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Antisecretory and antiulcer effect of the H_2-receptor antagonist famotidine in the rat: comparison with ranitidine

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1 The effects of the new H_2-receptor antagonist famotidine, administered orally, on gastric secretion and emptying as well as on experimentally-induced gastric and duodenal ulcers were studied in the rat. Ranitidine was used as a reference compound.

2 Both compounds inhibited acid secretion in a dose-dependent manner. Calculated ED_{50} values were 0.80 and 6.84 mg kg^{-1} for famotidine and ranitidine, respectively. However, the duration of the antisecretory action was the same for both drugs.

3 The effect of the two drugs, administered at equiactive antisecretory doses, on gastric emptying was different. Ranitidine significantly accelerated the emptying rate whereas famotidine had no effect.

4 Famotidine reduced, in a dose-dependent manner, ulcer incidence in stomachs of dimaprit-treated rats and in duodena of cysteamine-treated animals with a potency respectively 2 and 7 times higher than that of ranitidine.

5 Famotidine is therefore an effective antisecretory and untiulcer 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.

Introduction

The introduction of histamine H_2-receptor antagonists to the therapeutic agents used against ulcer disease has allowed great progress in the treatment of peptic ulcers. H_2-blockers represent the first group of drugs shown conclusively to increase the rate of healing of peptic ulcers and produce rapid relief of symptoms. With their ease of ingestion, schedule of progressive reduction in number of daily doses and few untoward effects, these agents have quickly replaced antacids and anticholinomimetics used until now to treat peptic ulcer.

The value of cimetidine and ranitidine in the short-term treatment of ulcer disease is now established beyond doubt. However, because of the relapsing nature of the disease (Hirschowitz, 1983), long-term maintenance therapy is required in order to reduce the incidence of relapse. In this regard, the aim of the research in the field of H_2-antagonists was, therefore, to find newer compounds more potent, more selective and with fewer untoward effects in comparison with the old molecules.

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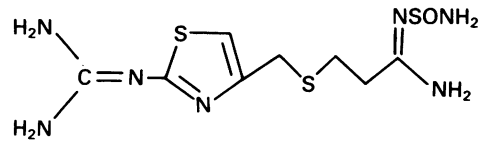
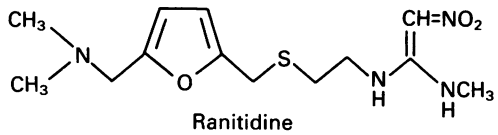
Famotidine (code number YM-11170 or MK-208) is a new histamine H_2-receptor antagonist, which has been successfully employed in the short-term treatment of peptic ulcer and other acid-related diseases (for review see Bianchi Porro, 1985). Being a guanylthiazole derivative, its chemical structure differs from that of cimetidine (imidazolic compound) and ranitidine (a furan derivative) (Figure 1).

In vivo studies (Takagi *et al.*, 1982; Ishihara & Okabe, 1983), have shown that famotidine displays strong antisecretory activity (from 40 to more than 100 times that of cimetidine, depending on the experimental conditions). 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, Buyiniski *et al.* (1984) and Humphray *et al.* (1986) found both drugs had the same time-course for secretory inhibition.

In the present investigation we studied the antisecretory and antiulcer action of famotidine in rats. Special attention was paid to the duration of its acid inhibitory effect. Since some H_2-antagonists are able to affect gastric motility (Bertaccini & Scarpignato,



Famotidine



Ranitidine

Figure 1 Chemical structures of famotidine and ranitidine.

1982), the effect of the compound on gastric emptying was also examined. Ranitidine, a widely employed histamine H_2-antagonist, was used as a reference compound. Preliminary results of the present investigation were presented at The International Symposium on Famotidine, held in Ischia, Italy (June 1986).

Methods

Animals

Wistar rats of either sex weighing 150–250 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 previously (Scarpignato *et al.*, 1984). Since vagal stimulation following pylorus ligation in the rat causes mobilization of histamine (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 type (Scarpignato *et al.*, 1986).

