Effects of FRG-8701 on Gastric Acid Secretion, Gastric Mucosal Lesions by Necrotizing Agents and Experimental Gastric or Duodenal Ulcer in Rats

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Accepted August 6, 1990

Abstract—Effects of FRG-8701, a new histamine H2-receptor antagonist, on gastric acid secretion, necrotizing agents-induced gastric lesions and acute gastric or duodenal ulcer in rats were studied. In lumen-perfused rats, intravenous injection of FRG-8701 reduced gastric acid secretion, and its antisecretory effect was almost equipotent to that of famotidine but the duration of action was substantially longer. In pylorus-ligated rats, the antisecretory effect of intraduodenal FRG-8701 administration was about 7 times more potent than that of cimetidine. FRG-8701 effectively inhibited macroscopic gastric hemorrhagic lesions induced by various kinds of necrotizing agents. Intraperitoneal injection was effective in preventing the lesions as well as oral treatment. The oral ED50 values for these lesions ranged from 1.1 to 9.4 mg/kg. On the other hand, famotidine failed to reduce these lesions, and the cytoprotective effect of cimetidine was observed only in high doses compared with the doses for antisecretory activity. In addition, the cytoprotective effect of FRG-8701 was not affected by the treatment of indomethacin or N-ethylmaleimide. FRG-8701 showed antiulcer activity against stress and indomethacin gastric ulcer and mepirizole duodenal ulcer. Its antiulcer effect was 5–15 times more potent than that of cimetidine. These results indicate that FRG-8701 is a new antiulcer drug that exerts a potent cytoprotective effect in addition to its gastric antisecretory activity.

Since Black et al. (1) first defined the H2-receptor and characterized a number of H2-antagonists, various kinds of H2-antagonists have been developed and used clinically. The introduction of H2-antagonists has revolutionized the treatment of peptic ulcers with its potent inhibition of gastric acid secretion. It has been, however, demonstrated that the recurrence ratio of peptic ulcer is relatively high after healing by long-term H2-antagonist therapy. In the clinical stage, patients are treated with H2-antagonist in combination with defensive factors potentiating-agents to prevent the ulcer relapse. On the other hand, interest has grown in discovering therapeutic agents that prevent ulcer formation or relapse by increasing defensive factors in the gut. The property of a drug that protects the gastric mucosa against necrotizing agents such as acid and ethanol has been coined cytoprotection (2). Although these cytoprotective mechanisms are unknown, the protective effect by an agent is mainly considered to be due to the increase of gastric mucosal defensive integrity.

From this point of view, in our search for an H2-receptor antagonist that exerts both antisecretory and cytoprotective activities, we have found FRG-8701, N-[3-[3-(piperidinylmethyl)phenoxy]propyl]-2-(furfurylsulfinyl)acetamide (Fig. 1). In present study, the effects of FRG-8701 on gastric acid secretion, necrotizing agents-induced gastric lesions and ulceration in rat stomach and
duodenum were mainly investigated and compared with those of reference H$_2$-receptor antagonists.

Materials and Methods

1. In vitro studies

Male Hartley guinea pigs (Sankyo Labo Service Co.) weighing 250–350 g were used in the following in vitro studies.

1.1 Isolated atria: The hearts were excised from animals and right atria were dissected carefully. Atria were suspended in Krebs-Henseleit (KH) solution maintained at 32°C and aerated with 95% O$_2$ and 5% CO$_2$. The tissue was attached with an initial load of 1 g to an isometric transducer (Nihon Kohden, TD-112S) and allowed to stabilize for 60 min before histamine application. The control chronotropic response to 10$^{-5}$ M histamine was first established. The histamine response was repeated 10 min after the tissue was incubated with various concentrations of FRG-8701 or reference H$_2$-antagonist. Data were expressed as a percentage of the control histamine response.

1.2 Isolated ileum: A 2- to 3-cm piece of ileum was removed from the animal and suspended in KH solution maintained at 32°C and aerated with 95% O$_2$ and 5% CO$_2$. The tissue was attached to an isotonic transducer (Nihon Kohden, TB-651T) with an initial load of 1 g and allowed to stabilize for 30–60 min.

A control concentration-response curve to histamine or acetylcholine was established in a cumulative fashion until a consistent maximal response was obtained. After 10 min incubation with 10$^{-5}$ M FRG-8701, the histamine or acetylcholine response curve was repeated. Data were expressed as a percentage of the maximum histamine or acetylcholine response without FRG-8701.

