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RANITIDINE: SINGLE DOSE PHARMACOKINETICS AND ABSOLUTE BIOAVAILABILITY IN MAN

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1 Ranitidine single dose pharmacokinetics and absolute bioavailability have been studied in five healthy male volunteers. Following an overnight fast, 150 mg was given intravenously as a bolus injection or orally as a tablet formulation to each subject on separate occasions.

2 Following intravenous administration, plasma levels declined biexponentially. The mean (± s.d.) distribution half-life ($t_{½}\alpha$) was 6.6 ± 1.6 min; plasma half-life ($t_{½}\beta$) was 1.7 ± 0.2 h; the volume of distribution (V) was 96 ± 9 1; total body clearance (CL) was 647 ± 94 ml/min and renal clearance (CL_R) 520 ± 123 ml/min.

3 Following oral administration plasma levels showed a bimodal pattern with a first peak at 1.1 ± 0.4 h and a second peak at 3 ± 0 h. The absolute availability was 60 ± 17%. The plasma half-life ($t_{½}$) of 2.3 ± 0.4 h was significantly longer ($P < 0.05$) after oral than after i.v. administration.

4 Renal excretion of unchanged ranitidine accounted for 79 ± 9% of the dose after i.v. administration and for 27 ± 7% after oral administration.

5 Our results suggest a more extensive biotransformation of ranitidine and biliary excretion of metabolites after oral administration while i.v. administered ranitidine is preferentially excreted unchanged in the urine.

Introduction

Ranitidine hydrochloride (*N*-[2-[[[5- [(dimethylamino)methyl]-2-furanyl] methyl]thio]ethyl]- *N'*-methyl-2-nitro-1,1-ethenediamine hydrochloride) is a new competitive antagonist of histamine at H_2-receptor sites (Figure 1).

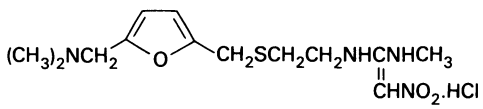

Figure 1 Formula of ranitidine hydrochloride

It has been reported to be four times more active on a molar basis than cimetidine in inhibiting pentagastrin stimulated gastric acid secretion in man (Domschke *et al.*, 1979). Its clinically recommended oral dose is 150 mg twice daily.

This study was undertaken to determine single dose pharmacokinetic characteristics of 150 mg ranitidine and as ranitidine is available both for oral and intravenous administration, its absolute bioavailability was also determined.

Methods

Subjects

Five healthy male volunteers, ranging in age from 20 to 22 years, and in weight from 64 to 75 kg, participated in the study. Informed consent was obtained according to institutional policy. All subjects had a normal history, physical examination and laboratory tests (complete blood count, serum ureum, uric acid, creatinine, total protein, bilirubin, alkaline phosphatase, glucose, SGOT and SGPT and complete urinalysis).

Experimental design

After an overnight fast 150 mg of ranitidine was administered either orally as a tablet formulation or as an intravenous bolus (2 min) injection to each volunteer. The oral and i.v. studies were performed on two separate occasions at least one week apart. A standard breakfast was allowed 2 h after drug administration.

Venous blood samples (6 ml) were withdrawn on heparine through an indwelling butterfly needle, immediately before and at 15, 30, 45, 60 min and 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 34 and 48 h after dosing. After

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i.v. injection additional samples were taken at the end of the injection and at 2, 5, 7 and 10 min after drug administration. Plasma was removed and frozen at −20°C until analysis.

Urine was collected before the start of the experiment (blank) and during the periods 0–2 h, 2–4 h, 4–6 h, 6–12 h, 12–24 h and 24–48 h after drug administration. All urine volumes were measured and aliquots were stored at −20°C until analysis.

Assay procedures

Ranitidine hydrochloride was measured using a liquid chromatographic method described by Carey *et al.* (1979).

