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Pharmacological properties of a newly synthesized H^+/K^+ ATPase inhibitor, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline

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Abstract

A new compound, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (DBM-819), given intraduodenally in pylorus-ligated rats, inhibited basal acid secretion with an ED_{50} value of 3.5 mg/kg. In addition, DBM-819 reduced histamine- and pentagastrin-stimulated gastric acid secretion with ED_{50} values of 4.0 and 5.1 mg/kg, respectively. The duration of the anti-secretory effect was approximately 18 h when DBM-819 was administered orally to rats with a chronic gastric fistula. Oral administration of DBM-819 protected against gastric lesions induced by ethanol, NaOH, indomethacin and aspirin, and the duodenal ulcer induced by cysteamine, in a dose-dependent manner with ED_{50} values of 7.0, 20, 3.1, 4.0 and 6.0 mg/kg, respectively. Taken together, these results suggest that DBM-819 acts as an effective oral anti-ulcer agent in vivo, and that DBM-819 could be developed as a new therapeutic agent for peptic ulcer disease.

Keywords: Gastric acid secretion; Anti-ulcer activity; Gastric ulcer; Duodenal ulcer

1. Introduction

Gastric H^+/K^+ ATPase inhibitors have been considered as effective remedies for acid-related diseases. Among such inhibitors, the substituted benzimidazole derivatives such as omeprazole and lansoprazole have been used clinically (Gustavsson et al., 1983). These compounds bind covalently to the H^+/K^+ ATPase and inactivate it irreversibly (Lorentzon et al., 1985). Thus, the return of acid secretion following inhibition may require de novo synthesis of new enzyme, which makes it difficult to predict and reproduce the pharmacokinetics and pharmacodynamics. An accompanying paper describes the in vitro biochemical properties of a new compound, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline (DBM-819), which is a potent and reversible inhibitor of the gastric H^+/K^+ ATPase. The reversibility of the H^+/K^+ ATPase inactivation by DBM-819 would overcome the side effects associated with the irreversibility of the effects of substituted benzimidazoles.

In the present study, we examined the pharmacological properties of DBM-819 as an anti-ulcer agent in the pylorus-ligated rat, in the stomach lumen-perfused rat, and in several experimental animal ulcer models. The results demonstrate that DBM-819 inhibits in vivo basal gastric acid secretion, as well as histamine- and pentagastrin-stimulated gastric acid secretion. In addition, DBM-819 protects against the development of gastric lesions induced by various agents. The effect of omeprazole—a substituted benzimidazole H^+/K^+ ATPase inhibitor—was also investigated for comparison.

2. Materials and methods

2.1. Materials

Histamine dihydrochloride, pentagastrin, sodium hydroxide (NaOH), cysteamine, indomethacin, and aspirin were obtained from Sigma (St. Louis, MO, USA). Absolute ethanol was obtained from Hayman Limited (Essex,

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UK). Carboxymethylcellulose was obtained from Showa Chemical (Tokyo, Japan). Formalin (17%) was obtained from Merck (Darmstadt, Germany). Polyethyleneglycol 400 and urethane were obtained from Junsei Chemical (Tokyo, Japan). Diethylether was obtained from Oriental Chemical Industries (Seoul, Korea). Sprague–Dawley rats (male, 6 weeks old, 180–250 g) were obtained from Charles River (Atsugi, Japan) and housed under constant conditions (23 ± 2°C, 12-h light) for 3–4 days before experimentation. Experimental conditions and animal studies conformed with the Guidelines of the Declarations of Helsinki and Tokyo.

2.2. In vivo anti-secretory effect of DBM-819

The in vivo anti-secretory effect of DBM-819 was determined using pylorus-ligated rats according to Shay et al. (1945). Sprague–Dawley rats (150–250 g) were starved for 24 h before experimentation. The pylorus of the rats was ligated under diethylether anesthesia. DBM-819 in a 10% polyethyleneglycol 400 suspension was administered intraduodenally. Control groups were given 10% polyethyleneglycol 400 solution alone. Five hours after surgery, the stomach was isolated and the accumulated gastric juice was collected. After centrifugation of the gastric juice at 5000 rpm for 10 min, the supernatant was analyzed for gastric acid volume, pH, and acid output using an Orion 960 autochemistry analyzer (Boston, MA, USA). The total acid output was calculated as the product of the gastric acid concentration and the volume of gastric juice.

