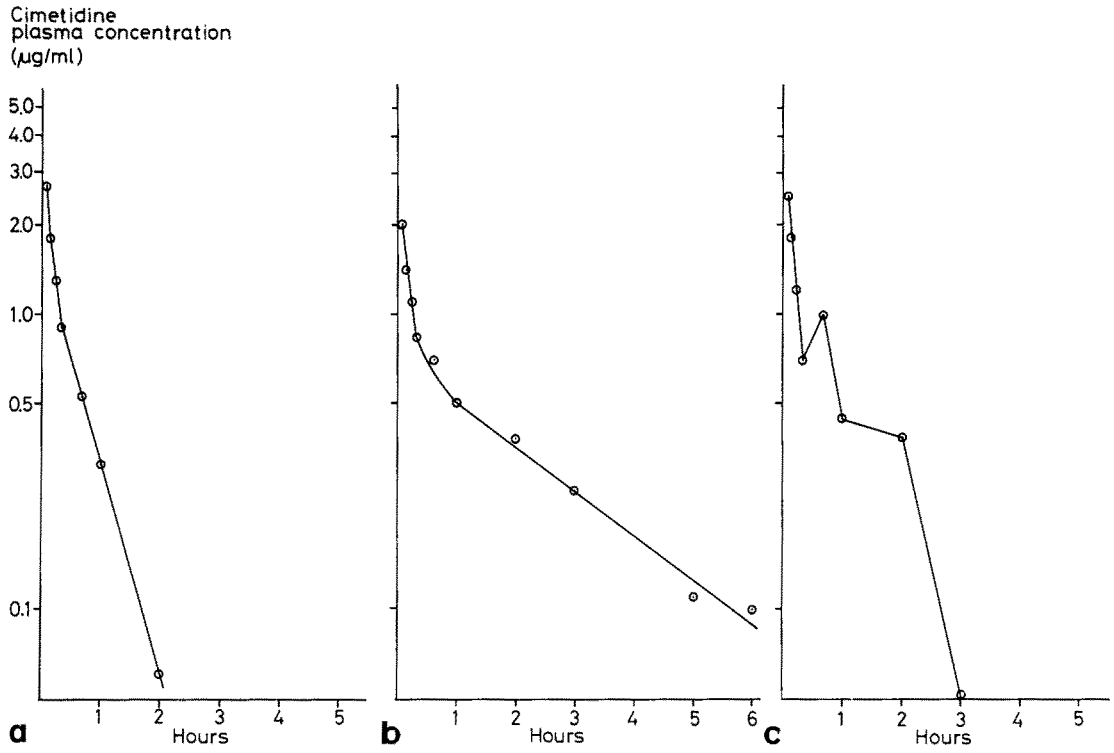

Fig. 1. Plasma concentration of cimetidine in three subjects following intravenous administration of cimetidine 100 mg **a.** Subject LH **b.** Subject KN **c.** Subject LOE

Table 1. Pharmacokinetics of cimetidine after intravenous administration of 100 mg

Subject	$t_{½\beta}$ (h)	Vd_β (l/kg)	Cl (l/kg × h)	fe (%)	AUC (μg/ml × h)
AF	1.3	1.5	0.81	74	2.1
EL	4.7	4.3	0.63	67	2.6
KN	2.0	1.9	0.65	71	2.4
LH	1.0	1.7	1.15	72	1.1
LM	1.3	1.4	0.76	78	2.5
LOE	0.9	1.4	1.0	74	1.6
LW	3.2	3.3	0.71	76	2.6
MM	2.5	1.6	0.45	82	3.2
TE	2.1	1.9	0.61	78	2.2
UB	1.9	1.7	0.63	–	2.1
Mean ±SD	2.1 ± 1.15	2.1 ± 1.0	0.74 ± 0.2	75 ± 4	2.2 ± 0.6

administration, when the subjects usually had coffee and a snack.

Blood samples were taken at regular intervals for up to 10 h through an indwelling forearm cannula (Venflon, Viggo-Sweden) into heparinized Venoject tubes. When cimetidine was administered intravenously, this was done in the other arm. The blood samples were centrifuged within 10 min and the plasma was frozen and stored until subsequent analysis – within a week. Urine was collected for 24 h.