2. In vivo studies

Male Sprague Dawley (SD) rats (Charles River, Inc., Japan) weighing 180–200 g were fasted overnight before experiments in the following in vivo studies, but in the case of mepirizole-induced duodenal ulcer, rats were deprived of food and water 24 hr after mepirizole administration.

2.1 Acid secretion in lumen-perfused rat: Animals were anesthetized with urethane (1.4 g/kg, i.m.) and surgically prepared as described by Ghosh and Schild (3). The stomach of the rat was perfused with warm saline at the rates of 1 ml/min, and acid in the perfusate was estimated by titration to pH 7.0 every 15 min. The animals were infused continuously via caudal veins with histamine 2HCl (4 mg/kg/hr), and test compounds were injected intravenously 1 hr after initiation of histamine infusion. Data were expressed as a percentage of the value of acid secretion 1 hr after the initiation of histamine infusion.

2.2 Acid secretion in pylorus-ligated rat: While under ether anesthesia, the abdomen was opened and the pylorus was ligated. Test compounds were given intraduodenally at the time of ligation. Four hours after pylorus ligation, rats were sacrificed and the gastric contents were centrifuged and analyzed for volume and acidity. Acid concentration was determined by titration to pH 7.0. Total acid output was calculated as the volume times the acid concentration.

2.3 Necrotizing agents-induced gastric lesions: Gastric mucosal lesions were produced using various kinds of necrotizing agents: absolute ethanol, 0.6 N HCl, 1% ammonia (1% NH$_3$), 0.4 N HCl + 50% ethanol (HCl-ethanol), and 0.15 M taurocholic sodium + 0.4 N HCl, according to the method of Robert et al. (2). Each drug or vehicle of 5% arabic gum solution was given to individual rats orally 30 min prior to oral treatment of 1 ml of necrotizing agent. One hour after necrotizing agent treatment, the animals were sacrificed. The stomach was removed and inflated by injecting 10 ml of 2% formalin. Subsequently, the stomach was incised along the curvature and examined for macroscopic hemorrhagic damages under a dissecting microscope (×10). The area of each lesion (mm$^2$) was measured, and the sum of the area was regarded as the lesion index. In addition, FRG-8701 was given intraperitoneally before HCl-ethanol treatment. In some cases, indomethacin, a cyclooxygenase inhibitor (10
mg/kg), or N-ethylmaleimide, an SH blocker (5 mg/kg) was given subcutaneously 2.5 hr or 10 min before FRG-8701 treatment.

2.4 Acute gastric or duodenal ulcer: Stress ulcer was induced by immersing rats in water (23°C) for 6 hr according to the method of Takagi and Okabe (4). Indomethacin ulcer was produced by subcutaneous injection of indomethacin at 20 mg/kg, and the rats were sacrificed 6 hr after the treatment. Duodenal ulcer was induced by administration of mepirizole at the dose of 200 mg/kg, and the rats were sacrificed 24 hr later (5, 6).

Each drug or vehicle was given 30 min before the ulcerogenic treatment; and in the case of mepirizole duodenal ulcer, drugs were given twice, 30 min before mepirizole administration and 9 hr later.

After formalin fixation, the area (mm²) of the lesion in each animal was summed under a dissecting microscope (×10) and used as the ulcer index.

3. Chemicals

FRG-8701 and famotidine were synthesized by Fujirebio Pharmaceutical Research Laboratories. Other drugs used were as follows: cimetidine (Industrie Chemiche Farmaceutiche Italiani, Italy), ethanol, HCl, histamine dihydrochloride and N-ethylmaleimide (Wako, Japan), acetylcholine chloride and mepirizole (Daiichi Pharmaceuticals, Japan), taurocholic sodium (Hoechst, W.G.), and indomethacin (Sigma, U.S.A.).

In the cases of the in vitro studies and intravenous application of the H₂-antagonists, each drug was dissolved in 0.3 N HCl and neutralized with 0.3 N NaOH. When given orally, each drug was suspended in 5% arabic gum solution. Histamine dihydrochloride, acetylcholine chloride and N-ethylmaleimide were dissolved in saline, and indomethacin was dissolved in 4% NaHCO₃ solution. Mepirizole was suspended in 5% arabic gum solution. Taurocholic sodium was dissolved in 0.4 N HCl.

4. Statistical analysis

Data were presented as the mean±S.E. The fifty percent inhibiting concentration (IC₅₀) and 50% effective dose (ED₅₀) values were calculated according to Filler’s theorem (7). Statistical analysis was performed by Student’s t-test or the Aspin-Welch test. When necessary, the Cochran t-test was used. Values of P<0.05 were regarded as significant.

