Effects of the New Anti-Ulcer Agent KB-5492 on Experimental Gastric Mucosal Lesions and Gastric Mucosal Defensive Factors, as Compared to Those of Teprenone and Cimetidine

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ABSTRACT—Effects of KB-5492, a new anti-ulcer agent, on various experimental gastric mucosal lesions and mucosal defensive factors in rats were compared with those of teprenone and cimetidine. KB-5492 administered orally at 12.5–200 mg/kg inhibited water-immersion stress- and indomethacin-induced gastric mucosal lesions in a dose-dependent manner with ED50 values of 46 and 27 mg/kg, respectively, indicating that KB-5492 was more potent than teprenone but less potent than cimetidine. KB-5492, administered orally at 12.5–100 mg/kg, also inhibited ethanol-induced gastric mucosal lesions in a dose-dependent manner with an ED50 of 23 mg/kg, so KB-5492 was 3 times more potent than teprenone, whereas cimetidine produced no obvious inhibition. In addition, KB-5492, administered orally at 25 and 50 mg/kg twice daily for 10 consecutive days, significantly accelerated the healing of acetic acid-induced gastric ulcers more potently than teprenone and cimetidine. KB-5492 at anti-ulcer doses significantly increased gastric mucosal blood flow in normal anesthetized rats and inhibited the reduction of gastric mucosal hexosamine content induced by aspirin, but did not affect gastric acid secretion in pylorus-ligated rats. These results indicate that KB-5492 has potent and broad anti-ulcer properties, which are probably exerted by its enhancement of gastric mucosal defensive factors through increasing gastric mucosal blood flow and/or retaining gastric mucus, and not by its inhibition of gastric acid secretion.

It is generally accepted that peptic ulcers are caused by a disruption in the balance of aggressive factors (gastric acid and pepsin) and mucosal defensive factors (blood flow, mucus, HCO3− secretion, etc.) (1). Anti-ulcer agents have therefore been used either for suppressing aggressive factors or for enhancing mucosal defensive factors. However, in recent years, it has been considered that different anti-ulcer agents should be used for gastric and duodenal ulcers, because of the pathophysiological differences between the two ulcer types. That is, as gastric acid secretion is generally greater in duodenal ulcer patients than in normal subjects (2–4), agents such as H2-receptor antagonists or proton pump inhibitors, which strongly inhibit gastric acid secretion, show prominent effects on duodenal ulcers. In contrast, since gastric acid secretion is usually normal or below normal in gastric
ulcer patients, gastric ulcers are presumed to be caused by weaknesses in gastric mucosal resistance (4, 5). Therefore, agents which enhance mucosal defensive factors would be expected to show desirable effects against gastric ulcers. Although various agents in this category have already been developed so far, they have not been particularly effective, so antisecretory agents are used preferably, even in the treatment of gastric ulcers.

Seeking a novel agent which would enhance mucosal defensive factors more potently than existing agents, we developed 4-methoxyphenyl 4-(3,4,5-trimethoxybenzyl)-1-piperazineacetate monofumarate monohydrate (KB-5492, Fig. 1). Shimohara et al. have already reported that KB-5492 inhibits various experimental gastric mucosal lesions more potently than sofalcone (6). In addition, they speculated that the anti-ulcer activity of KB-5492 was mediated by enhancing mucosal defensive factors, since KB-5492 did not affect either basal or histamine-stimulated gastric acid secretion. However, the details underlying its mechanism of action remain to be clarified.

In the present study, we compared the anti-ulcer activity of KB-5492 with those of teprenone, an agent known to enhance mucosal defensive factors, and cimetidine, an H2-receptor antagonist. The effects of KB-5492 on gastric mucosal blood flow and the mucosal content of hexosamine, a component of gastric mucus, were also investigated in order to clarify its mechanism of action.

**Fig. 1. Chemical structure of 4-methoxyphenyl 4-(3,4,5-trimethoxybenzyl)-1-piperazineacetate monofumarate monohydrate (KB-5492).**

**MATERIALS AND METHODS**

**Animals**

Male Sprague-Dawley rats weighing 170–250 g were used. The animals were deprived of food but were allowed free access to water for 24 hr prior to the experiments, unless otherwise stated.

**Drugs**

KB-5492 (Kanebo), teprenone (extracted from Selbex®, Eisai), cimetidine (Toho) and aspirin (Wako) were suspended in 1% gum arabic solutions. Indomethacin (Sigma) was dissolved in 3% NaHCO3 solution. Other drugs used were urethane (Kishida) and pentobarbital sodium (Nembutal®, Dainippon).

