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Effect of Famotidine and Ranitidine on Gastric Secretion and Emptying in the Rat

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ABSTRACT

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The antisecretory and gastric motor effects of the new H_2-receptor antagonist famotidine (MK-208) were compared with those of ranitidine in the rat. The Shay rat preparation (5 hr) was used for studying gastric secretion. Gastric motility was assessed by measuring gastric emptying of a liquid meal. Both compounds inhibited acid secretion in a dose-dependent fashion. Calculated ED_{50} values were 0.80 and 6.84 $mg \cdot kg^{-1}$ for famotidine and ranitidine, respectively. Therefore, in this animal model, famotidine was about 9 times more potent than ranitidine. The duration of antisecretory action however, was virtually the same for both drugs. The effect of the two drugs - administered at equiactive antisecretory doses - on gastric emptying was different. Indeed, ranitidine significantly accelerated emptying rate, whereas famotidine was ineffective. The results of the present investigation demonstrate that famotidine is a potent and selective antisecretory compound.

Key words: gastric motility, H_2-antagonists

INTRODUCTION

The development of the histamine H_2-receptor antagonists has radically altered the approach to treatment of peptic ulcer. These compounds represent the first group of drugs shown conclusively to increase the rate of healing of peptic ulcer and produce rapid relief of symptoms. The value of cimetidine and ranitidine in the short-term treatment of ulcer disease is now established beyond doubt. Similarly, low-dose, long-term maintenance therapy has been shown to reduce unequivocally the incidence of relapse and to offer a very real alternative to surgery.

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The natural history of the disease, however, was modified neither by these nor by the other antiulcer compounds, so peptic ulcer remains chronically relapsing [Hirschowitz, 1983] and, after healing, pharmacological treatment must be continued for a long time and perhaps forever [Cimetidine forever (editorial), 1978].

Considerable research and effort has been directed towards the development of new H_2-receptor antagonists with the aim of obtaining more potent and safe drugs. Hundreds of compounds have been synthesized in several laboratories. Many of them presented no advantages over the older molecules and some showed serious toxicological problems. Only a small number of compounds reached human pharmacology and are now under clinical investigation. Among these, famotidine (compound marked YM-11170 or MK-208) has been successfully employed in the short-term treatment of peptic ulcer and other acid-related diseases (for review see Bianchi Porro, 1985).

In vivo studies [Ishihara and Okabe, 1983; Takagi et al., 1982; Takeda et al., 1982] have shown that this compound displays strong antisecretory activity (from 40 to more than 100 times that of cimetidine, depending on the experimental conditions) and high efficacy in different models of experimentally induced gastric and duodenal lesions. Nevertheless, a controversy exists as to the duration of its antisecretory action. Although Takagi et al. [1982] reported famotidine to be longer-lasting in comparison with cimetidine, Buyniski et al. [1984] found that both drugs had the same time course for secretory inhibition.

The aim of the present investigation was therefore to study the antisecretory action of famotidine and especially its duration of action in rats. Since almost all antisecretory compounds can also affect gastric motility [Scarpignato, 1985], the effect of the compound on gastric emptying was also examined. Ranitidine, never studied in comparison with famotidine, was used as a reference compound.

Results of the present investigation have been presented at the International Symposium on Famotidine held in Ischia, Italy (June 1986).

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 250 g were purchased from Morini (S. Polo, Italy). They were used at least 1 week after their arrival at the laboratory.

Measurement of Gastric Secretion

Acid secretion was measured in pylorus-ligated rats as described in a previous paper [Scarpignato et al., 1984]. Since vagal stimulation after pylorus ligation is followed in the rat by histamine mobilization [Code, 1982], this model appears to be suitable for the evaluation of antisecretory properties of H_2-receptor antagonists and has been successfully employed in our laboratory to study new compounds of this family [Scarpignato et al., 1986].

Two sets of experiments were carried out. In the first, dose–response curves for each antagonist were constructed. Drugs, diluted in physiological saline, were administered orally 1 hr before pylorus ligation, which was performed under diethyl ether anesthesia; care was taken not to damage the blood supply. After surgery, the animals were loaded subcutaneously with 5 ml of physiological saline. The rats were sacrificed 5 hr later and the stomach was removed after ligation of the cardia. The stomachs were opened along the greater curvature and the gastric contents were collected into graduated tubes and centrifuged. pH and acid concentration were then measured potentiometrically in the clear supernatant.

