RANITIDINE UPON MEAL-INDUCED GASTRIC SECRETION: ORAL PHARMACOKINETICS AND PLASMA CONCENTRATION EFFECT RELATIONSHIPS

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1 Ranitidine oral kinetics and plasma concentration-effect relationships upon meal-induced gastric secretion were investigated in normal subjects. Four oral doses of ranitidine (50, 100, 150 or 200 mg) and placebo were tested.

2 Oral ranitidine showed a terminal half-life of about 2 h 25 min. Maximal plasma level was about 240 ng/ml for a 100 mg dose, and occurred about 1 h after dose. From the range of 50 to 200 mg dose, no indication of non-linearity was observed in the drug kinetics.

3 Ranitidine administration resulted in a dose-related reduction in meal-stimulated acid secretion reaching 46, 70, 82 and 92%, respectively. Mean ranitidine plasma concentrations producing 50 and 80% inhibition of acid secretion were 73 and 180 ng/ml, respectively, with great inter-individual variability. 150 and 200 mg ranitidine oral doses maintained IC₅₀ for at least 4.5 and 5.5 h, respectively. Upon oral administration, ranitidine exerted no effect on gastric emptying of the meal but slightly decreased the gastrin response to the meal.

Introduction

The discovery of histamine H₂ receptor antagonists has considerably improved the management of attacks of peptic ulcer disease (Finkelstein & Isselbacher, 1978; Grossman, 1978). However, as conventional H₂ receptor antagonists, such as cimetidine, achieve ulcer healing in 80% of patients at the very most (Bardhan, 1978) and furthermore may produce adverse (Kruss & Littman, 1978; Lavarenne & Moreau, 1980), the search for more selective and less toxic H₂ receptor antagonists remains mandatory.

Ranitidine hydrochloride, a furan ring derivative (*N*-2-(5-(dimethylaminomethyl)-furan-2-yl methylthio)ethyl-N1-methyl-nitroethene-1,1-diamine hydrochloride), is a new potent histamine H₂-receptor antagonist (Bradshaw *et al.*, 1979). Although it lacks the imidazole ring of histamine, it has shown powerful inhibitory effects on gastric acid secretion in animals and man (Bohman *et al.*, 1980; Domschke *et al.*, 1980; Konturek *et al.*, 1980; Peden *et al.*, 1979; Sewing, *et al.*, 1980).

The purpose of this study was to evaluate the anti-secretory effect of ranitidine upon meal-stimulated gastric secretion in normal individuals. The drug's oral pharmacokinetics and the relationships between its plasma concentrations and inhibitory effects were investigated.

Methods

Subjects

Five healthy volunteers (three men and two women, aged 22–45 years) participated in the study. Informed consent was given by each subject. None had a history of oesophageal or peptic ulcer, liver disease or haematological disorder. Approval for the study was obtained from the Human Research Committee at the Delegation Generale à la Recherche Scientifique et Technique (DGRST) (July 1979). Four oral doses of either ranitidine (50, 100, 150 or 200 mg) or a placebo

were administered to each subject, in randomized sequences and in a double-blind manner. In the morning after a 12 h fast, each individual received four half-tablets containing either 0 or 50 mg of ranitidine each. The tests were separated by at least three days. Blood pressure, heart rate and respiration were monitored regularly during the study and the subjects were observed for subjective symptoms. No drug related side effects were noted.

Stimulation of gastric secretion

Placebo or ranitidine was administered orally at time zero. One hour later, a triple lumen plastic catheter (a Salem pump tube No 14, external diameter 5 mm, internal diameter 2.5 mm) with an additional plastic catheter (external diameter 3 mm, internal diameter 1.5 mm) was introduced via the naso-pharynx and located at the most dependent part of the stomach. Correct positioning of the gastric probe was checked by the water recovery test. The subjects were in a semi-recumbent position.

The stomach was emptied and a 400 ml liquid protein test meal was introduced over a 2–3 min period. The test-meal was composed of 36 g of Liebig meat extracts corresponding to 20 g of protein (molecular weight about 13.000 daltons), 6 g of carbohydrates, 0.1 g of lipids, 14 mEq of Na^+ and 129 mEq of K^+ . The osmolality of the liquid test meal was 660 mosm and the pH was adjusted to 4.5 by addition of a HCl acid solution.