**Production of gastric mucosal lesions**

**Water-immersion stress-induced lesions:** The experiment was performed according to the method of Takagi and Okabe (7). Rats were placed in a restraint cage and then immersed vertically to the level of the xiphoid process in a water bath at 23°C. After 17 hr, the animals were sacrificed. The stomach was removed, fixed by inflating with 12 ml of 1% formalin, and then incised along the greater curvature. The length (mm) of each lesion formed on the glandular portion was measured under a dissecting microscope, and the sum of the lengths of lesions in each animal was calculated. Drugs were administered orally 15 min before the water-immersion.

**Indomethacin-induced lesions:** Indomethacin (30 mg/kg) was administered to the rats subcutaneously. After 5 hr, the animals were sacrificed. The stomach was removed and fixed with formalin; lesion length was then measured in the same manner as described under “Water-immersion stress-induced lesions”. Drugs were administered orally 15 min before indomethacin treatment.

**Ethanol-induced lesions:** One milliliter of 99.5% ethanol was administered to the rats orally. After 1 hr, the animals were sacrificed. The stomach was removed and fixed with formalin; lesion length was then measured in the
same manner as described under "Water-immersion stress-induced lesions". Drugs were administered orally 30 min before ethanol treatment.

Acetic acid-induced gastric ulcers

The experiment was performed according to the method of Takagi et al. (8). Rats were anesthetized with ether and the abdomens were incised. The anterior wall of the stomach was exposed, and then 0.02 ml of 20% acetic acid was injected into the submucosal layer at the junction of the fundus and the antrum. Drugs were administered orally twice daily for 10 consecutive days, beginning 2 days after the operation. On the day following the final drug administration, the animals were sacrificed. The stomach was removed, fixed with formalin, and incised along the greater curvature. Subsequently, the ulcer area (mm\(^2\)) was measured.

Determination of gastric secretion

The experiment was performed according to the method of Shay et al. (9). Rats were deprived of food for 48 hr prior to the experiment. Water was given freely during the fasting period, but withheld during the last 2 hr. The abdomen was incised under ether anesthesia and the pylorus was ligated. After 4 hr, the animals were sacrificed. Gastric contents were centrifuged, and the volume of gastric juice was measured. Subsequently, acidity was determined by titrating to pH 7.0 with 0.05 N NaOH. Drugs were administered intraduodenally immediately after pylorus-ligation.

Measurement of gastric mucosal blood flow

Rats were anesthetized with urethane (1.25 g/kg, i.p.), and then the abdomens were incised. In the case of intraduodenal drug administration, a polyethylene tube (SP-45, Natsume) was inserted into the duodenum without ligating the pylorus; and in the case of intragastric administration, a polyethylene tube was inserted into the gastric lumen via the forestomach after the pylorus and the esophagus were ligated. A needle-type platinum electrode (MHD-60, M.T. Giken) was inserted into the corpus mucosa from the serosal side, and a reference electrode (MH-10, M.T. Giken) was set in the subcutaneous tissue of the abdomen. Drugs were administered intraduodenally or intragastrically in a volume of 5 ml/kg via the polyethylene tube. In the case of intragastric administration, drugs were drawn out 15 min later. Gastric mucosal blood flow was measured by the electrolytically generated hydrogen gas clearance method, using a hydrogen monitor (DHM-3001, M.T. Giken) at 15, 30, 60, 90 and 120 min after drug administration. Subsequently, the animals were sacrificed by intravenous injection of an excessive dose of pentobarbital sodium and the blood flow measured 30 min after death was regarded as the spontaneous diffusion of hydrogen gas. The essential gastric mucosal blood flow was determined by subtracting the spontaneous diffusion from the blood flow measured at each time interval and was expressed as a percentage of the initial value (at 0 min).

Measurement of gastric mucosal hexosamine content

Aspirin (200 mg/kg) was administered to the rats orally. After 5 hr, the animals were sacrificed by decapitation. Macroscopic mucosal lesions were observed in the same manner as described under "Water-immersion stress-induced lesions". Gastric mucosal hexosamine content was measured according to the method of Masamune and Yoshizawa (10), after the corpus mucosa was separated from the muscle layer according to the method of Kobayashi et al. (11). Drugs were administered orally 30 min before aspirin treatment.