In the second set of experiments, equiactive doses (that is, doses equivalent to the respective ED_{50} values calculated from the previously established dose–response curves) of both compounds were administered orally at different times (from 1 hr to 6 hr) before pylorus ligation in order to evaluate their duration of action.

Measurement of Gastric Emptying

Gastric emptying was measured by a method previously described and validated [Scarpignato, 1983; Scarpignato et al., 1984; Scarpignato et al., 1986]. The test meal consisted of 1.5 ml per rat of a prewarmed (35°C) solution of phenol red in 100 ml of aqueous methylcellulose (1.5%). Drugs were administered orally 30 min before the meal. The animals were killed 20 min after, by cervical dislocation. The stomach was then exposed by laparotomy and quickly ligated at pylorus and cardia and removed. The stomach and its content were homogenized in a Waring blender with 100 ml of 0.1 N NaOH. After centrifugation, phenol red was measured in the supernatant as previously detailed [Scarpignato et al., 1984].

Evaluation of Data

Acid output was obtained by multiplying the volume of gastric juice by acid concentration and expressed in mEq· 5 hr. Under our experimental conditions, acid output in control animals (rats receiving physiological saline) was 0.720 ± 0.032 mEq· 5 hr. The results obtained with both antagonists were calculated as percentage changes (inhibition) by comparing the level of secretion after administration of each dose of H_2-blocker with the average value observed after saline. Linear regression analysis between percentage values (as probits) and dose (as log) was performed in order to estimate the ED_{50} (i.e., the dose required to inhibit acid secretion by 50%) for each antagonist [Goldstein, 1964].

Gastric emptying (G.E.) for each rat was calculated according to the following formula:

$$\text{G.E.} = 1 - \left[\frac{\text{Amount of phenol red recovered from the test stomach}}{\text{Average amount of phenol red recovered from the standard stomachs}} \right] \times 100$$

where standard stomachs are represented by the stomachs of animals sacrificed immediately after the meal and considered as a standard (100% of phenol red in the stomach). The use of these animals, in groups of four per experiment, was found to be necessary to avoid errors connected with contractions of the stomach during terminal convulsions [Bertaccini and Scarpignato, 1982; Scarpignato, 1983]. Under our experimental conditions, in control rats (receiving only physiological saline) the meal leaving the stomach (i.e., G.E.) was 61.3 ± 4.7% (range 55–65) in comparison with the standards.

Evaluation of Data

All values are presented as mean ± SEM (or 95% confidence limits). Statistical analysis of data was performed by analysis of variance (ANOVA) and Duncan's multiple- range test by using a computer program running on an Apple II computer [Modrak, 1983].

Drugs

Famotidine and ranitidine were a generous gift from Merck, Sharp & Dohme (Rome) and Laboratori Glaxo (Verona), respectively.

RESULTS

Gastric Secretion Studies

Results obtained in the Shay rat preparation are depicted in Figure 1. It is evident that both H_2-antagonists were able to inhibit acid secretion in a dose–response fashion. Analysis of variance showed a significant regression between the degree of acid inhibition and the dose for each drug. Furthermore, there was parallelism between the dose–response curves of famotidine

