Stimulatory Effect of N-[4-[2-(Dimethylamino)ethoxy]benzyl]-3,4-Dimethoxybenzamide Hydrochloride (HSR-803) on Normal and Delayed Gastrointestinal Propulsion

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Received October 26, 1990 Accepted March 22, 1991

ABSTRACT—To estimate the effect of a new gastroprokinetic agent, N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride (HSR-803), on non-ulcer dyspepsia, the influence of HSR-803 on gastrointestinal propulsion was assayed in dogs, rats and mice in comparison with some gastroprokinetic agents. HSR-803 (30 mg/kg, p.o.) significantly enhanced gastric emptying in dogs, and it significantly improved the delayed gastric emptying induced by dopamine (0.4 mg/kg, i.p.) and morphine (1 mg/kg, s.c.) in rats. Metoclopramide (30 mg/kg, p.o.) also significantly restored the dopamine-induced delay, but at a dose of 10 mg/kg, p.o., it enhanced the morphine-induced delay in gastric emptying in rats. HSR-803 (10-100 mg/kg, p.o.) increased small intestinal transit in mice in a dose-dependent manner, and the effect was abolished by atropine (0.3 mg/kg, i.p.). Metoclopramide also increased small intestinal transit, but domperidone and cisapride had no effect. In delayed small intestinal transit in mice, HSR-803 (10-100 mg/kg, p.o.) improved the morphine (0.3 mg/kg, s.c.)-induced delay in a dose-dependent manner. In conclusion, because of the promotion of normal and delayed gastrointestinal propulsion, HSR-803 seems to be a promising gastroprokinetic agent for the treatment of non-ulcer dyspepsia. The action of HSR-803 is likely to be exerted through cholinergic stimulation.

It has been reported that a new gastroprokinetic agent, HSR-803, stimulates gastrointestinal motility in conscious dogs, probably through dopamine D2 receptor (D2) blocking and anti-acetylcholinesterase (anti-AChE) activities (1). Several gastroprokinetic agents, metoclopramide and domperidone are known to be D2 antagonists, and reported to have weak anti-AChE activity (1–3). A newly developed gastroprokinetic agent, cisapride, also has an anti-D2 action (4). The D2 blocking activity of HSR-803 was weaker than that of metoclopramide, domperidone and cisapride, while anti-AChE activity was more potent than that of metoclopramide and domperidone (5). Thus the pharmacological profile of HSR-803 was expected to differ from that of metoclopramide and domperidone.

One of the gastrointestinal disorders, non-ulcer dyspepsia having symptoms of discomfort in the epigastrium, fullness in the abdomen, nausea and emesis is mainly due to de-
layed gastric emptying. Metoclopramide, domperidone and cisapride have been used in the treatment of non-ulcer dyspepsia, because of their stimulatory effect on gastric emptying in animals and man (6-11). Therefore, in estimating the effect on non-ulcer dyspepsia, it is important to know the stimulatory effect of HSR-803 not only on the gastrointestinal contractions but also on the gastrointestinal functions. The aim of this study was to investigate the influence of HSR-803 on gastrointestinal propulsion.

MATERIALS AND METHODS

Gastric emptying in dogs

The experiment was performed according to the method reported by Harasawa et al. (12). Seven beagle dogs of either sex, weighing 7.5-11 kg, were used. Each dog was fasted overnight before the experiments. HSR-803 (10-30 mg/kg), or distilled water as a control, was orally administered to the dogs. Thirty minutes after the HSR-803 administration, the dogs were given a meal (20 g/kg, CD-5, Nihon Clea, Japan). Acetaminophen (30 mg/kg) in 1 capsule (capsule size No. 1, Japan Elanco Co., Ltd., Japan), which was soluble in the stomach, was orally administered immediately after the feeding. Blood samples were obtained at 0, 15, 30, 45, 60, 90 and 120 min after the acetaminophen administration, and the plasma acetaminophen concentration was measured by the dye method with a spectrophotometer (U-2000, Hitachi, Japan) according to the method of Routh et al. (13). Briefly, a specimen of serum was deproteinized with Na₂SO₃-Na₂SO₄, and the acetaminophen was extracted by mixing it with ethylene dichloride solution. Three milliliters of the ethylene dichloride layer was added to 1 ml of a solution of diphenylpicrylhydrazyl dye. The solution was mixed and then heated at 60°C for 1 hr. The absorbances of the solutions were read at a wavelength of 527 nm. In a preliminary experiment, we measured the plasma acetaminophen concentration when acetaminophen dissolved in water was administered; and it was found that the plasma acetaminophen concentration peaked at 15 min after the administration (20.0 ± 5.4 μg/ml).