To 1 ml plasma or 0.2 ml urine (diluted to 1 ml with water) were added 1 ml of 0.05 M disodium hydrogen phosphate pH 9.0, 50 μl of the internal standard solution AH 20480 (*N*-[3-[5-[(dimethylamino)-methyl]-phenoxy]propyl]-*N'*-methyl-2-nitro-1, 1-ethenediamine, 10 μl/min) and 5 ml of octanol-1. After shaking for 15 min and centrifuging at 2 000 rev/min for 10 min, 4.5 ml of the upper organic layer was transferred to another tube and 250 μl of 0.05 M phosphate buffer pH 6.0 was added. After shaking for another 15 min and centrifuging for 10 min at 2 000 rev/min, the organic layer was discarded. Of the aqueous phase 100 μl was injected onto an h.p.l.c.-column, 100 min × 5 mm i.d., stainless steel (Shandon Southern, Runcorn, Cheshire), containing 5μ Spherisorb ODS reverse phase material.

A Pye Unicam LC3-XP pump and a Rheodyne syringe loading sample injector model 7120 were used. The Pye Unicam LC3-UV detector was operated at a wavelength of 320 nm and the column temperature maintained at 40°C. Peak area integrations and calculations were done by a Spectra-Physics SP-4100 integrator.

A standard curve was run with each set of determinations and prepared by adding known amounts of ranitidine hydrochloride (ranging from 0.01 μg/ml to 10 μg/ml) to plasma or urine.

Linearity of the standard curves was found in the range from 0.01 μg/ml to 10 μg/ml. Sensitivity of the method was approximately 0.01 μg/ml. Reproducibility of the method was shown by extracting concentrations of 0.25 μg/ml and 0.05 μg/ml from plasma ($n = 4$), and concentrations of 1 μg/ml from urine ($n = 4$). The coefficients of variation were respectively 2.0 and 8.4% for plasma, and 6.7 and 14.2% for urine.

Pharmacokinetic analysis

Intravenous administration Ranitidine plasma level data have been analysed according to a two-compartment open pharmacokinetic model designed for rapid injection of a drug into the vascular compartment. The decline in ranitidine plasma concentration after i.v. administration was fitted by a computer program for each subject using the least-squares regression analysis and the method of residuals to the sum of the two exponentials: $C^t_p = Ae^{-\alpha t} + Be^{-\beta t}$, where C^t_p represents the plasma concentration at time t after the dose, α and β are the first-order rate constants of the fast and slow disposition processes, respectively, and A and B are the zero-time intercepts of the two components of the biexponential curve (Gibaldi & Perrier, 1975; Wagner, 1975).

The area under the plasma concentration-time curve (AUC) was determined by the trapezoidal rule and extrapolated to infinity. The elimination half-life of ranitidine ($t_{1/2}\beta$) was determined using the equation $t_{1/2}\beta = 0.693/\beta$, where β is the overall elimination rate constant estimated from the slope of the terminal log linear portion of plasma concentration decline. The apparent volume of distribution was calculated from the equation:

$$V_\beta = \frac{D}{AUC_{0-\infty}.\beta}$$

where D is the administered i.v. dose.

The volume of the central compartment (V_1) and the volume at steady-state (V_{ss}) were calculated from the following equations:

$$V_1 = \frac{D}{A + B} \text{ and } V_{ss} = \frac{k_{12} + k_{21}}{k_{21}} V_1.$$

Total systemic clearance (CL_{Tot}) was estimated by dividing the dose by the total area under the curve: $CL_{Tot} = D/AUC_{0-\infty}$. Renal clearance ($CL_R$) was calculated from $CL_R = X_u\ 0\text{–}6/AUC_{0-6}$, where X_u 0–6 is the amount of unchanged ranitidine recovered in the urine in the first 6 h after drug administration and AUC_{0-6} h the corresponding area under the curve.

Oral administration Plasma half-life after oral dosing was calculated using the overall elimination rate constant (k_{el}) which was derived by linear regression analysis using the 3 to 12 h plasma concentration data points. The area under the plasma concentration-time curve was determined by the trapezoidal rule and extrapolated to infinity.