Two sets of experiments were carried out. In the first one, dose-response curves for each antagonist were constructed. Drugs, diluted in physiological saline, were administered orally (2 ml kg^{-1}) 1 h before pylorus ligation which was performed under diethyl ether anaesthesia; care was taken not to damage the blood supply. After surgery, the animals were loaded subcutaneously with 5 ml of physiological saline; 5 h later the rats were killed and the stomachs removed after ligation of the cardia. The stomachs were opened along the greater curvature, the gastric contents 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 the respective ED_{50} values calculated from the previously established dose-response curves) of both compounds were administered orally at different times (from 1 to 6 h) 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; 1986). The test meal consisted of 1.5 ml per rat of a prewarmed (35°C) solution of phenol red (50 mg dissolved in 100 ml of aqueous methylcellulose; 1.5% w/v). Drugs were administered orally (2 ml kg^{-1}) 30 min before the meal. Control animals received the same volume of physiological saline. Twenty min after the meal, rats were killed by cervical dislocation. The stomach was then exposed by laparotomy, 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. The analytical procedure for the assay of phenol red was the same as that described in detail previously (Scarpignato, 1983). It involves precipitation of proteins with 20% trichloroacetic acid, realkalinization with NaOH and colorimetric assay at 560 nm.

Experimentally-induced ulcers

Gastric damage was induced in fasted (24 h) female rats by specific H_2-receptor stimulation through a single large dose (150 mg kg^{-1} intravenously) of dimaprit, a selective H_2-agonist (Del Soldato, 1982). In our experimental conditions, this dose of the gastric secretory stimulant provoked gastric erosions in 90–100% of the animals.

Duodenal ulcer was induced in fed female rats (Robert *et al.*, 1974) by the selective ulcerogenic agent cysteamine (Selye & Szabo, 1973). This compound was injected subcutaneously at a dose of 300 mg kg^{-1} which, under our experimental conditions, induced duodenal but not gastric damage in 90–100% of the animals with only 10% mortality.

In both experiments, test compounds were administered by gavage (2 ml kg^{-1}) 1 h before the injection of the ulcerogenic agent. Again, control rats were treated with the same volume of saline. The animals were killed 1 and 24 h after dimaprit and cysteamine, respectively. The stomach and duodenum were then exposed by laparotomy and examined for the presence of lesions by an investigator unaware of the treatment.

Evaluation of data

Acid output over the 5 h period was calculated as the product of the volume of gastric juice and the concentration of acid and was expressed as mEq. Under our experimental conditions, acid output in control animals (rats receiving physiological saline, $n = 50$) was 0.720 ± 0.032 mEq. Results obtained with both antagonists were calculated as % 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 % values (as probits) and dose (as log) was performed in order to estimate the ED_{50} value (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:

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

where standard stomachs represent the stomachs of animals killed immediately after the meal and considered as a standard (100% of phenol red in the stomach). The use of these animals, in groups of 4 per experiment, was found to be necessary to avoid errors connected with contractions of the stomach during terminal convulsions (Bertaccini & Scarpignato, 1982; Scarpignato, 1983). Under our experimental conditions, in control rats (receiving only physiological saline, $n = 40$) the meal leaving the stomach (i.e. G.E.) was $61.3 \pm 4.7\%$ (range 55–65) in comparison with the standards.

In experiments on gastrointestinal ulceration, in order to avoid subjective evaluation of the results (i.e. scoring system), we quantitated the effect of the drugs by considering only the quantal response, that is the number of animals protected from lesions after administration of the different doses of each antagonist. The ED_{50} values for protection were calculated according to Litchfield & Wilcoxon (1949).

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

Drugs and chemicals

Famotidine and ranitidine were generous gifts from Merck Sharp & Dohme (Rome, Italy) and Laboratori Glaxo (Verona, Italy), respectively. Cysteamine (2-mercaptoethylamine) hydrochloride was purchased from Sigma. Dimaprit was kindly provided by Dr M.E. Parsons (SKF, Welwyn Garden City, Herts). All other chemicals (analytical grade) were from Merck (Darmstadt, FRG).