Throughout the 90 min duration of the test, 3–5 ml of gastric content were aspirated every 2 min through the wider lumen of the gastric tube. The pH was determined with a pHmeter (Heito type PS 51 T) and the samples were returned to the stomach while 0.4 M sodium bicarbonate was infused into the stomach by the second lumen of the tube at a rate required to maintain the gastric pH at 4.5. The number of mmoles of bicarbonate necessary to maintain the gastric pH constant is assumed to be equal to the number of mmoles of acid secreted (Fordtran & Walsh, 1973). Twenty ml of gastric fluid were aspirated through the main lumen of the gastric tube and returned with a syringe 2 to 3 times every minute to ensure that the gastric content was well mixed and homogenous.

The acid secretion rate was evaluated for every 15 min (mmol/15 min) and for the duration of the test (mmol/90 min). Inhibition of acid secretion by ranitidine was calculated by comparison of acid output under ranitidine with placebo values for each 15 min period.

Assessment of gastric emptying of the liquid test meal

Gastric emptying of the liquid protein meal was assessed 45, 75 and 90 min after introduction of the

meal by repeated measurements of both intragastric volume (IGV) and protein concentration (PC) in the gastric content. IGV was estimated using a double dilution technique (George) with phenol red according to the following equation: $\text{IGV} = \text{V2} (\text{C2} - \text{C3}) / (\text{C3} - \text{C1})$ where V2 and C2 represent respectively volume and concentration of the added phenol red solution, C1 represent the concentration of phenol red in the gastric fluid before addition of V2, and C3 its concentration after intragastric introduction of V2 C2 and after thorough mixing with the syringe. Phenol red and protein concentrations in the gastric content were evaluated spectrophotometrically at 560 and 278 nm respectively, after appropriate dilution.

At 278 nm, optical absorption of phenol red was of small magnitude but was systematically subtracted from PC values using appropriate correction curves.

The amount of protein remaining in the stomach at any given time corresponded to the product $\text{IGV} \times \text{PC}$ and was expressed as percent of the total protein content of the meal initially introduced.

Gastrin and ranitidine assays

Blood was withdrawn through a non-heparinized indwelling catheter inserted into a cubital vein, at time 0, 30, 60, 90, 120, 150, 180, 210, 240 and 270 min after administration of either ranitidine or placebo.

Plasma ranitidine was assayed by high pressure liquid chromatography (Carey & Martin, 1979). The detection limit was 10 ng/ml.

Gastrin radioimmunoassay was carried out according to Yalow & Berson (1970) from serum samples obtained at 0, 60, 90, 120, 150, 180, 240 min after administration of either ranitidine or placebo. The antigastrin antibody used was obtained from guinea pigs injected with crude porcine gastrin. Highly purified porcine gastrin G17 served as standard and 125 I synthetic human 17 gastrin I as tracer. Intra-assay reproducibility of the radioimmunoassay was within 7%. All samples were assayed in duplicate and the average value used as serum concentration (Accary & Bonfils, 1973).

Pharmacokinetic analysis

Ranitidine oral concentration-time data were analysed by standard procedures. Terminal data were fitted to the equation

$$C(t) (\text{terminal}) = \text{Be}^{-\text{Bt}} \quad (\text{equation 1})$$

The area under curve from the first to the last measures, $(\text{AUC})^n_1$, was calculated by the trapezoidal rule. The area under curve from zero to infinite time was obtained by extrapolation, as follows:

$$(AUC)^\infty_1 = 0.5 \cdot t_1 \cdot C_1 + (AUC)^n_1 + \frac{C_n}{\beta} \quad (\text{equation 2})$$

where (t_1, C_1) was the first concentration-time data and C_n was the last measured concentration.

Analysis of variance (Fisher & Yates, 1943)

Since four doses (50, 100, 150, and 200 mg) have been administered, the parameters $C_{\max}/D$ (D =dose), $t_{1/2}$, β and $(AUC)^\infty_0/D$ were submitted to an analysis of variance to detect a possible dose-dependent non-linearity of the drug kinetics.