Absolute bioavailability of ranitidine after oral administration was derived from the ratio of the total AUC following oral administration to the total AUC of the equivalent intravenous dose i.e.

$$F_p = \frac{AUC_{0-\infty}\ \text{p.o.}}{AUC_{0-\infty}\ \text{i.v.}}$$

where F_p is the fraction of the oral dose reaching the systemic circulation.

It is understood that, should ranitidine undergo first-pass enterohepatic circulation, oral bioavailability, F_p, is not an index of drug absorption.

Results

Ranitidine plasma concentration profiles after 150 mg intravenous and oral administration are shown in Figure 2. The corresponding pharmacokinetic parameters (mean values ± s.d.) are presented in Tables 1 and 2. As can be seen plasma levels after i.v. administration decline in a biexponential manner. An initial rapid fall ($t_{½}\alpha$: 6.6 ± 1.6 min) over the first 30 min is followed by a slower decline over the remaining period (0.75–12 h) characterized by a $t_{½}\beta$ of 1.73 ± 0.15 h.

The apparent distribution volume during the

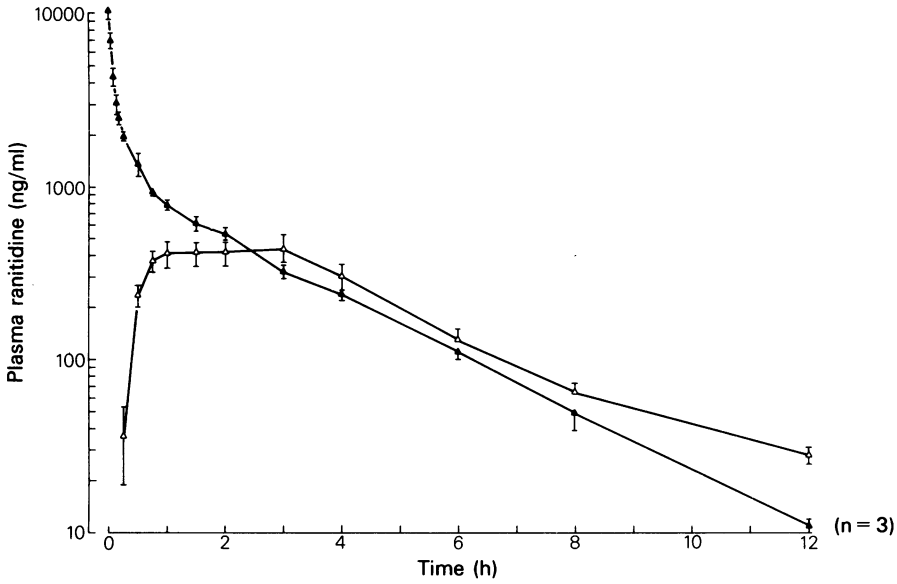

Figure 2 Mean (± s.e. mean) plasma concentrations of ranitidine after administration of 150 mg intravenously (▲) and orally (△) to five healthy volunteers.