Results

In vitro studies: Positive chronotropic response to histamine at 10⁻⁵ M was dose-dependently inhibited by FRG-8701 famotidine or cimetidine; and the IC₅₀ values of FRG-8701, famotidine and cimetidine were 3.3, 3.0 and 108.6 (×10⁻⁷ M), respectively. The inhibitory potency of FRG-8701 was almost the same as that of famotidine and approximately 33 times greater than that of cimetidine (Table 1).

FRG-8701 at 10⁻⁵ M did not cause any significant displacement of the histamine or acetylcholine concentration-response curve in the ileal preparation (Fig. 2).

Gastric acid secretion: In anesthetized rats with perfused stomach, the control acid output response at 1 hr after the initiation of

| Table 1. Inhibitory potency of FRG-8701, famotidine and cimetidine on the positive chronotropic action to histamine in guinea pig isolated atria |
|---------------|---------|----------------|----------------|
| Compound      | N       | IC₅₀ (×10⁻⁷ M) | Relative potency vs. cimetidine |
|               |         | (95% C.L.)     |                               |
| FRG-8701      | 7       | 3.3 (2.5–4.3)  | 33                           |
| Famotidine    | 7       | 3.0 (2.1–4.4)  | 36                           |
| Cimetidine    | 7       | 108.6 (74.5–158.6) | 1                             |

N: number of tissue used. Data were obtained from the responses to 10⁻⁵ M histamine with or without the drugs. IC₅₀ values were calculated by Filler’s theorem.
Fig. 2. Effect of FRG-8701 on the contraction of acetylcholine or histamine in guinea pig ileum. FRG-8701 at $10^{-5}$ M was added to the bath 10 min before acetylcholine or histamine. Data were expressed as a percentage of the maximum acetylcholine or histamine response without FRG-8701. Each point indicates the mean±S.E. N: number of tissues used.

Histamine infusion was 31.3±4.4 Eq/15 min. FRG-8701 at 0.1 or 0.3 mg/kg injected intravenously produced a dose-dependent fall in acid output (Fig. 3). The reference H$_2$-antagonists also inhibited acid output in a dose-dependent manner. As shown in Fig. 3, the antisecretory potency of intravenous FRG-8701 appeared to be the same as that of famotidine, and the recovery from the antisecretory activity of FRG-8701 was appreciably slower than the recoveries from those of cimetidine and famotidine. In the pylorus-ligated (4 hr) rats, each drug, given intraduodenally, dose-dependently inhibited the total acid output; and the ED50 values for 50% reduction of the total acid output are listed in Table 2.

Cytoprotective studies: FRG-8701 at 10 or 30 mg/kg, given orally or intraperitoneally, significantly prevented the formation of the gastric mucosal lesions induced by 0.4 N HCl + 50% ethanol (HCl-ethanol) (Fig. 4). Other necrotizing agents-induced gastric lesions were also inhibited by treatment of FRG-8701 (Table 2). The oral ED50 values against the lesions ranged from 1.1 to 9.4 mg/kg. Famotidine, unlike FRG-8701, did not show any influences on the lesions. Cimetidine inhibited the lesions at high doses, and the oral ED50 values ranged from 75.7 to 157.3 mg/kg.

Time after administration (hr)

Fig. 3. Antisecretory effect of FRG-8701 and reference H$_2$-receptor antagonists on the histamine-stimulated gastric acid secretion in lumen-perfused rats. Compounds were injected intravenously 1 hr after the initiation of histamine infusion. Data were expressed as a percentage of the value of acid secretion 1 hr after the initiation of histamine infusion. *: significant difference from the control value (P<0.05). †: administration of the compound. ○: control. A: FRG-8701 0.1 (●, N=3), 0.3 (▲, N=3) mg/kg, i.v. B: famotidine 0.03 (●, N=6), 0.1 (▲, N=5) mg/kg, i.v. C: cimetidine 3 (●, N=6), 10 (▲, N=5) mg/kg, i.v. N: number of animals.