Concentration-effect relationships

Ranitidine inhibitory effect, E , was evaluated by the formula

$$E = 100 \cdot (Q_p - Q_r) / Q_p \quad (\text{equation 3})$$

where Q_p and Q_r were respectively, acid output under placebo and under ranitidine. As acid output was measured only between 60 and 150 min after the administration of the drug, only the values of ranitidine concentration, $C(t)$, and inhibitory effect, $E(t)$ at $t = 90, 120$ and 150 min were used. Consequently for each subject and for each dose, three pairs of $(C(t), E(t))$ were available. The data were submitted to a standard regression analysis:

$$E = a \cdot \text{Log} C + b \quad (\text{equation 4})$$

(r : correlation coefficient). Equation 4 was tested for each subject, for each dose, for each time of measurement and for the whole set of data, pooled together. Occasionally, a difference in correlation was assessed by using the Fisher z -transformation:

$$z = 1/2 \log \frac{1 + r}{1 - r}$$

Results

Ranitidine plasma concentration and oral kinetics

Ranitidine plasma concentration-time data are depicted in Figure 1. Maximal drug level occurred at $t_{\max} = 60$ min after the dose, excepted only in two cases where $t_{\max} = 90$ min.

Pharmacokinetic parameters are shown in Table I. Terminal half-life, $t_{1/2}$, maximal concentration, $C_{\max}$, and area under curve, $(AUC)^\infty_0$, in reference to dose, were submitted to an analysis of variance. $C_{\max}$ was about 240 ng/ml for a 100 ng dose. Terminal half-life was 1.7 to 3 h for the four doses tested.

Figure 1 Plasma ranitidine concentrations (ng/ml) after oral administration of 50 (○), 100 (◆), 150 (▲) or 200 (△) mg to five healthy volunteers. Mean $\pm$ s.e. mean IGT = intra-gastric titration.

Inhibitory effects of ranitidine on acid secretion

The effects of incremental doses of ranitidine on protein meal-stimulated gastric acid output after oral administration are shown in Figure 2. The protein meal resulted in a 60 min steady acid response which was reduced in a dose-related manner under ranitidine. When expressed in terms of cumulative acid output over the 90 min period, acid reduction (%) reached, according to doses, 40 (50 mg), 70 (100 mg), 82 (150 mg) and 92 (200 mg), respectively. With the two highest ranitidine doses, stimulation of acid secretion by the test meal did not develop earlier than 45 min after introduction of the meal, and acid output was almost null.

Concentration-effect relationships (Table 2)

As indicated, regression equations, $E = a \cdot \text{Log} C + b$, were performed for each subject, for each dose, for each time of assay and for the whole set of data, pooled together. Concentration-effect relationships were highly significant in all subjects. However large interindividual variations were observed. Effect was not related to concentration at the low dose $D = 50$ mg. There was a significant degradation of the concentration-effect relationship from 90 min to 150 min after dose.

Effects of ranitidine on gastrin response to the protein-meal and on gastric emptying of the protein meal

Oral administration of ranitidine reduced the gastrin response to the meal with all doses of the anti-secretory agent (Figure 3). Compared with placebo, peak gastrin responses were lower for all ranitidine

Table 1 Oral ranitidine pharmacokinetic data in five normal subjects

Subject	$C_{max}/Dose$ ($ng\ ml^{-1}\ h\ mg^{-1}$)					$t_{1/2}\beta$ (h)	$(AUC)/Dose$ ($ng\ ml^{-1}\ h\ mg^{-1}$)				
	50 mg	100 mg	150 mg	200 mg			50 mg	100 mg	150 mg	200 mg	
1	2.36	0.88	1.81	1.91	3.10	3.06	8.79	4.48	6.34	6.42	
2	2.52	2.43	2.40	4.00	2.95	1.86	9.48	5.97	5.84	7.87	
3	3.08	1.78	2.91	2.71	2.10	3.00	7.86	6.54	7.14	6.06	
4	0.80	3.66	2.95	1.41	4.47	1.97	4.5	10.03	6.64	4.43	
5	1.56	3.18	1.37	2.30	2.17	1.20	3.96	5.41	3.81	5.97	
Mean	2.06	2.39	2.29	2.47	2.96	2.22	6.93	6.49	5.95	6.15	
s.d.*			0.42			0.29					0.84
F-value			0.18			3.14					0.26

Figure 2 Inhibitory effects of a placebo (●) and of ranitidine 50 (○), 100 (◆), 150 (▲) or 200 (△) mg administered orally on protein meal-stimulated gastric acid secretion. Mean $\pm$ s.e. mean in five healthy volunteers. Acid secretion was measured by the intra-gastric titration technique. On abscissa, time was counted from 1 h after administration of ranitidine.

doses. The difference between peaks was significant ($P < 0.05$), except for ranitidine 100 mg, but there was no clear-cut dose-effect relationship. Plotting plasma ranitidine ν serum gastrin concentrations suggested an inverse correlation which, however, was not statistically significant ($P < 0.1$).