2.3. Effects of DBM-819 in the stomach lumen-perfused rat

For the lumen-perfused rat studies, the method of Ghosh and Schild (1958) was used. Sprague–Dawley rats (10 weeks old, 300–350 g) were fasted for 24 h, anesthesized with an i.p. injection of 1.2 g/kg urethane and tracheotomized. A polyethylene tube was inserted and fixed in the forestomach through the esophagus, and another cannula was inserted into the pyloric region of the stomach through the duodenum. The animal was perfused with 37°C saline solution at a flow rate of 1.5 ml/min, using an infusion pump. The perfusate from the duodenum tube was collected at 15-min intervals, and its volume and acid concentration were determined using an Orion 960 autochemistry analyzer. Body temperature was maintained at 37°C using an overhead heating lamp and an electrically heated cushion. DBM-819 suspended in 0.5% carboxymethylcellulose was administered intraduodenally, and either pentagastrin (500 μg/kg) or histamine (2 mg/kg) in 0.9% saline was injected i.m. as a secretagogue 30 min after the administration of the compound. The percent inhibition was calculated by comparing the area under the acid output curves in the presence and absence of DBM-819.

2.4. Duration of DBM-819 action

The surgery of Sprague–Dawley rats (180–250 g) was carried out under ketamine anesthesia. A plastic cannula was inserted and tied in the rumenal part of the stomach. The other end of the cannula was exteriorized through the abdominal wall. The lumen of the cannula was plugged to permit normal feeding. Animals were given a 1-week recovery period before experimentation. After an overnight fast, the rats were placed in modified Bollman cages. DBM-819 (5 mg/kg or 10 mg/kg) suspended in 0.5% carboxymethylcellulose was given orally, and at least 1 h was allowed for absorption. After the stomach was washed with warm saline for 30 min, pentagastrin (500 μg/kg, i.m.) was administered, and three consecutive 1-h samples were collected by free drainage from the gastric cannula. The volume and acidity of the gastric juice were determined as described above.

2.5. Effects of DBM-819 on the experimentally induced ulcer models

2.5.1. Ethanol-induced gastric ulcer

Gastric mucosal lesions, as elicited by ethanol, were produced according to the method of Robert et al. (1979). Sprague–Dawley rats were fasted for 24 h prior to experimentation, with free access to water. DBM-819 suspended in 0.5% carboxymethylcellulose was given 1 h before oral administration of 95% ethanol (1 ml/rat). One hour later, each animal was killed by diethylether anesthesia, and the stomach was isolated. After the stomach was fixed in 13 ml of 1% formalin for 1 h, the greater curvature of the stomach was opened. The macroscopical lesion length was measured (in mm), summed, and compared with that of the group treated with 95% ethanol alone. All of the group allocations of the experimental animals were done in a randomized order and under blinded conditions.

2.5.2. NaOH-induced gastric ulcer

A modification of the method of Murakami et al. (1982) was used. Sprague–Dawley rats were treated orally with either DBM-819 or vehicle (0.5% carboxymethylcellulose). One hour later, the animals were given 0.3 N NaOH (1 ml/rat) and killed 1 h stet. The severity of the gastric lesions was determined as the sum of their lengths.

2.5.3. Indomethacin-induced gastric ulcer

A modification of the method of Urushidani et al. (1977) was used. Sprague–Dawley rats were fasted for 24 h before experimentation, and DBM-819 was given orally. One hour later, indomethacin (40 mg/kg) in 0.5% carboxymethylcellulose was given orally. Six hours later, the animals were killed by diethylether anesthesia, and the size of the gastric lesion was measured and compared with that of the control animals treated with vehicle alone.

2.5.4. Aspirin-induced gastric ulcer

A modification of the method of Guth et al. (1979) was used. Sprague–Dawley rats were fasted for 24 h before experiments, and DBM-819 was given orally. One hour later, aspirin (200 mg/kg) in 0.5% carboxymethylcellulose was given orally. Six hours later, the animals were killed and the gastric lesion was assessed.

2.5.5. Cysteamine-induced duodenal ulcer

The experiment was performed as described by Szabo et al. (1977), with slight modifications. Sprague–Dawley rats were administered cysteamine (400 mg/kg) in H_2O subcutaneously. DBM-819 was administered orally 1 h before cysteamine administration. The animals were killed 24 h after cysteamine dosing, and the gastroduodenal region was excised. The area of the duodenal lesions was measured and used as the ulcer index.

