

Ranitidine—a new H₂-receptor antagonist

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SUMMARY The pharmacokinetics and gastric antisecretory effects of a new histamine H₂-receptor antagonist, ranitidine hydrochloride, have been investigated in healthy subjects. In the pharmacokinetic study six subjects received 20 mg, 40 mg, and 80 mg ranitidine, both orally and intravenously. Plasma levels of ranitidine were dose-related and in most subjects after oral drug the concentration time curve was bimodal. The estimated elimination half-life was 140 minutes and the bioavailability of the oral drug was about 50%. Five subjects received bolus intravenous injections of ranitidine 20 mg, 40 mg, and 80 mg during continuous gastric stimulation with pentagastrin. There was a dose-related reduction in acid output ($P < 0.05$).

Recently, the aminomethylfuran derivative, ranitidine (N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine) (Fig. 1) has been described as a potent H₂-antagonist.¹ *In vivo* and *in vitro* studies have shown that ranitidine is a competitive H₂-antagonist without significant activity at histamine H₁-receptors or at cholinergic receptors. In experimental animals gastric secretion stimulated by histamine, pentagastrin or a test meal was inhibited by ranitidine. It was effective by both parenteral and oral routes and was approximately four to five times more potent than cimetidine. In the present two studies we investigated the effects of ranitidine in healthy volunteers.

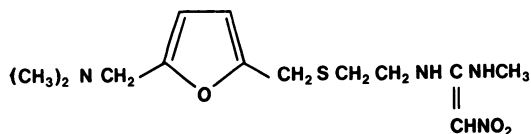


Fig. 1 Chemical structure of ranitidine.

Methods

SUBJECTS

Eleven healthy men were studied in two groups. In the first study there were six subjects with a mean age of 27 years (range of 23 to 31 years) and a mean weight of 69 kg (range of 58 kg to 76 kg). There were five subjects in the second study with a mean age of 29 years (range of 25 years to 35 years) and a mean weight of 71 kg (range of 63 kg to 76 kg). Informed consent was obtained from each volunteer.

TEST PROCEDURES

In both studies the subjects fasted overnight and the

tests began between 9 and 10.30 am.

The first study investigated the acceptability and pharmacokinetics of ranitidine hydrochloride after oral and intravenous administration. Each subject received on different occasions and by both routes 20 mg, 40 mg, and 80 mg measured as base, except one subject who did not receive the highest intravenous dose. The intravenous drug was diluted to 20 ml with normal saline and was injected into an antecubital vein over a period of two minutes. Blood samples were obtained through a Butterfly needle which was inserted into a vein in the other arm and kept patent with heparinised saline. The times of blood samples were pre-drug and 2, 5, 15, 30 and 45 minutes and 1, 1½, 2, 3, 4, 5, 6, 7, and 24 hours after administration of the drug. The subjects were supine during the intravenous injection and for the following hour, after which they were ambulant but rested semi-reclining for 15 minutes before the time of each blood sample. Pulse rate and blood pressure, using a Hawksley random zero sphygmomanometer, were also recorded at these times. A lead 2 electrocardiogram was recorded during the injection and for one-minute periods at the blood sample times during the post-drug hour. The subjects emptied their bladders before the injections and obtained control specimens. Urine was then collected over the fixed periods 0-2, 2-4, 4-6, 6-8, and 8-24 hours after the drug was given.

The oral drug was taken as 20 mg tablets with 200 ml tap water. Pulse rates, blood pressures, and blood samples were obtained in the manner described for the intravenous drug except that the subjects were semi-reclining for two hours after administration and the sample times were pre-drug and ½, 1, 1½, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours.

After the oral drug, urine samples were collected as described for the intravenous drug.

The second study investigated the inhibition of pentagastrin stimulated gastric acid secretion by intravenous ranitidine. Each subject received on different days 20 mg, 40 mg, and 80 mg ranitidine hydrochloride measured as base. The injections were given in the same way as in the first study, except that sometimes a superficial forearm vein was used.