Table 1 Pharmacokinetic data after i.v. administration of 150 mg ranitidine

	Subject						
	1	*2*	*3*	*4*	*5*	*Mean*	*s.d.*
Plasma concentration at end of injection (ng/ml)	6862	12262	12456	8228	12402	10442	2689
A (ng/ml)	5202	7512	3980	4966	6783	5689	1432
α (h^{-1})	7.48	7.78	6.65	6.32	4.46	6.54	1.30
$t_{½}\alpha$ (min)	5.58	5.34	6.24	6.60	9.30	6.61	1.56
B (ng/ml)	1223	952	1183	1407	1114	1176	165
β (h^{-1})	0.42	0.42	0.42	0.41	0.35	0.40	0.03
$t_{½}\beta$ (h)	1.65	1.66	1.64	1.70	2.00	1.73	0.15
AUC_{0-8} (ng ml^{-1} h)	3603	3212	3504	4236	4482	3808	530
$AUC_{0-\infty}$ (ng ml^{-1} h)	3717	3294	3582	4351	4726	3934	588
V_c (l)	23.3	17.7	29.0	23.5	19.0	22.5	4.4
V_{ss} (l)	80.9	79.2	87.0	71.9	64.1	76.6	8.8
V (l)	96.1	108.9	99.0	84.9	91.5	96.1	8.9
k_{12} (h^{-1})	4.35	4.34	3.70	3.52	2.21	3.62	0.87
k_{21} (h^{-1})	1.76	1.25	1.85	1.71	0.93	1.50	0.39
k_{el} (h^{-1})	1.78	2.61	1.52	1.50	1.67	1.82	0.46
CL (ml/min)	673	759	698	574	529	647	94
CL_R (ml/min)	505	651	635	444	363	520	123
Urinary recovery:							
0–2 h (% of dose)	56.8	59.9	68.1	51.0	46.9	56.5	8.2
0–24 h (% of dose)	72.7	85.5	90.1	77.0	68.0	78.7	9.1

Table 2 Pharmacokinetic data after oral administration of 150 mg ranitidine

	1	*2*	*3*	*4*	*5*	*Mean*	*s.d.*
C_{max} (ng/ml)	238	516	598	625	535	502	154
t_{max} (h)	0.5	3	1.5	3	3	2.2	1.2
AUC_{0-12} (ng ml^{-1} h)	1254	2544	1968	2997	2426	2237	661
$AUC_{0-\infty}$ (ng ml^{-1} h)	1316	2611	2103	3105	2525	2332	670
$t_{½}\beta$ (h)	2.38	1.93	2.91	2.14	2.23	2.32	0.37
k_{el} (h^{-1})	0.29	0.36	0.24	0.32	0.31	0.30	0.04
Urinary recover:							
0–2 h (% of dose)	4.4	8.6	9.3	6.5	6.2	7.0	2.0
0–24 h (% of dose)	16.0	36.4	28.1	28.0	24.9	26.7	7.3
F_p	0.35	0.79	10.59	0.71	0.53	0.60	0.17

elimination phase (V) of 96.1 ± 8.9 l exceeds the body water volume. Total body clearance (647 ± 94 ml/min) exceeds the renal clearance (520 ± 123 ml/min).

Ranitidine is rapidly excreted in high concentrations through the kidney. In the urine 47 to 68% of the dose is recovered within 2 h after i.v. injection and the cumulative urinary excretion in 24 h ranges from 68 to 90% of the dose (Figure 3).

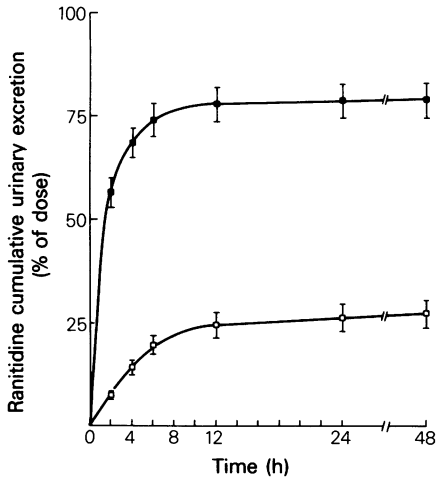

Figure 3 Mean (± s.e. mean) cumulative urinary recovery of ranitidine after administration of 150 mg intravenously (■) and orally (□) to five healthy volunteers.

Ranitidine absorption following oral administration is rapid showing an initial peak (ranging from 238 to 619 ng/ml) at 0.5–1.5 h after dosing. In four subjects the initial peak is followed by a second one (ranging from 223 to 625 ng/ml) appearing three hours after dosing. The terminal half-life $t_{½}\beta$ is 2.32 ± 0.37 h. The amount of unchanged ranitidine excreted in urine within 24 h ranges from 16 to 36% of the dose (Figure 3).