2.6. Statistical analysis

All values shown in the figures and tables represent the means ± S.E. ED_{50} values with 95% confidence limits were estimated from the linear regression analysis of the log dose vs. percent activity (relative to control) curves. Statistical evaluation of the results was performed by analysis of variance followed by Dunnett's test, and by the unpaired Student's *t*-test. A P value of less than 0.05 was regarded as statistically significant.

3. Results

3.1. In vivo anti-secretory effect of DBM-819

In order to determine whether DBM-819 has an anti-secretory effect in vivo, DBM-819 was given intraduodenally to pylorus-ligated rats, and its effect on gastric secretion was examined. Gastric acid secretion was inhibited in a dose-dependent manner, with marked inhibition (81% inhibition) being achieved at 10 mg/kg (Table 1). This reduction in acid output was due to a decrease in both the volume and H^+ concentration of the gastric juice. The ED_{50} value was estimated to be 3.5 ± 0.3 mg/kg i.d. Omeprazole inhibited basal gastric acid secretion with an ED_{50} value of 3.2 ± 0.4 mg/kg i.d.

Table 1
Effects of DBM-819 and omeprazole on gastric secretion in pylorus-ligated rats[a]

Drugs	Dose (mg/kg)	Acid output (μeq/5 h)	ED_{50} (mg/kg)
Control	–	762 ± 30.3	
DBM-819	5	242 ± 85.0[b]	
	10	146 ± 61.9[b]	3.5 ± 0.3
	20	29.7 ± 23.0[b]	
	40	14.3 ± 11.9[b]	
Control	–	625 ± 79.7	
Omeprazole	5	228 ± 34.2[b]	
	10	154 ± 39.2[b]	3.2 ± 0.4
	20	136 ± 43.0[b]	
	40	32.4 ± 7.60[b]	

[a] Drugs were administered into Sprague–Dawley rats intraduodenally after pylorus ligation. Animals were killed 5 h after ligation. Each value represents the mean ± S.E. ($N = 10$).

[b] $P < 0.05$ compared with control group.

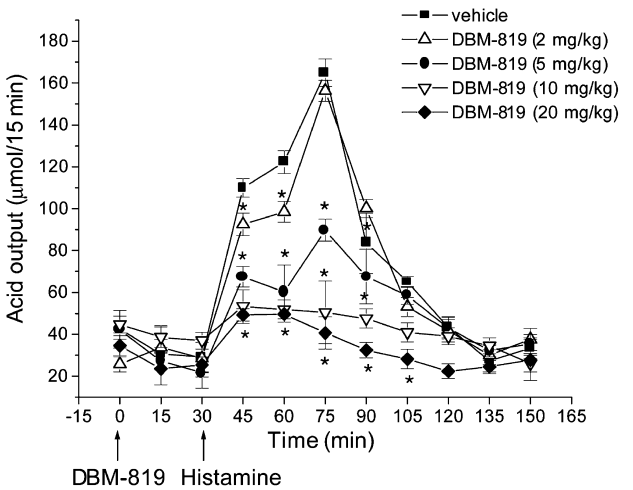

Fig. 1. Effect of DBM-819 on acid output in the lumen-perfused rat stomach under histamine stimulation (2 mg/kg). DBM-819 was administered intraduodenally at doses of 2, 5, 10 and 20 mg/kg. Other experimental details were as described in Materials and methods. Data represent the means ± S.E. ($n = 8$). * $P < 0.05$ vs. control.

3.2. Effects of DBM-819 in the stomach lumen-perfused rat

The effect of DBM-819 in the anesthetized stomach lumen-perfused rat was examined using the Ghosh and Schild technique (Ghosh and Schild, 1958). As shown in Fig. 1, DBM-819 given intraduodenally produced a dose-dependent inhibition of histamine-stimulated gastric secretion. At a dose of 5 mg/kg, DBM-819 caused a significant suppression of acid secretion (57% inhibition). The onset of the action of DBM-819 was rapid, being detectable 15 min after administration. An injection of histamine at a dose of 2 mg/kg induced a submaximal secretory response, and the histamine-induced stimulation of acid secretion lasted 1.5 h. From these experiments, an inhibitory ED_{50} value of 4.0 ± 0.2 mg/kg i.d. was calculated (from the area under the acid output curve) in the presence of various concentrations of DBM-819. Vehicle (0.5% carboxymethylcellulose) by itself did not affect gastric acid secretion. The reference compound, omeprazole, showed inhibitory activity with an ED_{50} of 2.3 ± 0.3 mg/kg.