Each gastric secretion test was carried out using a Salem sump tube size 14CH with continuous suction from an Anpro AN41 sump pump and intermittent clearing of the tube and suction with a syringe as necessary. Throughout each test the subject sat on a couch with the backrest at 45°. The nasogastric tube was positioned by measurement, as described by Hanson and Hobsley² and its function was checked by means of the water recovery test. On each occasion the subjects received a continuous intravenous infusion of pentagastrin 10 µg per hour for three hours (mean dose 0.14 µg/kg-h). After first emptying the stomach, gastric contents were collected over 15-minute periods for one hour. The injection of ranitidine was then given and the collections were continued for a further two hours. Pulse rate, blood pressure, and a lead 2 electrocardiogram were recorded before starting the pentagastrin, immediately before the injection of ranitidine and for two hours afterwards at the times used in the first intravenous study.

During both studies a detailed record was kept of all occurrences which might have been side-effects of ranitidine. The subjects were asked to volunteer any symptoms and were also questioned directly after each study day.

LABORATORY MEASUREMENTS

Plasma levels of ranitidine were measured in all the blood samples from the first study, using a high pressure liquid chromatography method with a limit of sensitivity of 10 ng/ml.

Haematology and clinical chemistry measurements were obtained from some of the blood samples. These were the pre-drug and 24-hour samples, the one-hour samples after intravenous drug and the two-hour samples after oral drug. The measurements were haemoglobin, PCV, MCHC, RBC, MCV, MCH, WBC, and differential, ESR, glucose, BUN, creatinine, bilirubin, total plasma protein, albumin, alkaline phosphatase, ALT, AST, γ-GT, gastrin, serum sodium, and potassium.

All urine samples were tested in both studies with Ames Multistix for glucose, ketones, blood, protein, urobilinogen, bilirubin, and pH.

In the second study the volumes of the gastric collections were recorded and the concentration of

acid in each collection was measured by titration against 0.1 N sodium hydroxide to pH 7. The acid output for each 15-minute period was derived from the product of volume and acid concentration.

INTERPRETATION OF DATA

In the first study the ranitidine plasma concentration data were used to estimate the elimination half-life and bioavailability of the drug. The use of a compartmental model requiring two exponential terms did not give satisfactory agreement with the data for either route of administration. Therefore, a single exponential was fitted to the tail of each concentration time curve to estimate the ultimate half-life and the area under that part of the curve. The remaining area was calculated by means of the trapezium method. Wilcoxon's signed rank test was applied to the estimated half-lives for evidence of a difference between the two routes. The bioavailability was expressed as the percentage ratio of area of oral curve to area of intravenous curve.

In the second study the results were first tested by analysis of covariance to see if the level of acid secretion before ranitidine influenced the levels after-

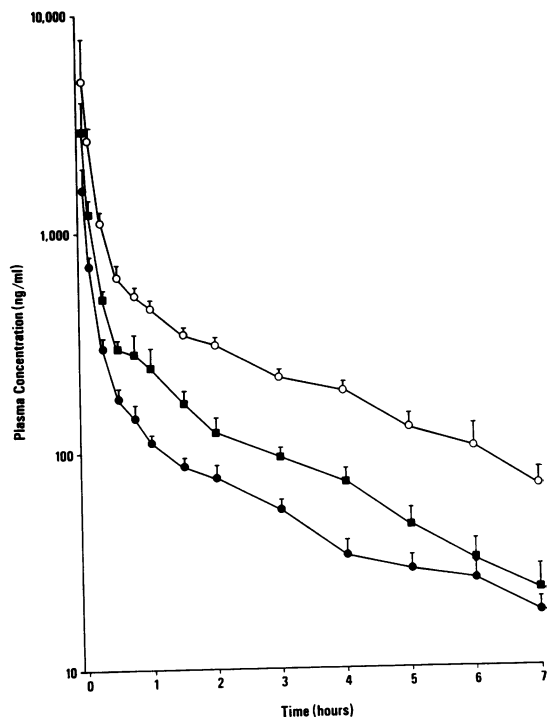


Fig. 2 Plasma concentrations of ranitidine in six subjects (mean and standard error) after intravenous administration of 20 mg (●), 40 mg (■), and 80 mg (○). Twenty-four hours after the doses the values were less than 10 ng/ml in all subjects.