Cimetidine in plasma and urine was assayed by a minor modification of a liquid chromatographic method (Randolph et al., 1977), using acetonitrile instead of ethanol in the last extraction step. The method was specific for cimetidine and the detection limit was 0.04 μg/ml.

Pharmacokinetic parameters after i. v. administration of cimetidine were estimated according to a linear two-compartment open model by a standard computer program (Wagner, 1975). The area under the plasma concentration vs time curve (AUC) was calculated by the trapezoidal technique. The area to infinite time beyond the last sample point was estimated by integration, on the assumption of first order kinetics. The infinite area never exceeded 20% of the total. The elimination rate constant β was estimated by linear regression analysis of the log concentration vs time data. The following calculations were also made:

$$\text{Plasma clearance (Cl)} = \frac{\text{Dose}_{\text{i.v.}}}{\text{AUC}_{\text{i.v.}}}$$

$$\text{Half-life } (t_{½\beta}) = \frac{0.693}{\beta}$$

$$\text{Apparent volume of distribution } (Vd_\beta) = \frac{Cl}{\beta}$$

$$\text{Fraction of dose excreted unchanged in urine (fe)} = \frac{Ae}{Dose_{i.v.}}$$

were A_e = Total amount of drug excreted unchanged in urine.

$$\text{Bioavailability } (F_{AUC}) = \frac{AUC_{oral}/Dose_{oral}}{AUC_{i.v.}/Dose_{i.v.}}$$

$$\text{Bioavailability } (F_{fe}) = \frac{Ae_{oral}/Dose_{oral}}{Ae_{i.v.}/Dose_{i.v.}}$$

$$\text{Renal Clearance } (Cl_R) = Cl \times fe$$

$$\text{Extraction Ratio (ER)} = \frac{(Cl - Cl_R) \times C_p/C_B}{Q}$$

where C_p = Plasma concentration
C_B = Blood concentration
Q = Hepatic blood flow

In Vitro Metabolism by Human Faecal Bacteria

Human faecal samples were incubated with the sulphoxide metabolite of cimetidine (10 µg/ml) in Luria broth, under aerobic and anaerobic conditions, overnight at 37° C. To two tubes, broth 5 ml was added and to further two tubes, broth 4 ml and human bile 1 ml. Each medium was incubated under nitrogen and with free exposure to air. A control experiment was performed in which fecal bacteria were absent. The sulphoxide metabolite was analyzed as previously described (Lee and Osborne, 1978).

Statistical analysis were performed with student's t-test and the sign test.

Results

There were considerable interindividual differences in the shape of the plasma concentration vs time curves after intravenous administration, as shown in Figures 1a–c. Some subjects demonstrated a rapid and others a much slower elimination phase. In two subjects irregularities occurred, as illustrated in Figure 1c.

Pharmacokinetic data for cimetidine calculated after the intravenous dose are listed in Table 1. The half-life ($t_{½\beta}$) and apparent volume of distribution (Vd_β) showed an almost five-fold variation between subjects. Mean hepatic extraction ratio, calculated from the relationship between hepatic blood flow (assumed to be 1,5 l/min; Bradly et al., 1945) and hepatic blood clearance (Rowland, 1973) was found to be 0.13.

Pharmacokinetic data for cimetidine calculated after oral doses are presented in Table 2. Half-life ($t_{½\beta}$) showed smaller variation than after intravenous administration, with mean values of 2.5, 1.5 and 1.7 h, respectively, after 100, 400 and 800 mg.

The relationship between AUC and dose did not support a dose – dependent relationship, as suggested by Griffiths et al. (1977).