DBM-819 given by intraduodenal injection also produced a dose-dependent inhibition of pentagastrin-stimulated acid secretion (Fig. 2). The inhibition was 22.9%, 48.2%, 69.1% and 94.4%, at doses of 2, 5, 10, and 20

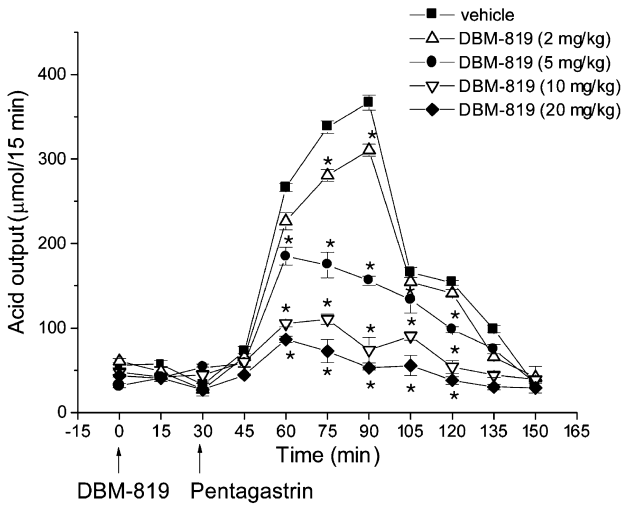

Fig. 2. Effect of DBM-819 on acid output in the lumen-perfused rat stomach under pentagastrin stimulation (500 μg/kg). DBM-819 was administered intraduodenally at doses of 2, 5, 10 and 20 mg/kg. Other experimental details were as described in Materials and methods. Data represent the means ± S.E. ($n = 8$). $^{*}P < 0.05$ vs. control.

mg/kg, respectively. An ED_{50} value of 5.1 ± 0.5 mg/kg i.d. was obtained for these data. The ED_{50} calculated for omeprazole was 1.8 ± 0.2 mg/kg i.d.

3.3. Duration of DBM-819 action

The duration of the anti-secretory effect of orally administered DBM-819 was evaluated in rats with a chronic fistula, and the results are presented in Fig. 3. In this study,

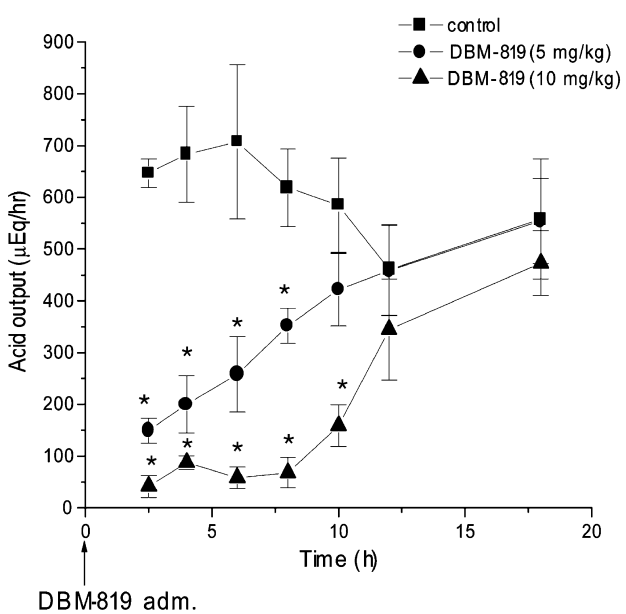

Fig. 3. Duration of the antisecretory effect of DBM-819 in the chronic fistula rat. DBM-819 (5, 10 mg/kg) was given orally, and after various times, pentagastrin (500 μg/kg)-stimulated acid secretion tests were carried out as described in Materials and methods. Data represent the means ± S.E. ($n = 5$). $^{*}P < 0.05$ vs. control.