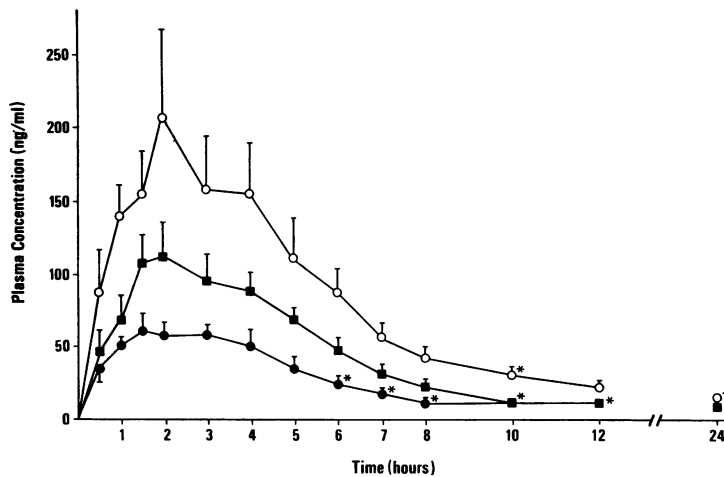


Fig. 3 Plasma concentrations of ranitidine in six subjects (mean and standard error) after oral administration of 20 mg (●), 40 mg (■), and 80 mg (○). Some individual values were less than 10 ng/ml (*).

wards. Analysis of variance was then used to test for a dose-related effect after ranitidine.

Results

After both intravenous and oral administration dose-related plasma concentrations of ranitidine were observed (Fig. 2 and Fig. 3).

After oral administration ranitidine was rapidly absorbed and individual plasma levels reached a peak at $\frac{1}{2}$, one, or $1\frac{1}{2}$ hours. In five subjects there was a second peak at three or four hours after dosing. Although it is not seen in the mean data (Fig. 3) this bimodal pattern was readily apparent in the individual results.

The median estimate of elimination half-life was 140 minutes and there was no evidence of a difference between the two routes of administration. The estimated bioavailability of oral compared with intravenous drug was 49% (41–57, 95% confidence limits).

The gastric acid output in individual subjects in response to pentagastrin stimulation before the

administration of ranitidine was similar on each occasion. Analysis of the data showed no evidence that the values obtained after ranitidine were influenced by the pre-drug values. Therefore, the absolute values after drug were used in the subsequent analyses rather than the changes in values. After the administration of ranitidine the volumes of gastric acid secretion and the concentrations were reduced in all five subjects. The mean results for each hour are shown in the Table and the mean 15-minute acid outputs in Fig. 4. The mean acid concentrations and acid outputs were significantly dose-related ($P < 0.05$) after the administration of ranitidine.

There were no changes in pulse rate, blood pressure, the electrocardiogram, haematology, clinical chemistry, or urine analysis attributable to ranitidine.

SIDE-EFFECTS

No side-effects occurred in the first study in relation to the oral drug and only one was reported after intravenous administration. This occurred five minutes after receiving 20 mg ranitidine by injection

Table Effects of intravenous ranitidine on pentagastrin-stimulated gastric secretion in five subjects (mean and standard deviation)*

	Dose (mg)	Before ranitidine		After ranitidine			
		-1 to 0 hour		0 to 1 hour		1 to 2 hours	
Volume (ml/15 min)	20	56	(11)	26	(9)	23	(5)
	40	49	(9)	21	(3)	22	(3)
	80	57	(18)	21	(10)	14	(6)
Acid concentration (mmol/l)	20	99	(10)	68	(26)	66	(34)
	40	86	(31)	46	(17)	49	(12)
	80	92	(7)	27	(13)	19	(15)
Acid output (mmol/15 min)	20	5.6	(1.0)	2.0	(0.9)	1.5	(0.9)
	40	4.5	(2.3)	1.2	(0.3)	1.1	(0.2)
	80	5.5	(1.6)	0.9	(0.3)	0.3	(0.2)