The percents of protein meal remaining in the stomach 45, 75 and 90 min after introduction of the protein liquid test meal were statistically different from individual to individual, but there was no statistical difference between mean meal emptying after ranitidine compared to placebo. These findings, together with the dose-related increase in plasma ranitidine concentration (Figure 1), indicate that the prolonged acid inhibitory effect obtained with high doses of ranitidine is unlikely to be due to delayed gastric emptying of the drug.

Discussion

Our data confirmed previous reports. Ranitidine terminal half-life, $t_{1/2}$ was found to be 2.1 ± 0.1 h (mean $\pm$ s.e. mean), (Lebert *et al.*, 1981), 1.9 ± 0.1 h (McNeil *et al.*, 1981) and 2.25 ± 0.1 h in our data. Table 1 shows that, submitted to an analysis of variance, the ratios $C_{max}/dose$, $(AUC)^x_0/dose$ and the terminal half-life, $t_{1/2}\beta$, indicated no significant dose-effect. Analogous observations have been reported, for the range of dosage from 20 to 100 mg (McNeil *et al.*, 1981).

The intragastric titration technique of Fordtran & Walsh (1973) has been used in these studies as it is regarded as a technique of choice for pharmacological assessment of antiseecretory drugs in human (Bonfils *et al.*, 1982; Kaojaren *et al.*, 1981; Richardson, 1978). Results from our laboratory

Table 2 Oral ranitidine concentration — acid inhibitory effect relationships ($E = a \text{ LogC} + b$, $E =$ inhibitory effect, see text for definition, $C =$ oral ranitidine concentration, $r =$ correlation coefficient). Part A = individual relationships in five normal subjects, part B = relationships for each dose, part C = relationships at each time of measures. When all the data were pooled together, the global relationship was $E = 32.1 \text{ LogC} - 86.9$ ($r = 0.80$, $P < 0.0001$).

Subjects	Part A			Dose (mg)	Part B			Time (min)	Part C		
	a	b	r		a	b	r		a	b	r
1	46.1	-167	0.79**	50	12.0	-10.8	0.31 ^{NS}	90	35.5	-94.4	0.93*
2	33.2	-93.3	0.88**	100	49.9	-169	0.82**	120	34.1	-92.3	0.81**
3	34.1	-92.3	0.93**	150	30.1	-76.7	0.63*	150	22.2	-46.4	0.60*
4	30.6	-83.2	0.90**	200	43.6	-152	0.73**	—	—	—	—
5	23.9	-37.1	0.84**	—	—	—	—	—	—	—	—
Mean	33.6	-94.5	—	—	33.9	-102.2	—	—	30.6	-77.7	—
s.d.	8.1	46.5	—	—	16.8	73	—	—	7.3	27.1	—

NS = non significant
* = $P < 0.01$ ** = $P < 0.001$

Figure 3 Serum gastrin responses to protein meal stimulation after oral administration of a placebo (●) or of ranitidine 50 (○), 100 (◆), 150 (▲) or 200 (△) mg to five healthy volunteers. Gastrin responses were studied concurrently with acid responses as measured by the intragastric titration (IGT) technique.

indicated that IGT yields in normal individuals reproducible secretory responses which are equal to peak responses to pentagastrin, in agreement with earlier reports (Fordtran & Walsh, 1973). IGT in response to a protein meal provides a measurement of the physiological acid secretory response, since acid response results from integration of cholinergic release through gastric distension, gastrin release, and probably also from the triggering of intestinal stimulatory mechanisms (Grossman, 1979). When testing antisecretory drugs IGT, therefore, offers considerable advantages over the analytical study of the effects of the drug on each stimulant taken in isolation (Bonfils *et al.*, 1982).