Statistics

Results were expressed as the mean ± S.E. Statistical significance was determined by one-way analysis of variance followed by Dunnett's or Duncan's test. The ED\(_{50}\) value was calculated by the least squares method for a regression line.
RESULTS

Effects of drugs on water-immersion stress-induced lesions

As shown in Fig. 2, oral administration of KB-5492 at 25–200 mg/kg inhibited lesion formation in a dose-dependent manner; the ED$_{50}$ was 46 mg/kg. Teprenone at 50–400 mg/kg and cimetidine at 12.5–100 mg/kg also showed similar effects; the ED$_{50}$ values were 124 and 22 mg/kg, respectively.

Effects of drugs on indomethacin-induced lesions

As shown in Fig. 3, oral administration of KB-5492 at 12.5–100 mg/kg inhibited lesion formation in a dose-dependent manner; the ED$_{50}$ was 27 mg/kg. Similarly, cimetidine at...
6.25–50 mg/kg showed a dose-dependent inhibition; its ED\textsubscript{50} was 19 mg/kg. Teprenone tended to aggravate the lesion at 25 and 50 mg/kg, but inhibited it at 100 and 200 mg/kg. 

Effects of drugs on ethanol-induced lesions

As shown in Fig. 4, oral administration of KB-5492 at 12.5–100 mg/kg inhibited lesion formation in a dose-dependent manner; the ED\textsubscript{50} was 23 mg/kg. Teprenone also inhibited it at 25–200 mg/kg; its ED\textsubscript{50} was 69 mg/kg. However, cimetidine did not show any obvious inhibition at 50–400 mg/kg.

Effects of drugs on acetic acid-induced gastric ulcers

As shown in Fig. 5, KB-5492, administered orally at 25 and 50 mg/kg twice daily for 10

Fig. 4. Effects of KB-5492, teprenone and cimetidine on ethanol-induced gastric mucosal lesions in rats. One milliliter of 99.5% ethanol was administered orally to the rats, and the animals were sacrificed 1 hr later. Drugs were administered orally 30 min before ethanol treatment. Each column represents the mean ± S.E. of 8 animals. *\textsuperscript{P} < 0.05, **\textsuperscript{P} < 0.01, significantly different from the control (Dunnett’s test).

Fig. 5. Effects of KB-5492, teprenone and cimetidine on acetic acid-induced gastric ulcers in rats. Rats were anesthetized with ether, and then the abdomens were incised. The anterior wall of the stomach was exposed, and 0.02 ml of 20% acetic acid was injected into the submucosal layer at the junction of the fundus and the antrum. Drugs were administered orally twice daily for 10 consecutive days, beginning 2 days after the operation. On the day following final drug administration, the animals were sacrificed. Each column represents the mean ± S.E. of 18–21 animals. *\textsuperscript{P} < 0.05, **\textsuperscript{P} < 0.01, significantly different from the control (Dunnett’s test).
consecutive days, significantly accelerated healing; the ulcer area was reduced by 58% and 77%, respectively, as compared with the control. Cimetidine, at 50 mg/kg twice daily, also significantly accelerated healing, but the reduction rate (58%) was inferior to that of KB-5492 at the same dose. Teprenone tended to accelerate healing at 50 mg/kg twice daily, but the reduction rate (33%) was not significant.

Effects of drugs on gastric secretion

As shown in Table 1, KB-5492, administered intraduodenally at 30–300 mg/kg, did not affect gastric secretion in pylorus-ligated rats. In contrast, teprenone at 300 mg/kg and cimetidine at 100 mg/kg significantly reduced gastric juice volume, acidity and acid output.

Effects of drugs on gastric mucosal blood flow

Intraduodenal administration: The mean initial value (at 0 min) of gastric mucosal blood flow was 51.0 ml/min/100 g (n = 30). As shown in Fig. 6, KB-5492 at 50–200 mg/kg gradually but dose-dependently increased blood flow. When the dose was 200 mg/kg, the maximum effect was observed 90 and 120 min after administration; and at these times, the blood flow increased by 64% and 62%, respectively, of its initial value, which was significantly different from the control. In contrast, teprenone at 200 mg/kg did not show any effects on gastric mucosal blood flow.

Intragastric administration: The mean initial value (at 0 min) of gastric mucosal blood flow was 54.7 ml/min/100 g (n = 24). As shown in Fig. 7, KB-5492 at 200 mg/kg, but not at 100 mg/kg, increased blood flow by 35% of its initial value 15 min after administration; this effect lasted until 120 min after administration; significant differences from the control were detected 15 and 120 min after administration. Teprenone at 200 mg/kg slightly increased blood flow by 16% and 11% of its initial value 90 and 120 min, respectively, after administration.