Gastric emptying in rats

Male Wistar rats, weighing about 200 g, fasted for 24 hr were used. HSR-803 (10-100 mg/kg), metoclopramide (3-30 mg/kg), domperidone (3-30 mg/kg), cisapride (0.3-3 mg/kg) and 0.5% carboxymethylcellulose (CMC) as a control were orally administered in a volume of 5 ml/kg. Thirty minutes after the drug administration, except in the case of domperidone (2 hr after the administration), dopamine (0.4 mg/kg, i.p.), morphine (1 mg/kg, s.c.) and saline (as a control) were injected, and then 0.05% phenol red solution (1.5 ml/rat) was orally administered immediately after the injection. Each rat was sacrificed at 15 min after the phenol red administration except rats sacrificed immediately for the recovery of the whole amount of phenol red, and the stomach was removed. The stomach was cut into several pieces in 20 ml distilled water and shaken for 10 min. The pieces of stomach were rinsed with 20 ml distilled water, and then the total 40 ml volume of distilled water containing the gastric content was centrifuged (3000 rpm) for 10 min. Two milliliters of the supernatant was added to 3 ml of 1 N NaOH to develop color, and the absorbance was measured at the wavelength of 558 nm with a spectrophotometer (U-2000, Hitachi). Gastric emptying was calculated as follows:

\[
\text{Gastric emptying (\%)} = \frac{A - B}{A} \times 100
\]

A: The whole amount of phenol red recovered from the stomach immediately after the phenol red administration
B: The amount of phenol red remaining in the stomach 15 min after the phenol red administration

Small intestinal transit in mice

Male ddY mice weighing about 22 g fasted for 24 hr before the experiment were used. HSR-803 (10-100 mg/kg), metoclopramide
(3–30 mg/kg), domperidone (3–30 mg/kg), cisapride (0.3–3 mg/kg) and 0.5% CMC as a control were orally administered in a volume of 0.2 ml/10 g of body weight. At 30 min after the drug administration, except in the case of domperidone (2 hr after the administration), a 5% charcoal meal (0.1 ml/10 g of body weight) was orally administered. Each mouse was sacrificed 20 min after the charcoal meal administration, and the gastrointestinal tract from the stomach to the caecum was removed. The length from the pylorus to the front of the traveling charcoal (A) and the total length of the small intestine (B) were measured. Small intestinal transit was expressed as follows:

\[ \text{Small intestinal transit (\%)} = \frac{A}{B} \times 100 \]

Atropine (0.3 mg/kg) was intraperitoneally injected just before the HSR-803 administration. Morphine (0.3 mg/kg) was subcutaneously injected just before the charcoal meal administration.

**Drugs**

HSR-803, domperidone and cisapride were synthesized by Central Research Laboratories, Hokuriku Seiyaku Co., Ltd. HSR-803 was dissolved in distilled water for the dog experiment and suspended in 0.5% CMC for the rat and mouse experiments. Domperidone and cisapride were suspended in 0.5% CMC to the required concentration. Metoclopramide monohydrochloride (Sigma, U.S.A.) was suspended in 0.5% CMC to the required concentration. Acetaminophen (Nacalai Tesque, Inc., Japan) was put into a capsule and administered orally. Dopamine hydrochloride (Nacalai Tesque, Inc.), morphine hydrochloride (Dainippon Pharmaceuticals Inc., Japan) and atropine sulfate monohydrate (Wako Chemicals, Japan) were dissolved in saline to the required concentration.

**Data analysis**

Experimental data were expressed as the mean ± S.E. of the mean. In the experiments on rats and mice, Student's t-test (non-paired) was used for the statistical analysis, and P values less than 0.05 were considered to be significantly different from the control. In the experiment on dogs, Student’s paired t-test was used.