The present study provides dose-response relationships for the effects of the new histamine H_2 -receptor antagonist, ranitidine, on meal-induced gastric secretion, in conditions approaching those of the daily life. In contrast to earlier reports (Hagenmuller *et al.*, 1979; Konturek *et al.*, 1980) a large range of doses was used.

Table 2 suggested that a dose of 50 mg was unable to elicit a significant-concentration effect relationship. It is interesting to note a gradual degradation of the concentration effect correlation with time: from 90 to 150 min after drug, the correlation coefficient decreased from 0.93 to 0.60 ($P < 0.01$).

As can be deduced from Table 2, the 50% and 80% inhibition of meal-stimulated gastric acid secretion were obtained with ranitidine concentrations of 73 ng/ml (range, 111, 78, 75, 65, 38 ng/ml) and 180 ng/ml (range, 212, 207, 185, 156, 134 ng/ml) respectively. The IC_{50} value is thus very similar to that noted earlier by Peden *et al.* (1979) in duodenal ulcer patients but is markedly lower than that noted for cimetidine which

varies from 500 ng/ml (Burland *et al.*, 1975) to 1,000 ng/ml (Bodemar *et al.*, 1977). Gugler *et al.* (1981) indicated an exact IC_{50} value of 780 ng/ml in normal individual.

The 4/1 to 7/1 potency ratio between ranitidine and cimetidine is approximately the same whether both drugs are compared on the basis of IC_{50} values or on that of acid inhibitory effects of equivalent doses (Hagenmuller *et al.*, 1979; Konturek *et al.*, 1980; Mignon *et al.*, 1980, 1981; Walt *et al.*, 1981). At the cell level (Cheret *et al.*, 1981), i.e. independently from drug bioavailability and acid measurements, comparison of pA_2 for ranitidine and cimetidine, in respect to competitive inhibition for histamine stimulation of adenylate cyclase activity, also showed a 4/1 potency ratio. On the whole, this suggests that difference in potency between ranitidine and cimetidine for inhibition of acid secretion does not result, in the same subject, from difference in bioavailability.

As to duration of ranitidine action, dose-dependence is suggested via prolongation of plasma ranitidine high levels: as shown in Figure 1, ranitidine plasma concentration was 200 ng/ml or more during meal stimulation of gastric secretion when 150 or 200 mg ranitidine doses were administered orally before the meal; 200 mg dose did not seem to offer much advantage over 150 mg for the suppression of meal-induced acid secretion (Figure 2). Both dosages, however, were clearly superior to lower dosages and maintained ranitidine plasma concentrations above the IC_{50} for at least 4.5 h with 150 mg and 5.5 h with 200 mg (Figure 1). Such concentrations are probably high enough to considerably reduce the interdigestive and nocturnal acid secretion as suggested by the observations of Peden *et al.* (1979).

We found that ranitidine exerted an inhibitory effect upon meal-induced gastrin release. However,

no clear dose-response relationship could be obtained for this effect. Owing to the technique used, inhibition of meal-induced gastrin release cannot be ascribed to changes in antral pH nor to variations in protein content of the stomach or of the intestine since emptying of the protein meal was not altered by ranitidine. Reduced gastric distension, through ranitidine-induced diminution of gastric secretory volume can also partly account for the altered gastrin response to the test meal; however, fundic as well as antral distensions are poor stimuli for gastrin release in normal subjects (Bergegardh *et al.*, 1976; Richardson *et al.*, 1976). Ranitidine inhibitory effect on meal-induced gastrin response was not suggested by the results of Konturek *et al.* (1980) and Hagenmuller *et al.* (1979), but these authors did not perform ranitidine dose-response studies. Further investigations are obviously needed to check our findings and document their relevance in respect to tolerance to the drug.

Under the conditions of the experimental method of meal-stimulated gastric secretion, it can be concluded that ranitidine is a potent inhibitor of gastric secretion after oral administration from four to seven times superior to cimetidine. It has no effect on gastric emptying of the meal, but slightly decreases gastrin response. Although obtained in normal individuals, the results of the present study led us to confirm that ranitidine is a very effective means of reducing acid secretion in peptic ulcer disease and related disorders.

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