Effects of drugs on gastric mucosal hexosamine content

As shown in Table 2, oral administration of

| Drug | Dose (mg/kg, i.d.) | No. of rats | Volume ml/rat | Acidity mEq/1 | Acid output μEq/hr | Inhibition (%) |
|------|-------------------|-------------|---------------|---------------|-------------------|----------------|
| Control | —                 | 9           | 3.36 ± 0.40   | 118.3 ± 4.8   | 100.2 ± 13.8    | —              |
| KB-5492 | 30                | 9           | 3.08 ± 0.40   | 116.6 ± 3.8   | 91.0 ± 13.1     | 9              |
|       | 100               | 9           | 3.27 ± 0.32   | 110.6 ± 3.7   | 90.7 ± 9.5      | 9              |
|       | 300               | 9           | 2.31 ± 0.28   | 107.8 ± 4.8   | 63.2 ± 8.9      | 37             |
| Cimetidine | 100              | 8           | 1.31 ± 0.24** | 58.8 ± 3.1**  | 19.6 ± 3.7**    | 80             |
| Control | —                 | 8           | 3.40 ± 0.54   | 120.3 ± 2.3   | 101.1 ± 15.3    | —              |
| Teprenone | 30                | 8           | 3.67 ± 0.43   | 119.5 ± 2.0   | 109.6 ± 12.9    | —8             |
|       | 100               | 8           | 2.32 ± 0.30   | 104.4 ± 4.4*  | 61.1 ± 8.6*     | 40             |
|       | 300               | 8           | 1.89 ± 0.22*  | 92.9 ± 6.0**  | 42.3 ± 3.5**    | 58             |

The pylorus of each rat was ligated under ether anesthesia. After 4 hr, the animals were sacrificed. Gastric contents were centrifuged, and the volume of gastric juice was measured. Subsequently, acidity was determined by titrating to pH 7.0 with 0.05 N NaOH. Drugs were administered intraduodenally immediately after pylorus-ligation. Each value represents the mean ± S.E. *P < 0.05, **P < 0.01, significantly different from the control (Dunnnett’s test).
aspirin at 200 mg/kg induced macroscopic lesions in the gastric mucosa 5 hr after administration. Both KB-5492 and teprenone, administered orally at 100 and 200 mg/kg, inhibited lesion formation in a dose-dependent manner, and the lesion lengths at 200 mg/kg were significantly reduced as compared with the control group. Cimetidine almost completely inhibited lesion formation at 100 mg/kg.

As shown in Table 3, 5 hr after aspirin treatment, gastric mucosal hexosamine content was reduced to less than 70% of that in the normal group. Both KB-5492 and teprenone at 100 and 200 mg/kg inhibited the reduction of hexosamine content in a dose-dependent manner, and the hexosamine content at 200 mg/kg was significantly greater than that in the group treated with aspirin alone. Cimetidine at 100 mg/kg slightly, but not significantly, inhibited the reduction of hexosamine content.
DISCUSSION

In the present study, KB-5492, administered orally at 12.5–200 mg/kg, was shown to inhibit water-immersion stress- and indomethacin-induced acute gastric mucosal lesions in a dose-dependent manner. The inhibitory effects of KB-5492 on these gastric mucosal lesions were more potent than those of teprenone, an agent known to enhance gastric mucosal defensive factors, but were slightly weaker than those of cimetidine, an H2-receptor antagonist. In addition, KB-5492 accelerated the healing of acetic acid-induced chronic gastric ulcers more potently than did teprenone and cimetidine.

As it has been reported that gastric acid is involved in the formation of water-immersion...
stress-induced (12) or indomethacin-induced (13) gastric mucosal lesions. We therefore examined the effect of KB-5492 on gastric acid secretion in pylorus-ligated rats. KB-5492, administered at anti-ulcer doses (30–300 mg/kg, i.d.), did not show any effect on gastric acid secretion. This result is consistent with that obtained by Shimohara et al. (6) and adds further confirmation to the idea that the anti-ulcer effect of KB-5492 is not exerted by inhibition of gastric acid secretion.