The severity of HCl-ethanol-induced damage was not influenced by subcutaneous
### Table 2. Comparison of cytoprotective and antisecretory effects of FRG-8701, famotidine and cimetidine

| Compounds | ED50 (mg/kg, p.o.) (95% C.L.) | ED50 (mg/kg, i.d.) |
|-----------|-----------------------------|-------------------|
|           | 100% ethanol | 0.6 N HCl | HCl+ethanol | HCl+TAC | 1% NH₃ | Antisecretory potency |
| FRG-8701  | 3.8 (2.1–6.9) | 6.3 (2.13–18.5) | 9.4 (2.5–35.6) | 1.1 (0.2–4.9) | <3.0 | 2.3 (1.4–3.9) |
| Famotidine | 150.0< | 150.0< | 150.0< | 150.0< | 0.6 | 0.6 (0.3–1.0) |
| Cimetidine | 75.7 (34.5–166.0) | 157.1 (110.5–208.4) | 153.9 (70.5–335.6) | 96.8 (63.0–148.9) | 157.3 | 15.4 (9.4–25.1) |

Compounds were orally given 30 min before necrotizing agent treatment. Antisecretory potencies of the compounds, given intraduodenally, were calculated from the results of gastric secretion in pylorus-ligated rats (4 hr). Data were obtained for each of the compounds in 10–11 animals per dose, using 3 to 4 doses. ED50 was calculated by Filler’s theorem. HCl+ethanol, 0.4 N HCl+50% ethanol; HCl+TAC, 0.4 N HCl+0.15 M taurocholic sodium.

### Table 3. Antulcer effect of FRG-8701, famotidine and cimetidine on stress- and indomethacin-induced gastric lesions and mepirizole-induced duodenal lesion in rats

| Experimental models | ED50 (mg/kg, p.o.) | Relative potency vs. cimetidine |
|---------------------|-----------------|--------------------------------|
|                     | FRG-8701 | Famotidine | Cimetidine | FRG-8701 |
| Stress              | 1.7 (0.7–3.8) | 1.4 (0.6–3.2) | 25.1 (11.2–57.5) | 14.8 |
| Indomethacin        | 6.9 (3.0–16.2) | 1.3 (0.5–3.5) | 55.0 (28.8–107.2) | 8.0 |
| Mepirizole          | 2.8 (1.7–4.5) | 0.3 (0.1–0.9) | 14.1 (8.7–22.9) | 5.0 |

Each value indicates ED50 (95% C.L.) which was calculated by Filler’s theorem. Data were obtained for each compound in 6–9 animals per dose, using 3 doses.
treatment with indomethacin at 10 mg/kg by itself. N-ethylmaleimide at 5 mg/kg, given subcutaneously, significantly augmented the severity of the gastric mucosal injury. However, neither indomethacin nor N-ethylmaleimide affected the protective action of FRG-8701 on the HCl-ethanol-induced gastric mucosal lesion (Fig. 5).

**Studies of antiulcer activity:** FRG-8701, given orally, dose-dependently prevented the development of gastric lesions induced by stress (restraint and water immersion) and indomethacin (Table 3). Duodenal ulcer induced by meperizole was also inhibited with FRG-8701. The ED50 values of FRG-8701 for each ulcer model ranged from 1.7 to 6.9 mg/kg. Famotidine and cimetidine also dose-dependently reduced the lesions, and the ED50 values are listed in Table 3.

**Discussion**

The present studies demonstrated that FRG-8701 is a potent antisecretory agent in rats. In histamine-stimulated and lumen-perfused rats, the intravenous potency of FRG-8701 was greater than that of cimetidine and appeared to be the same as that of famotidine from Fig. 3. In addition, persistent inhibition of acid secretion was observed 3–4 hr after administration of FRG-8701, while...
the antisecretory effect of famotidine and that of cimetidine disappeared during the same period. These results indicate that FRG-8701 has relatively long-lasting antisecretory effects in comparison with famotidine and cimetidine. In pylorus-ligated rats, the intraduodenal antisecretory effect of FRG-8701 was about 7 times more potent than that of cimetidine and 4 times less potent than that of famotidine. The present studies showed that the inhibitory potency of FRG-8701 on the chronotropic responses of isolated atria to 10^{-5} M histamine was 33 times greater than that of cimetidine and almost equal to that of famotidine. The selectivity of FRG-8701 for H_2-receptors was indicated by its lack of inhibitory activity against the histamine or acetylcholine response in isolated guinea pig ileum under conditions where the maximal H_2-inhibition in the atria was produced. Since the relative antisecretory potencies among the H_2-antagonists are nearly identical to their relative H_2-blocking activities in the isolated atria (8, 9), the H_2-blocking activity of FRG-8701 in the atria may explain why its antisecretory effects are equivalent to that of famotidine in intravenously administered rats with lumen-perfusion.