Results

Gastric secretion studies

Results obtained in pylorus-ligated rats are depicted in Figure 2. It is evident that both H_2-antagonists inhibited acid secretion in a dose-dependent manner. Analysis of variance showed a significant regression between the degree of acid inhibition and the dose for each drug. Furthermore, the dose-response curves for famotidine and ranitidine were parallel, thus suggesting an identical mechanism of action for both drugs (Goldstein, 1964). The calculated ED_{50} values (together with 95% confidence limits) were $0.80\ mg\ kg^{-1}$ p.o. (0.43–1.28) and $6.84\ mg\ kg^{-1}$ p.o. (5.13–10.90) for famotidine and ranitidine, respectively.

Figure 3 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 to 6 h 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 h after administration (3 h before surgery) and disappeared later.

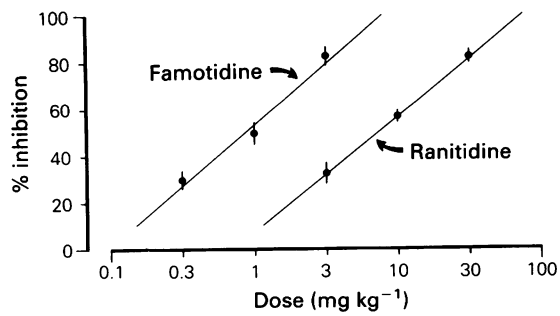


Figure 2 Inhibition of acid secretion by famotidine and ranitidine, administered orally, in the pylorus-ligated rat. Each point represents the mean of the values obtained from 10 animals. Vertical lines indicate s.e. The lines are the calculated least-squares regression lines.

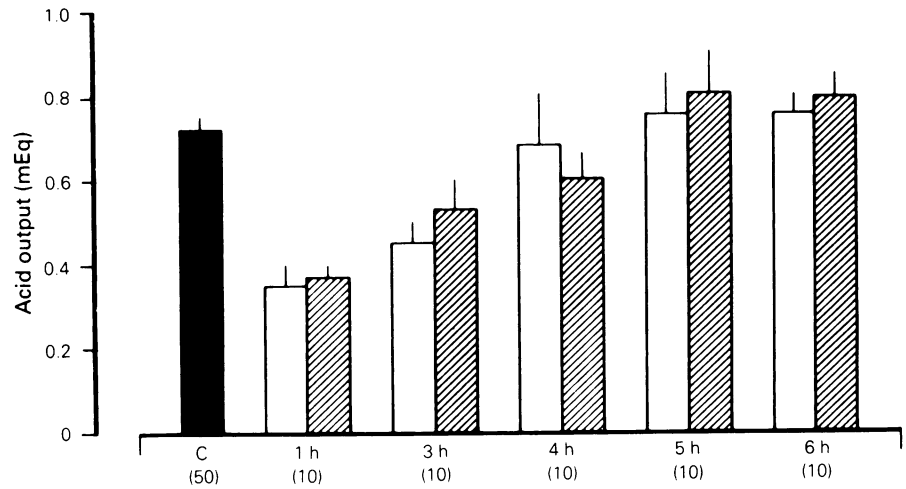


Figure 3 Effect of equiactive antisecretory doses (the respective ED_{50} values) of famotidine (open columns) and ranitidine (hatched columns) on acid secretion in response to pyloric ligation in the rat. Drugs were administered orally 1 to 6 h before surgery. Numbers in parentheses represent the number of animals studied for each drug. Each column represents the mean of the values of acid output over 5 h; vertical lines show s.e. Solid column represents control secretion obtained in saline-treated rats.

Gastric emptying studies

The effect of equiactive antisecretory doses of famotidine and ranitidine on gastric emptying of liquids is depicted in Figure 4. In contrast to ranitidine, which accelerated emptying rate, famotidine was unable to affect significantly the emptying of gastric contents, even at doses 10 and 30 times higher than antisecretory ED_{50} values.