The calculated fraction of dose available (F_{pl} value) ranges from 0.35 to 0.79 with a mean ± s.d. value of 0.60 ± 0.17.

After oral administration of a 150 mg tablet of ranitidine subjects did not report any side effects. After the i.v. bolus injection three subjects experienced a brief sensation of facial warmth (2 × flushing). The two other volunteers reported lacrimation during the injection.

Discussion

It has been shown that the effect of ranitidine in inhibiting pentagastrin stimulated gastric secretion is dose related (Woodings *et al.*, 1980). Although the recommended oral dose of ranitidine is 150 mg twice daily the absolute bioavailability of this dose has not been determined.

The values for the pharmacokinetic parameters presented in this study are largely in agreement with earlier findings. Our AUC value, expressed per mg of i.v. dose, is 26.2 ng ml^{-1} h while Bogues *et al.* (1981) reported 29.7 ng ml^{-1} h for a 100 mg i.v. dose and McNeil *et al.* (1981) 24.4 ng ml^{-1} h for a 20 mg i.v. dose. The same authors found mean elimination half-lives of respectively 2.12 h and 1.91 h which are comparable with our finding of 1.73 h. From these data it can be concluded that ranitidine does not show dose-dependent kinetics with doses between 20 and 150 mg given intravenously.

The total volume of distribution (V) after 150 mg i.v. from our study is 41% greater than the mean body weight. This is in agreement with the observation of McNeil *et al.* (1981) who reported a value of 47% after a 20 mg i.v. dose and also with the data of Bogues *et al.* (1981) from which we calculated a distribution volume between 37 and 47% above the body weight after 100 mg i.v. These data indicate some binding of ranitidine in the tissues.

The renal clearance of unchanged ranitidine of 520 ml/min in our study is in accordance with the findings obtained by other investigators: e.g. McNeil *et al.* (1981) who reported CL_R of 489 ml/min; Bogues *et al.*

(1981) and Carey *et al.* (1981) who reported a similar CL_R value of 512 ml/min. These clearance values are considerably greater than the endogenous creatinine clearance indicating that, apart from glomerular filtration, an extensive tubular secretion of the unchanged drug also takes place. In addition, since different doses ranging from 20 to 150 mg have been used, the identical values for renal clearance indicate that tubular excretion does not show a saturation phenomenon within this dosage range.

Total body clearance (647 ml/min) is approximately 20% higher than the corresponding renal clearance indicating that ranitidine undergoes non-renal elimination involving biotransformation and/or extra-renal excretion in addition to renal excretion. Recently Carey *et al.* (1981) reported that metabolites in the urine amounted to approximately 9% of the dose after 100 mg i.v. administration and 7% after oral administration of the same dose, with ranitidine-*N*-oxide being the major metabolite.

Mean 24 h urinary recovery of unchanged ranitidine is 79% of the dose in our study while McNeil *et al.* (1981) found a mean value of 69% and Carey *et al.* (1981) 68%. This 70–80% urinary recovery after i.v. administration together with urinary excretion of metabolites of approximately 10% suggests that in man some unchanged ranitidine and/or metabolites are also excreted extra-renally e.g. via the bile.

After oral administration, plasma concentration time curves in four of our five subjects are bimodal. A similar pattern was also observed by Woodings *et al.* (1980) and Bogues *et al.* (1981). Since this phenomenon is not found after i.v. administration a possible explanation for the second peak could be that some of the orally administered rantitidine is released from a pre-systemic storage depot. An alternative and more likely explanation is that, due to a massive influx of ranitidine from the gut into the liver, there is a substantial biotransformation of ranitidine to its *N*-oxide metabolite after oral administration. Following biliary excretion some of this metabolite may undergo reduction to ranitidine by the gut flora and be reabsorbed. In the dog, the *N*-oxide is the major metabolite of ranitidine and has been shown to be preferentially excreted via the bile (Carey *et al.*, 1981). The existence of such mechanisms would also explain our finding of a significantly longer apparent half-life after oral (2.32 h) than after i.v. (1.73 h) administration of the same dose. Bogues *et al.* (1981) found a comparable $t_{1/2}$ prolongation from 2.12 after i.v. to 2.98 h after oral administration of 100 mg of ranitidine. McNeil *et al.* (1981) on the other hand reported that the elimination half-life was independent of the route of administration and we have no ready explanation for this discrepancy.