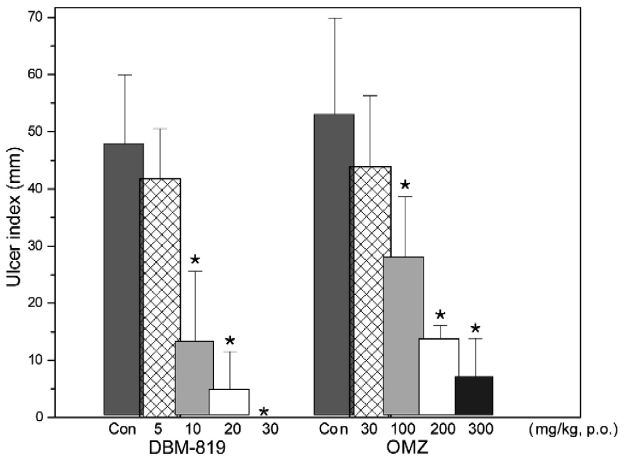

Fig. 4. Effect of DBM-819 on ethanol-induced gastric lesions. DBM-819 was given 1 h before the administration of 1 ml of 95% ethanol. Data represent the means ± S.E. ($n = 10$). $^{*}P < 0.05$ vs. control.

acid secretion was stimulated by an i.m. injection of pentagastrin (500 μg/kg), and it reached a plateau after 30 min. Acid secretion was measured for up to 18 h after the administration of DBM-819. DBM-819 (10 mg/kg p.o.) had a significant inhibitory effect on pentagastrin-stimulated acid secretion when measured 10 h after administration (the mean peak level of inhibition was 65.5%), but it had little effect 18 h after dosing. When a lower dose of DBM-819 (5 mg/kg) was given, acid secretion was restored 12 h after dosing. By comparison, the action of omeprazole (10 mg/kg, p.o.) lasted for 48 h under our experimental conditions.

3.4. Effects of DBM-819 on the experimentally induced ulcer models

3.4.1. Ethanol-induced gastric ulcer

Oral administration of 95% ethanol produced severe band-like mucosal hemorrhage in the glandular stomach.

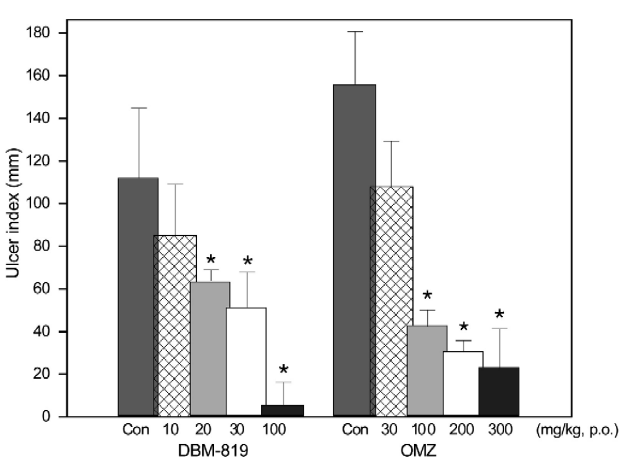

Fig. 5. Effect of DBM-819 on NaOH-induced gastric lesions. DBM-819 was given 1 h before the administration of 1 ml of 0.3 N NaOH. Data represent the means ± S.E. ($n = 10$). $^{*}P < 0.05$ vs. control.

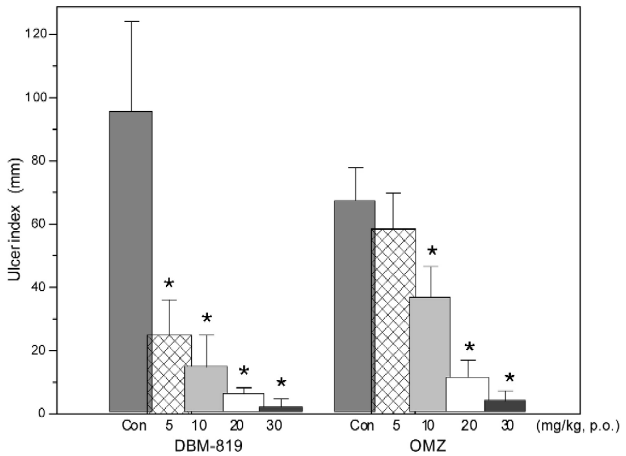

Fig. 6. Effect of DBM-819 on indomethacin-induced gastric lesions. DBM-819 was given 1 h before the administration of 40 mg/kg indomethacin. Data represent the means ± S.E. ($n = 10$). $^{*}P < 0.05$ vs. control.