Evaluation of antiulcer activity

Gastric damage. One hour after intravenous administration, dimaprit induced gastric damage in almost all the treated animals. As previously described (Scarpignato *et al.*, 1986), this damage consisted of single prepyloric antral erosions. Both H_2-antagonists were able to reduce ulcer incidence in a dose-dependent manner (Figure 5).

Duodenal ulcer Twenty four hours after cysteamine administration, two ulcers – usually in the opposite poles of the duodenum – were present in almost all the animals treated with the ulcerogenic compound. Again, ulcer incidence was reduced by both famotidine and ranitidine in a dose-dependent manner (Figure 6).

The calculated ED_{50} values (i.e. the effective dose which protected 50% animals from lesions) for each antagonist and each model are shown in Table 1.

Discussion

H_2-antagonists were shown to be capable of inhibiting acid secretion in pylorus-ligated rats (Scarpignato *et al.*, 1986). The existence of an extrinsic, vagal supply of histaminergic nerve fibres to the gut wall (Häkanson *et al.*, 1981) suggests the release of histamine after vagal

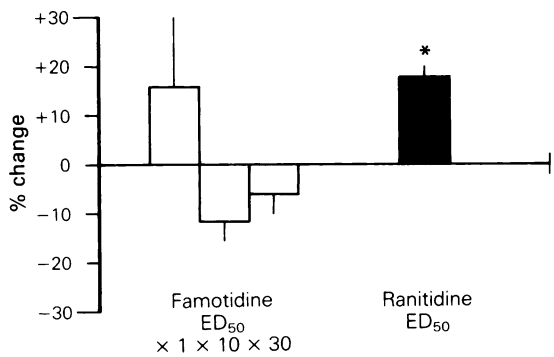


Figure 4 Gastric emptying in conscious rats. Drugs were administered orally 30 min before the test meal. ED_{50} values are the antisecretory ones (see text). Ordinate scale: % changes in comparison with controls ($n = 30$), taken as 0. Each column represents the mean of the values obtained from 10–15 animals. Vertical lines show s.e.mean. $*P < 0.05$.

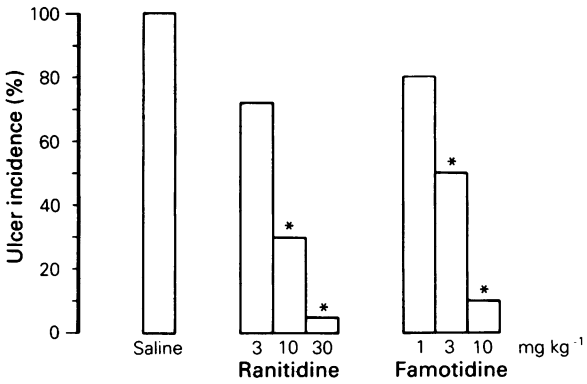


Figure 5 Effect of famotidine and ranitidine on gastric ulcers induced by dimaprit in the rat. $*P < 0.05$.

stimulation and explains the efficacy of H_2-blockers in inhibiting vagally-induced acid secretion.

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 & Pendleton, 1984; Bertaccini *et al.*, 1986) and *in vivo* (Coruzzi *et al.*, 1986; 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 h of pyloric ligation), Takeda *et al.* (1982) found oral famotidine to be about 50 times more potent than cimetidine. Since ranitidine has been shown to be 5 to 7 times more potent than cimetidine (for review see Brittain & Daly, 1981), the potency ratio between ranitidine and famotidine (i.e. 6.8) found in our experiments is not an unexpected figure. This value overlaps that previously

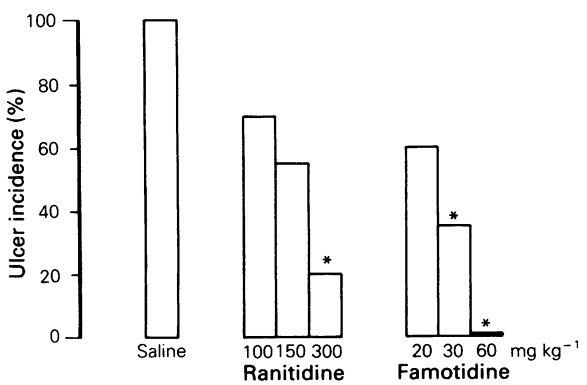


Figure 6 Effect of famotidine and ranitidine on duodenal ulcers induced by cysteamine in the rat. $*P < 0.05$.