Ethanol-induced gastric mucosal lesions are caused by the direct action of ethanol, and gastric acid has little part in such lesion formation (14). Moreover, it is well-known that ethanol-induced gastric mucosal lesions are not inhibited by anti-secretory agents like cimetidine, but are inhibited by agents which enhance mucosal defensive factors (15). In addition, in our present study, KB-5492 and teprenone, but not cimetidine, showed inhibitory effects. These results further indicate that KB-5492 may enhance gastric mucosal defensive factors. We then examined the effects of KB-5492 on gastric mucosal blood flow and gastric mucus amount, which are considered to be closely related to mucosal defensive mechanisms.

KB-5492, administered intraduodenally or intragastrically, increased gastric mucosal blood flow. Gerkens et al. (16) and Kudo (17) suggested that the reduction of gastric mucosal blood flow contributed to the lesion formation induced by indomethacin and water-immersion stress. Miller (18) regarded the increase in gastric mucosal blood flow as one of the mechanisms of gastric mucosal protection by prostaglandins. Therefore, the present results suggest that the anti-ulcer effect of KB-5492 is partly mediated by the increase in gastric mucosal blood flow. Regarding the effect of KB-5492 on increasing gastric mucosal blood flow, a slight difference was observed between the two administration routes in the onset of its effect. In the case of intragastric administration, the effect was rapid in onset, reaching a maximum 15 min after administration, whereas the maximum effect was attained 90 and 120 min after intraduodenal administration. The cause of the difference is presumed to be that following intragastric administration, the drug can reach the submucosal microvessels, its site of action, more rapidly than following intraduodenal administration. In contrast, teprenone at 200 mg/kg showed no obvious effects on gastric mucosal blood flow, regardless whether it was administered intraduodenally or intragastrically.

Oral administration of aspirin at 200 mg/kg induced macroscopic lesions in the gastric mucosa and reduced the mucosal content of hexosamine, a component of gastric mucus, 5 hr after administration. Regarding a possible mechanism for this phenomenon, Rainsford (19) showed that aspirin weakened gastric mucosal resistance by inhibiting the biosynthesis of gastric mucus. Azuumi et al. (20) also reported that aspirin reduced gastric mucosal glycoprotein content prior to the macroscopic lesion formation, and they suggested that aspirin-induced mucosal lesions were caused by the reduction of gastric mucus. Murakami et al. (21) and Oketani et al. (22) examined the effect of teprenone on the amount of gastric mucus in aspirin-treated rats, and consequently they speculated that teprenone inhibited aspirin-induced mucosal lesions by preventing the reduction of gastric mucus, particularly of macromolecular glycoproteins. In the present study, KB-5492, as well as teprenone, significantly inhibited both the macroscopic lesion formation and the reduction of mucosal hexosamine content induced by aspirin. Therefore, we presumed that KB-5492 also inhibits aspirin-induced mucosal lesions by retaining gastric mucus. Besides being a factor in aspirin-induced lesions, it has been reported that the reduction of gastric mucus is a possible cause of the lesion formation induced by water-immersion stress (23), indomethacin (24) and ethanol (25). In addition, it has been suggested that the healing of acetic acid-induced ulcers is closely related to the amount of mucus in the gastric mucosa (26, 27). Therefore, KB-5492 may exert inhibitory and/or curative effects against these lesions.
also, in part by retaining gastric mucus.

Cimetidine almost completely inhibited the macroscopic lesion formation induced by aspirin. However, it did not show significant inhibition of the reduction of gastric mucosal hexosamine content. This is inconsistent with the result obtained by Azuumi et al. (28) that cimetidine inhibited both the macroscopic lesion formation and the reduction of mucosal glycoprotein content induced by aspirin. They also demonstrated that mucosal glycoprotein content remained low after the macroscopic lesions had naturally diminished 9 hr after aspirin treatment (20). Moreover, the mucosal lesion formation in our study (shown in Table 2) is much more severe than that reported by Azuumi et al. (20, 28). Therefore, it is presumed that cimetidine could hardly restore the biochemical function (i.e., glycoprotein synthesis) in the gastric mucosa under such severe experimental conditions as in the present study, even though it could inhibit the macroscopic lesion formation. It is considered that not only the reduction of gastric mucus, but also the aggression of gastric acid, contributes to the lesion formation by aspirin (29, 30). Therefore, it would appear that the inhibitory effect of cimetidine on aspirin-induced lesions in the present study is due mainly to its antisecretory activity (31, 32).

The present results indicate that KB-5492 has potent and broad anti-ulcer properties, which are probably exerted by its enhancement of gastric mucosal defensive factors through increasing gastric mucosal blood flow and/or retaining gastric mucus. However, other mechanisms besides these actions may be included. Further studies are required to clarify the exact mechanism of action of KB-5492.

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