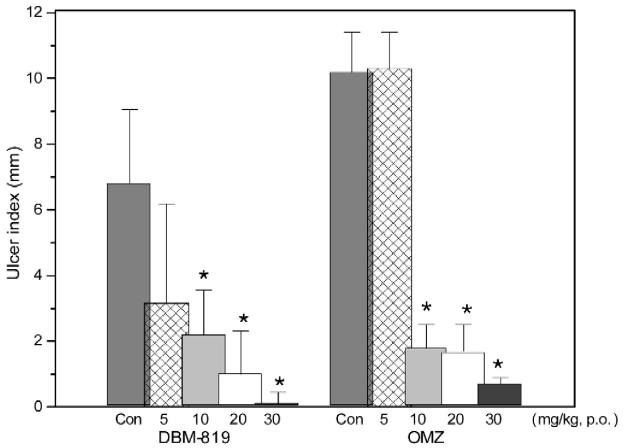

Fig. 8. Effect of DBM-819 on cysteamine-induced duodenal lesions. DBM-819 was given 1 h before the administration of 400 mg/kg cysteamine. Data represent the means ± S.E. ($n = 10$). $^{*}P < 0.05$ vs. control.

Control rats treated with ethanol alone had gastric lesions of 47.8 ± 12.1 mm. DBM-819 treatment reduced the mucosal lesions in a dose-dependent manner (Fig. 4). The ED_{50} value was 7.0 ± 0.8 mg/kg p.o. By comparison, the ED_{50} value of omeprazole was 70 ± 9.1 mg/kg. The effect of DBM-819 was therefore 10 times stronger than that of omeprazole.

3.4.2. NaOH-induced gastric ulcer

Similar to the effects of ethanol, oral administration of 0.3 N NaOH produced band-like mucosal lesions in the stomach. The lesion index in the control group was 112 ± 32.7 mm. The effect of DBM-819 was studied at doses of 10, 20, 30 and 100 mg/kg. Significant inhibition was observed at 30 and 100 mg/kg p.o. (Fig. 5). The ED_{50} values of DBM-819 and omeprazole were 20 ± 2.1 and 41 ± 3.2 mg/kg, respectively.

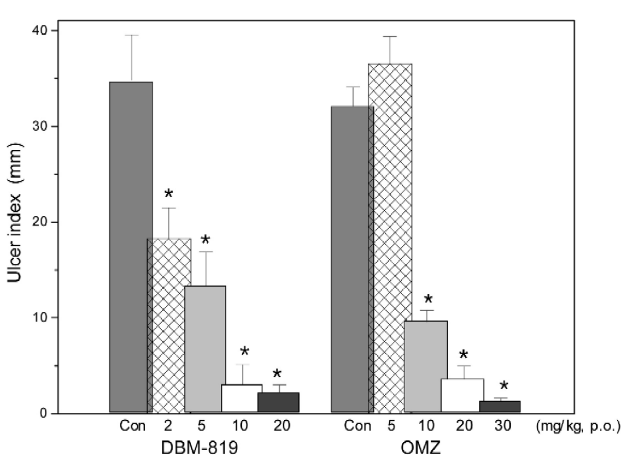

Fig. 7. Effect of DBM-819 on aspirin-induced gastric lesions. DBM-819 was given 1 h before the administration of 200 mg/kg aspirin. Data represent the means ± S.E. ($n = 10$). $^{*}P < 0.05$ vs. control.

3.4.3. Indomethacin-induced gastric ulcer

DBM-819 was administered orally at doses of 5, 10, 20 and 30 mg/kg. Indomethacin produced several lesions in the glandular stomach; the ulcer index in the control rats was 89.6 ± 5.70 mm. Indomethacin-induced gastric erosion was inhibited significantly and dose dependently by DBM-819, with an ED_{50} value of 3.1 ± 0.5 mg/kg p.o. (Fig. 6). Omeprazole also inhibited lesion formation with an ED_{50} value of 10.5 ± 0.8 mg/kg p.o. The effect of DBM-819 was greater than that of omeprazole.