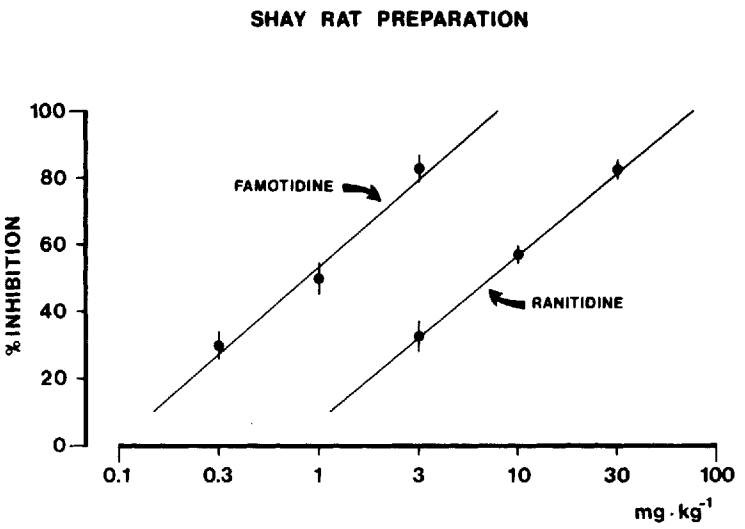

Fig. 1. Inhibition of acid secretion by famotidine and ranitidine in the rat. Each point refers to the mean of the values obtained from 10 animals. Vertical bars are standard errors. The lines are the calculated least-squares regression lines.

TABLE 1. Antisecretory Effect of Famotidine and Ranitidine in the Rat

Compound	ED50 (mg/kg)	95% Confidence limits
Famotidine	0.80	0.43–1.28
Ranitidine	6.84	5.13–10.90
Ratio	8.6	

and ranitidine, thus suggesting an identical mechanism of action for both drugs [Goldstein, 1964]. The calculated ED_{50} values (together with 95% confidence limits) are shown in Table 1.

Figure 2 shows the antisecretory effect of equiactive doses of both compounds (i.e., the ED_{50} values calculated from the above dose–response curves, administered 1–6 hr before surgery). It appears clear that the degree of acid inhibition induced by each antagonist was virtually the same whatever the time elapsed between drug administration and pyloric ligation. The antisecretory effect was evident until 8 hr after administration (3 hr before surgery) and vanished later.

Gastric Emptying Studies

The effects of equiactive antisecretory doses of famotidine and ranitidine on gastric emptying of liquids are summarized in Table 2. Conversely from ranitidine, which accelerated the emptying rate, famotidine was unable to significantly affect the emptying of gastric contents, even at doses 10 and 30 times higher than antisecretory ones.

DISCUSSION

The results of the present investigation confirm the strong antisecretory activity of famotidine, already pointed out in different in vitro [Harada et al., 1983; Shepherd-Rose and Pendleton, 1984] and in vivo [Pendleton et al., 1985; Takagi et al., 1982; Takeda et al., 1982] studies. In experimental conditions very similar to those of the present study (Shay rat preparation, 4 hr of pyloric ligation), Takeda et al. [1982] found oral famotidine to be about

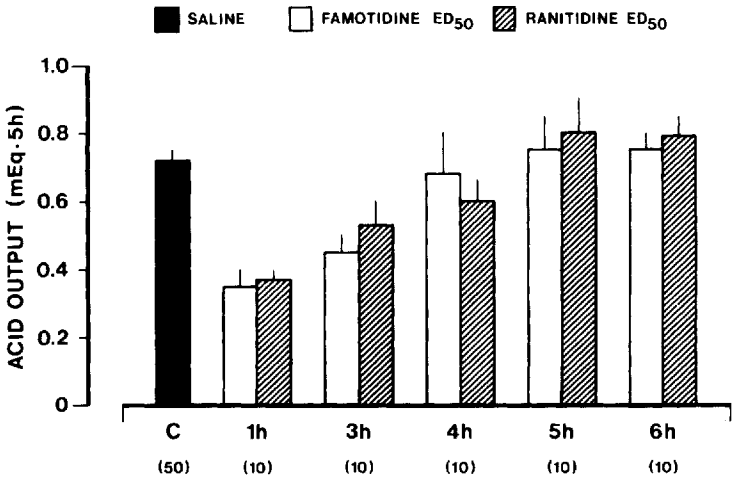

Fig. 2. Effect of equiactive antisecretory doses (the respective ED_{50} values) of famotidine and ranitidine on acid secretion in response to pyloric ligation in the rat. Drugs were administered orally 1–6 hr before surgery. Numbers in brackets represent the number of animals studied for each drug. Each column refers to the mean of the values obtained; vertical bars are standard errors.