Table 2. Pharmacokinetic constants calculated after oral administration of cimetidine 100, 400 and 800 mg

Dose (mg)	Subject	$t_{½\beta}$ (h)	AUC (µg/ml × h)	F_{AUC} (%)	F_{fe} (%)
100	AF	2.2	2.1	100	89
	LW	2.9	2.0	77	63
	TE	2.4	1.7	77	85
	Mean ± SD	2.5 ± 0.4	1.9 ± 0.2	85 ± 13	79 ± 14
400	AF	1.7	10.3	124	64
	EL	1.9	13.5	130	51
	KN	1.6	12.1	126	52
	LH	2.0	9.6	218	50
	LM	1.7	13.3	133	54
	LOE	1.2	8.6	134	50
	LW	1.5	11.5	111	37
	MM	1.2	8.5	66	57
	TE	1.2	8.8	100	44
	UB	1.4	7.6	90	–
	Mean ± SD	1.5 ± 0.3	10.4 ± 2	123.2 ± 40	51 ± 8
800	AF	1.1	10.3	61	84
	LOE	2.1	20.4	160	43
	LW	1.1	16.7	80	58
	TE	2.3	16.6	94	71
	Mean ± SD	1.7 ± 0.6	16.0 ± 4	99 ± 43	64 ± 18

Table 3. Urinary excretion (24 h) of unchanged cimetidine

Subject	% of dose			
	Intravenous 100 mg	oral 400 mg	oral 100 mg	oral 800 mg
AF	74	47	66	62
EL	67	34	–	–
KN	71	37	–	–
LH	72	36	–	–
LOE	78	50	–	32
LM	74	42	–	–
LW	76	28	48	44
MM	82	47	–	–
TE	78	34	66	56
UB	–	53	–	–
Mean	75	40	–	–
± SD	5.5	7.5	–	–

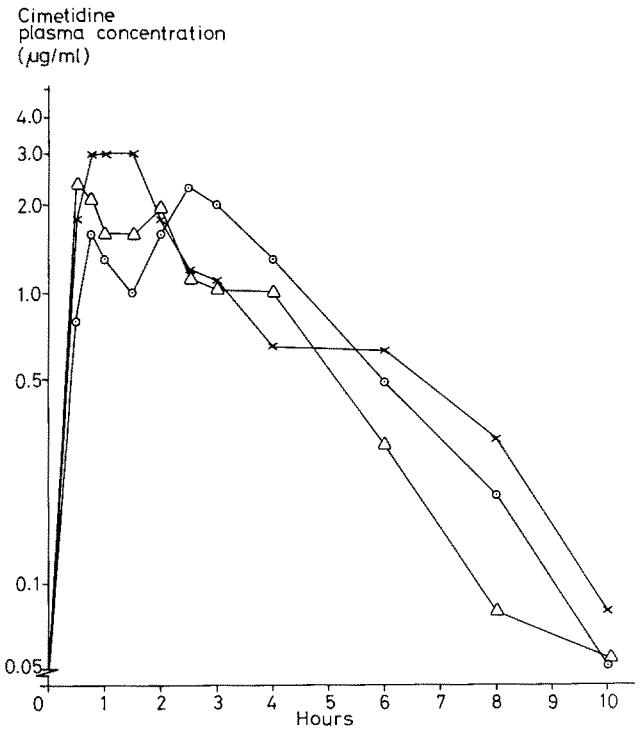

Fig. 2. Plasma concentration of cimetidine in three subjects after oral administration of cimetidine 400 mg: × = LH, ⊙ = LOE, △ = UB

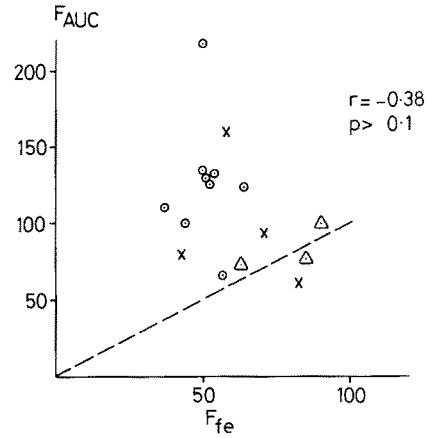

Fig. 3. Relationship between bioavailability estimated from AUC-measurement (F_{AUC}) and from urinary excretion of unchanged drug (F_{fe}) after different oral doses.
△ = 100 mg, ⊙ = 400 mg, × = 800 mg. The interrupted line is the line of identity

The 24 h urinary recoveries of unchanged cimetidine after intravenous and oral administration are shown in Table 3. The relative recovery after oral administration of 400 mg was significantly lower ($p < 0.01$) than after intravenous administration (100 mg).