FRG-8701 effectively prevented formation of the gastric hemorrhagic mucosal lesions induced by various necrotizing agents in the dose range exhibiting the antisecretory effect in pylorus-ligated rats. Although the cytoprotective action of cimetidine remains controversial (10–13), the reduction of lesions was observed by cimetidine treatment, but its cytoprotective doses were apparently different from its antisecretory doses. It seems likely that FRG-8701 exerts such a cytoprotective action mainly through a systemic action because both orally and intraperitoneally administered FRG-8701 were effective, indicating that the cytoprotection of FRG-8701 was not induced through the mechanisms of a mild irritant. It is important that the cytoprotective action is not caused by the antisecretory action. In the present study, a sufficient amount of exogenous acid (0.6 N HCl, 0.4 N HCl + 50% ethanol, 0.4 N HCl + taurocholic sodium) was used; and famotidine, unlike FRG-8701, failed to prevent formation of the gastric mucosal lesion even at high doses. These results indicate that FRG-8701 elicits the cytoprotective action on the gastric mucosa by some mechanism other than inhibition of acid secretion or histamine H_2-receptor antagonism.

Szabo and Trier (14) proposed that gastric cytoprotection might be mediated through at least two different mechanisms, one involves prostaglandins and the other involves sulfhydryl-containing substances of the mucosa. Pretreatment with N-ethylmaleimide, by itself, significantly aggravated the HCl-ethanol lesions and these results were consistent with those of Takeuchi et al. (15). They suggested that the enhancement of vascular permeability by N-ethylmaleimide may account for the aggravation of ethanol-induced gastric lesions. On the other hand, in spite of sufficient amounts of indomethacin to decrease endogenous prostaglandins, the severity of mucosal lesions in response to HCl-ethanol was hardly affected. However, there was significant protection by FRG-8701 regardless of the treatment by indomethacin or N-ethylmaleimide. These results suggest that endogenous prostaglandins and sulfhydryls may not be involved in the mechanism of gastric cytoprotection afforded by FRG-8701. Although the mechanisms of cytoprotection by FRG-8701 are unknown, an increasing action on gastric mucosal blood flow was observed by intravenous administration of FRG-8701 in our preliminary studies (data not shown). This increasing action on gastric mucosal blood flow may be partially responsible for its cytoprotective effect. Further studies are in progress to explain it.

FRG-8701 was also very effective in preventing the formation of experimental gastric and duodenal ulcers. Its antulcer activity was 5–15 times more potent than that of cimetidine and almost identical to that of famotidine in the case of stress ulcer. The ulcer formation elicited by stress, indomethacin and meperazine is noticeably inhibited by bilateral vagotomy or antacid treatment (4, 6, 16). It is, therefore, postulated that gastric acid plays an important role in ulceration by these treatments. In fact, the prevention of ulcer formation is ascribed to the suppression of acid secretion based on the results that its effective doses in the inhibition of indomethacin
or mepirizole ulcer are sufficient to decrease the acid secretion. On the contrary, cytoprotective activity may participate in the inhibitory effect of FRG-8701 on stress ulcer in addition to the antisecretory effect since FRG-8701 prevented the ulcer at doses less than the ED50 for reduction in the acid output in pylorus-ligated rats.

Histamine H2-receptor antagonists can be categorized into two classes. The first class is agents that can be considered to be relatively short-acting in vivo like cimetidine and ranitidine. The second class is composed of compounds that have potent and long-lasting antisecretory activity. FRG-8701 belongs in this second class. Recent clinical studies suggested that adequate ulcer healing can be achieved solely by controlling nocturnal gastric acid secretion, thus precluding the need for maintenance of a full 24-hr antisecretory effect (17). Thus, the second class compounds could replace cimetidine and ranitidine because they can be delivered as a convenient once daily dosage. However, the occurrence of gastric hyperplasia after long-term treatment with certain long-acting antisecretory agents such as loxidine (18) and omeprazole (19) has raised doubts about the safety and desirability of prolonged gastric achlorhydria. From this point of view, it would seem that FRG-8701 with a moderate duration of antisecretory activity, e.g., greater than cimetidine and ranitidine but less than loxidine and omeprazole, would be a beneficial and desirable agent. In the light of ulcer relapse, it was reported that gastric lesions to ulcerogenic stimuli were aggravated after H2-antagonist treatment (20, 21), and suggested that the increased mucosal vulnerability associated with H2-antagonists might be responsible for the high ulcer recurrence ratio after H2-antagonist therapy (21). However, further studies are needed to explain the high relapse ratio. As a result of potent cytoprotection, FRG-8701 seems to possess reinforcement effects on gastric mucosal defensive integrity in addition to its antisecretory effect. As such, this agent is expected to be useful for the treatment of peptic ulcers in humans.

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