3.4.4. Aspirin-induced gastric ulcer

As shown in Fig. 7, treatment with DBM-819 reduced mucosal lesions in a dose-dependent manner. The lesion index in the control group was 34.8 ± 4.22 mm. The ED_{50} values of DBM-819 and omeprazole were 4.0 ± 1.3 and 8.1 ± 1.2 mg/kg, respectively.

3.4.5. Cysteamine-induced duodenal ulcer

The effect of DBM-819 was studied at doses of 5, 10, 20 and 30 mg/kg. Cysteamine produced one or two penetrating ulcers in the proximal duodenum when administered subcutaneously. The ulcer index in the control rats was 6.45 ± 0.76 mm. Duodenal ulcer formation was significantly inhibited by 10 and 20 mg/kg doses of DBM-819. The ED_{50} value was 6.0 ± 0.6 mg/kg p.o. (Fig. 8). Omeprazole also inhibited the ulcers, with an ED_{50} value of 6.5 ± 0.4 mg/kg p.o.

4. Discussion

In the present study, DBM-819 showed potent antisecretory and anti-ulcer activity, as predicted from its biochemical properties described in the accompanying pa-

per. Using an in vivo system, DBM-819 was shown to be an effective inhibitor of basal acid secretion when administered intraduodenally, with an ED_{50} of 3.5 ± 0.3 mg/kg. The inhibition of gastric acid secretion was attributed to a reduction in the volume and concentration of gastric juice. In addition to the basal acid secretion, DBM-819 was effective at inhibiting both pentagastrin- and histamine-stimulated acid secretion in the stomach lumen-perfused rat model, with ED_{50} values of 5.1 ± 0.5 and 4.0 ± 0.2 mg/kg, respectively. The onset of inhibition by DBM-819 was rapid upon intraduodenal administration, occurring after only 15 min. The anti-secretory potency of DBM-819 was similar to that of omeprazole in these experiments.

DBM-819 demonstrated a moderate duration of action in rats when administered orally. When 10 mg/kg p.o. was given to rats, the anti-secretory effect was still detectable at 18 h, after having produced 94% inhibition at 2.5 h. In contrast, omeprazole (10 mg/kg) had a longer duration of action, being detectable at 48 h after oral administration under our experimental conditions (results not shown).

To further investigate the anti-ulcer effect of DBM-819, its effect was examined in the experimental ulcer models induced by ethanol, NaOH, indomethacin, aspirin and cysteamine. The pathogenesis of the ulceration induced by these agents is diverse (Guth, 1982). For example, aspirin and indomethacin-induced gastric ulcers are caused by suppression of prostaglandin biosynthesis and disruption of the gastric mucosal barrier (Ohe et al., 1980). Ethanol has been shown to produce gastric damage by impairment of the gastric defensive factors such as mucus and mucosal circulation (Trier et al., 1987). Aspirin, indomethacin and ethanol-induced gastric lesions are therefore not prevented by suppression of gastric acid secretion, whereas cysteamine-induced duodenal damage is dependent on the amount and concentration of the gastric acid.

DBM-819 protected against gastric damage induced by ethanol, NaOH, indomethacin and aspirin. Furthermore, DBM-819 significantly reduced duodenal ulceration caused by cysteamine. The anti-ulcer effect of DBM-819 appeared to be superior to that of omeprazole in gastric acid-independent damage models. For instance, in the ethanol, indomethacin, NaOH and aspirin models, DBM-819 protected against acute gastric lesions with ED_{50} values of 7.0, 3.1, 20 and 4.0 mg/kg p.o. respectively, compared with omeprazole, which exhibited corresponding values of 70, 10.5, 41 and 8.1 mg/kg p.o. However, the potency of DBM-819 in the gastric acid-dependent model (cysteamine-induced ulcer) was similar to that of omeprazole, which is consistent with the results obtained in the pylorus-ligated rat model. It therefore appears that the anti-ulcer activity of DBM-819 is the result of both anti-secretory and cytoprotective properties.

In conclusion, the present study shows the pharmacological properties of DBM-819 as an effective anti-ulcer agent. The anti-ulcer action of DBM-819 appears to be partly due to the inhibition of gastric acid secretion via reversible inhibition of gastric H^+/K^+ ATPase activity, and partly due to cytoprotection of the gastroduodenal mucosa. Detailed studies on the toxicology and pharmacokinetics of DBM-819 are in progress in order to assess the utility of DBM-819 in peptic ulcer therapy.

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