In our study the AUC per mg after a 150 mg oral dose is 15.5 ng ml^{-1} h. Compared to the AUC after the same dose given i.v. a mean apparent bioavailability of 60% (range 35–79%) was obtained for the oral dose. Woodings *et al.* (1980) recently reported a mean bioavailability of 49% (range 41–57%) after 20 to 80 mg doses *per os*; Bogues *et al.* (1981) reported 56% (s.d. ± 10) after a 100 mg oral dose while McNeil *et al.* (1981) reported 88% (range 63–124) after a 20 mg oral dose. The greater bioavailability found by the latter author may not only result from relatively greater AUC values after oral administration but also from smaller AUC values after i.v. administration which he reported. On the other hand oral AUC values generally show a large variability between subjects and this phenomenon could also explain the variability in absolute bioavailability observed by all authors.

The 24 h urinary recovery of unchanged ranitidine after oral administration of 150 mg is low (27% of dose) in comparison with the urinary recovery found after 150 mg i.v. (79% of dose). Although McNeil *et al.* (1981) reported a higher urinary recovery of 51% after the oral administration of 20 mg ranitidine, Carey *et al.* (1981), reported a similar low value of 27% after oral administration of 100 mg. The difference in urinary recovery after oral and i.v. dosing is essentially accounted for by the difference in excretion during the first 2 h following administration since 57% of the i.v. dose is recovered in the urine within the first 2 h as compared to only 7% after the oral dose. Percentage of dose excreted in the urine between 2 and 24 h is similar after the two routes of administration.

Estimate of absolute drug bioavailability based on urine data:

$$(Fu = \frac{X_u^{48}\ \text{p.o.}}{X_u^{48}\ \text{i.v.}} = 0.35)$$

was clearly lower than the availability estimate determined from the AUC values:

$$(F_p = \frac{AUC_{0-\infty}\ \text{p.o.}}{AUC_{0-\infty}\ \text{i.v.}} = 0.60).$$

The reason for this discrepancy is not clear from the available data. Since intravenously administered ranitidine showed a high recovery in urine as unchanged drug (X_u^{48}: 79% of dose) indicating urinary excretion as the major pathway for ranitidine elimination, the observed discrepancy may result from an associated too low recovery of the drug in the urine after the oral dose (X_u^{48} = 27%). This low recovery in urine in turn might conceivably be due either to a relatively larger fraction of ranitidine being metabolized when given orally and/or a higher percentage of the low drug plasma concentration following the oral route to undergo tubular reabsorption during its passage through the kidneys.

High tubular fluid concentrations from the high plasma levels after i.v. dosing, especially during the

first 2 h, might saturate a tubular reabsorption mechanism of the drug with consequent higher recovery in urine.

The urinary findings of ranitidine metabolites as reported by Carey *et al.* (1981) (9% of dose after i.v. route and 7% of dose after the oral route of 100 mg ranitidine), however, should indicate the first possibility to be less likely as explanation for the observed discrepancy in F_p and F_u.

In patients with duodenal ulcer 50% inhibition of acid output is known to be achieved with plasma concentrations of 100 ng/ml (Peden *et al.*, 1979). After administration of a single 150 mg tablet formulation, this inhibitory plasma concentration is reached within 30 min and maintained during 6 h. Hence 150 mg twice daily seems to be a reasonable therapeutic dosage regimen.

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