Typical plasma concentration vs time curves after a single oral 400 mg dose in three subjects are shown in Figure 2. Eight of ten subjects demonstrated a marked second peak, which was more pronounced after the 800 mg dose. The occurence or non-occurence of double peaks was constant in each individual, and was independent of the dose.

The relationship between bioavailability estimated from AUC (F_{AUC}) and from urinary excretion of unchanged drug (F_{fe}) for the different oral doses is shown in Figure 3. On 14 out of 16 occasions, F_{AUC} exceeded F_{fe}, with a statistical significant difference ($p < 0.05$) between the two estimates of bioavailability. Consequently, no significant correlation was found between F_{AUC} and F_{fe}.

Marked interindividual differences were found in F_{AUC} (range 66–218%). Eight subjects had an estimated F_{AUC} exceeding 100%. However, there were substantial within – subject differences in F_{AUC} between doses. Comparing F_{AUC} and F_{fe} for the oral doses, there was no evidence for dose-dependent kinetics. The relationship between Cl_R and urinary flow indicated no essential influence of urinary flow on F_{AUC}.

There were no apparent differences when all the pharmacokinetic parameters were compared between subjects who were or were not regular tobacco users, or between those using or not using oral contraceptives. Neither was there any difference between male and female subjects.

Incubation in vitro of cimetidine sulphoxide with human faecal bacteria resulted in complete reduction of the sulphoxide metabolite to cimetidine, both in the presence and absence of human bile. No reduction of the sulphoxide metabolite occured when faecal bacteria were absent.

Three subjects experienced adverse reactions, one a burning sensation in the epigastric region shortly after intravenous administration, and two felt extremely tired a few hours after the 800 mg dose.

Discussion

Cimetidine has a low hepatic extraction ratio but a high total plasma clearance, due to high urinary excretion of unchanged drug. After oral administration the plasma concentration vs time curves in most subjects exhibited two marked peaks, an observation reported previously (Bodemar et al., 1979; Griffiths et al., 1977; Walkenstein et al., 1978). The double peak seemed to be constant for a given individual, independent of dose.

The half lives and urinary excretion of unchanged drug after oral administration were in good agree-

ment with previous reports (Griffiths et al., 1977; Walkenstein et al., 1978).

Bioavailability, estimated as the area under the plasma concentration vs times curves, after oral as compared to intravenous doses, exceeded 100% in most cases. This observation was not found in an previous bioavailability study of cimetidine in man (Walkenstein et al., 1978), but has been found for other compounds, e. g. indomethacin (Alván et al., 1975; Kwan et al., 1976) and fluoride (Ekstrand et al., 1978). It was not likely that our finding was due to dose-dependent kinetics, or to within-subject differences in renal clearance caused by variation in urinary flow.

In theory, the observation of double plasma peaks could be due to cimetidine – induced irregularity of absorption in the gastrointestinal tract, or rather to an enterohepatic circulation. The observation of an estimated bioavailability from the AUC after oral intake exceeding 100% supports the latter hypothesis. The earlier finding that unchanged cimetidine is only excreted in minor amount in bile (Spence et al., 1977) does not contradict this hypothesis. Substantial amounts of the sulphoxide metabolite has been detected in bile from patients on cimetidine therapy (unpublished results). Experiments *in vitro* with both rat (Taylor et al., 1978) and human faecal bacteria have shown that this metabolite can be reduced to cimetidine. After reduction, cimetidine might be reabsorbed, thus giving rise to an enterohepatic circulation. The quantitative role of this proposed mechanism is still unknown.

The magnitude of enterohepatic circulation of drugs showes both within – and between – subject variation (Alván, 1978). This might explain the great variability in estimated bioavailability found between doses and subjects.

The results clearly demonstrate that bioavailability studies using AUC-measurements are misleading for several drugs, including cimetidine.

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