TABLE 2. Effect of Famotidine and Ranitidine on Gastric Emptying of the Concious Rat*

Compound	G.E. (%)	n[a]	Significance versus saline
Saline	61.3 ± 4.7	10	—
Famotidine ED50[b]	71.5 ± 3.9	30	NS
Famotidine ED50 × 10	54.2 ± 4.3	10	NS
Famotidine ED50 × 30	57.5 ± 4.4	10	NS
Ranitidine ED50	71.5 ± 1.9	10	$P < 0.01$

*Results are presented as means (± SEM).
[a]Number of animals used.
[b]The doses of each antagonist administered were those calculated from their respective dose-response curves in the Shay rat preparation.

50 times more potent than cimetidine. Since ranitidine was reported to be 5 to 7 times more potent than cimetidine (for review see Brittain and Daly [1981]), the potency ratio between ranitidine and famotidine (i.e., 8.6) found in our experiments is not an unexpected figure. The efficacy of the compounds was virtually the same, as both antagonists were capable of completely suppressing acid output in response to pyloric ligation. Furthermore, parallelism between their dose–response curves suggests an identical mechanism of action for both drugs (i.e., an interaction with H_2-receptors of parietal cells). In vitro activity of famotidine [Harada et al., 1983; Shepherd-Rose and Pendleton, 1984] indicates a direct action of the compound on acid secretion not mediated by metabolites or through changes in mucosal blood flow.

In some experimental [Takagi et al., 1982] and human (McCallum et al., 1985; Smith, 1985] studies, the antisecretory effect of famotidine appeared to be longer-lasting than that of cimetidine or ranitidine. However, in these studies, equiactive doses of the compounds were never employed. Since the duration of the antisecretory action is dose-related [Scarpignato et al., 1984; Smith, 1985], the use of nonequiactive doses may lead to erroneous conclusions. In the present study, we compared the respective ED_{50} values of the two antagonists, so that the observed duration of action would have been independent of their potency. In consistence with the results of Buyniski et al. [1984], we found no difference in the duration of antisecretory action between famotidine and ranitidine. Moreover, when equiactive doses of famotidine and

ranitidine were administered on dimaprit-induced hypersecretion in cats, a similar recovery from acid inhibition was observed (Coruzzi et al., personal communication).

H_2-antagonists were shown to be able to modify gastric emptying in rats by a mechanism totally independent of H_2-receptor blockade [Bertaccini and Scarpignato , 1982]. Data reported in the present investigation show that, in contrast with ranitidine, antisecretory doses (0.80 $mg \cdot kg^{-1}$) of famotidine are unable to modify gastric emptying significantly. Since Pendelton and co-workers [1985] reported, quite recently, that a large amount of the H_2-antagonist (27 $mg \cdot kg^{-1}$) accelerated the emptying rate, we additionally tested doses 10 and 30 times higher than antisecretory ones. The results obtained, however, were the same. An erratic accelerating effect was sometimes observed, but it fell short of statistical significance. It is difficult to find an explanation for this discrepancy, particularly as the above authors have employed our method [Scarpignato, 1983] to measure gastric emptying. However, they studied Sprague-Dawley rats and one of us [Scarpignato, 1983] had previously shown that quantitative differences exist in the gastric motor effect of a drug between different strains of animals. In agreement with our data, Bertaccini and co-workers (personal communication) found that this new H_2-antagonist, unlike other members of the family, is devoid of nonspecific effects of gastrointestinal motility, showing erratic but always weak stimulatory effects on in vitro preparations only at very high concentrations. In addition, recent experiments [Tupy Visich et al., 1986], performed on healthy volunteers, showed that famotidine has no effect on gastric emptying of a labeled mixed meal.

To summarize, the results of the present investigation demonstrate that famotidine is a potent and selective antisecretory compound. Its potency, but not its efficacy, is higher than that of ranitidine. Moreover, the duration of the antisecretory action is virtually the same for both drugs. Clinical experience with this compound is still limited, but according to current knowledge (reviewed by Bianchi Porro [1985]) famotidine appears at least as effective as the other H_2-receptor antagonists currently available. Therefore, it may be considered an appropriate first choice and a good alternative to other effective drugs for treatment of peptic ulcer disease.

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