*Values for standard deviation in parentheses

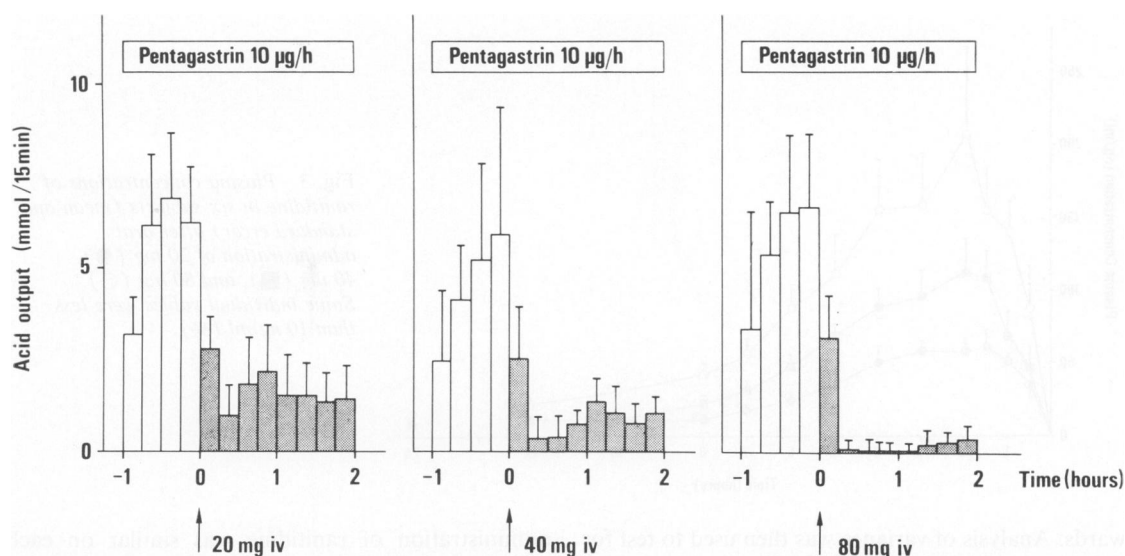


Fig. 4 Effects of intravenous ranitidine on pentagastrin-stimulated gastric secretion in five subjects (standard deviation)

when the subject complained of a brief sensation of warmth in the face. He did not have a similar experience with the higher doses. In the second study one subject felt sleepy one hour after receiving 80 mg and another felt faint and looked pale for five minutes starting five minutes after the 40 mg dose, but they had no symptoms after the other doses. One subject had a headache in the evening after all three gastric tests and immediately after the 80 mg injection he felt nauseated and retched for about a minute. He appeared pale and sweaty for five minutes and for a further 10 minutes complained of 'tingling in the stomach' after which he appeared to be recovered. One subject who was given the 80 mg dose into a superficial wrist vein complained of itching along the vein one minute after the injection. A flare developed around the vein, for most of the length of the forearm, which began to fade after six minutes but was visible for almost an hour. He had a headache during the evening and then vomited after eating a hasty meal.

Discussion

Inhibition of pentagastrin stimulated gastric acid secretion has been used to demonstrate the anti-secretory activity of H_2 -receptor antagonists such as metiamide and cimetidine.³ In this study we used a dose of infused pentagastrin which would cause submaximal stimulation of gastric secretion,⁴ and found that individual responses were reproducible. After the administration of ranitidine we found a significant dose-related inhibition of the gastric acid

secretion. Similar findings were reported by Domschke *et al.*⁶ who administered ranitidine by continuous intravenous infusion. This inhibitory effect of ranitidine is similar to that of other H_2 -receptor antagonists such as cimetidine. It seems reasonable to conclude therefore that, like cimetidine, ranitidine inhibits gastric secretion in man *via* blockade of gastric H_2 -receptors. This agrees with the findings of Peden *et al.*⁶ who reported a dose-related inhibition of pentagastrin-stimulated acid secretion in eight patients after 40 mg and 80 mg ranitidine had been administered intraduodenally.

In the pharmacokinetic study we found that ranitidine was well absorbed when given by mouth with a bioavailability of 49%. There should therefore be no difficulty in achieving inhibition of gastric secretion by the oral route. This has been demonstrated by Peden *et al.*⁶ who found marked inhibition of nocturnal gastric secretion in seven patients who took 80 mg ranitidine by mouth.

The plasma concentration time curves after oral ranitidine in five of our subjects were bimodal. A similar pattern has been described after administration of oral cimetidine to fasting subjects,⁷ but it has not yet been explained. The second peak in the plasma concentration time curves after ranitidine could be explained by enterohepatic circulation of ranitidine, but no information is available on this at the present time.

It is difficult to assess the significance of side-effects reported in small open studies such as these. The minor complaints like headache are perhaps more likely to be related to the total experimental

conditions rather than to the drug under investigation. Nevertheless, it is possible that the bolus intravenous injection of ranitidine may sometimes cause feelings of faintness or nausea and in one subject there appeared to be some irritation of the vein that received the injection. There were, however, no cardiovascular changes and no evidence of short-term toxicity.

In view of its inhibition of gastric secretion and good bioavailability we suggest therefore that ranitidine is a suitable drug for clinical trials in patients who have peptic ulceration or other pathological hypersecretory conditions.

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