Table 1 Effect of oral famotidine and ranitidine on experimentally-induced gastric and duodenal ulcers in the rat

Compound	ED_{50} (mg kg^{-1}) *Gastric ulcer*	*Duodenal ulcer*
Famotidine	2.65 (1.36–5.16)	23.5 (17.5–31.7)
Ranitidine	5.58 (2.81–11.07)	156.9 (105.2–233.9)

Results show mean ED_{50} values with 95% confidence limits in parentheses.

found by Buynisky *et al.* (1984) and Humphray *et al.* (1986) in Heidenhain pouch dogs. The efficacy of the compounds was virtually the same, as both antagonists were capable of suppressing completely 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 on the rat isolated fundus (Bertaccini *et al.*, 1986) 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; Pendleton *et al.*, 1983) and human (McCallum *et al.*, 1985; Smith, 1985) studies, the antisecretory effect of famotidine appeared to be longer-lasting in comparison with 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 non-equiactive doses may lead to erroneous conclusions. In the present study, we compared the respective ED_{50} values of both antagonists, so that the observed duration of action would have been independent of their potency. In accordance with the results of Buyniski *et al.* (1984) and Humphray *et al.* (1986), we found no difference in the duration of antisecretory action between famotidine and ranitidine. Moreover, when equiactive doses of famotidine and ranitidine were administered against dimaprit-induced secretion in cats, a similar rate of recovery from acid inhibition was observed (Coruzzi *et al.*, 1986).

H_2-antagonists were shown to be capable of modifying gastric emptying in rats by a mechanism totally independent of H_2-receptor blockade (Bertaccini & Scarpignato, 1982). The results of the present investigation show that, in contrast to ranitidine, antisecretory doses (0.80 mg kg^{-1}) of famotidine are unable to modify significantly gastric emptying. Our results are at variance from those obtained by Pendel-

ton and coworkers (1985); they found that high amounts of famotidine (27 mg kg^{-1}) accelerated emptying rate. In this regard, we tested, additionally, doses 10 and 30 times higher than the antisecretory ones. However, the results obtained 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. In agreement with our data, Bertaccini and coworkers (1986) found that famotidine, unlike other members of this group of drugs, is devoid of non-specific effects on 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 labelled mixed meal.

Previous work (Takeda *et al.*, 1982) has shown famotidine to be capable of preventing the development of experimentally-induced gastric ulcers. Also, healing of duodenal ulcer in the rat (Ishihara & Okabe, 1983) was accelerated by famotidine. In these models (indomethacin- and aspirin-induced gastric lesions as well as mepirizole-induced duodenal ulcer), the potency of famotidine was always higher than that of cimetidine.

In this paper we compared famotidine and ranitidine in two different models of gastric and duodenal ulcer reported to be suitable for the evaluation of H_2-receptor antagonists (Scarpignato *et al.*, 1986). The dimaprit-induced gastric damage results from H_2-receptor stimulation (Del Soldato *et al.*, 1982), whereas the pathogenesis of cysteamine-induced duodenal ulcer is complex. Although several factors have been suggested as being responsible for ulceration, recent data (Boesby *et al.*, 1983; Kim *et al.*, 1985) emphasize the involvement of histamine release in this process, thus explaining the high efficacy of H_2-antagonists in this model.

In the experiments presented here, both drugs reduced ulcer incidence, in a dose-dependent manner, both in the stomach and the duodenum, with a potency of famotidine higher (2 and 7 times, respectively) than that of ranitidine. However, their efficacy was the same.

In conclusion, our results demonstrate that, like ranitidine, famotidine is an effective antisecretory and antiulcer 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. As a consequence, no differences in healing rates of duodenal ulcer between famotidine and ranitidine was found in clinical practice (Bettarello, 1985).

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