**RESULTS**

**Gastric emptying in the dog**

As shown in Fig. 1, the plasma acetaminophen concentration in a control study was increased time dependently and peaked at 45 min (6.9 ± 1.2 µg/ml) after the acetaminophen administration. Our results were consistent with those reported by Koizumi et al. who measured gastric emptying in dogs by the acetaminophen method (14). This means that the food containing acetaminophen was gradually emptied from the stomach, and acetaminophen was absorbed in the small intestine. HSR-803 (30 mg/kg, p.o.) significantly increased the plasma acetaminophen concentration in comparison with the control at 15, 30,

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![Fig. 1. Effect of HSR-803 on the gastric emptying in beagle dogs.](image-url)
and 60 min after the acetaminophen administration, as shown in Fig. 1. The plasma acetaminophen of the dogs given HSR-803 (10, 30 mg/kg, p.o.) peaked more rapidly than that of the control dogs, and the peak values with HSR-803 were 8.8 ± 3.4 μg/ml and 12.7 ± 2.1 μg/ml, respectively. This means that HSR-803 enhanced the gastric emptying of the food in these dogs. HSR-803 at a dose of 10 mg/kg, p.o. tended to increase the plasma acetaminophen concentration, but not significantly (Fig. 1).

**Gastric emptying in the dopamine-treated rat**

As shown in Fig. 2, the gastric emptying in the control study was over 70%, suggesting that most of the stomach contents were emptied within 15 min. Dopamine (0.4 mg/kg, i.p.) significantly inhibited the gastric emptying (Fig. 2). HSR-803 (30 mg/kg, p.o.) significantly improved the dopamine-induced delay in gastric emptying, and metoclopramide (30 mg/kg, p.o.) restored it significantly (Fig. 2). Domperidone tended to restore the gastric emptying inhibited by dopamine in a dose-dependent manner, but not significantly (Fig. 2). Figure 2 also shows that cisapride (1 mg/kg, p.o.) significantly reduced the dopamine-induced inhibition, but the dose-response relationship seems to be bell-shaped. Our results with cisapride were consistent with a previous report (15). Therefore the optimal dose of cisapride needed to stimulate gastric emptying was 1 mg/kg, p.o., and the dose of 3 mg/kg, p.o. may be high enough to stimulate nonmigrative gastric contractions in vivo.

**Gastric emptying in the morphine-treated rat**

Figure 3 shows morphine (1 mg/kg, s.c.) inhibition of gastric emptying and the effects of HSR-803, metoclopramide and domperidone on the inhibition. Gastric emptying was significantly decreased by morphine, and HSR-803 (10–100 mg/kg, p.o.) improved the gastric

![Gastric Emptying in the dopamine-treated rat](image)

**Fig. 2.** Effects of HSR-803, metoclopramide, domperidone and cisapride on gastric emptying delayed by dopamine in rats. Each drug and 0.5% CMC as a control were orally administered. At 30 min after the drug administration, except domperidone (120 min), dopamine (0.4 mg/kg) was intraperitoneally injected, and then 0.05% phenol red was orally administered immediately after the injection. Gastric emptying was measured at 15 min after the phenol red administration. Each column and vertical bar represents the mean ± S.E. of the mean for 10–16 rats. Open columns show the gastric emptying in the rats without dopamine. Shaded columns show the gastric emptying in the dopamine-treated rats. **P < 0.05 vs. dopamine control, ***P < 0.01 vs. dopamine control. □: control, □□□□: dopamine control, □□□□: dopamine + drug.
emptying inhibited by morphine in a dose-dependent manner (Fig. 3). The effects of HSR-803 at doses of 30 and 100 mg/kg, p.o. were significant. In contrast to the dopamine-treated rat, metoclopramide significantly enhanced the inhibition of gastric emptying in the morphine-treated rat (Fig. 3). Domperidone had no effect on the gastric emptying inhibited by morphine.

Small intestinal transit in the normal mouse

Small intestinal transit was about 50% in the control study, showing that the front of a charcoal meal had reached the middle of the small intestine in 20 min. HSR-803 (10–100 mg/kg, p.o.) increased small intestinal transit in a dose-dependent manner, as clearly shown in Figs. 4 and 5. A significant effect of HSR-803 was observed at a lower dose (10 mg/kg, p.o.) than in the experiments on gastric emptying. Figure 4 also shows that small intestinal transit was significantly increased by metoclopramide (3–30 mg/kg, p.o.). However, domperidone and cisapride had no effect on small intestinal transit. The increase induced by HSR-803 was completely abolished...
by atropine (0.3 mg/kg, i.p.) (Fig. 5).

Small intestinal transit in the morphine-treated mouse

Subcutaneous injection of morphine is known to inhibit small intestinal transit in mice and is competitively antagonized by naloxone (16, 17). In the present study, small intestinal transit was significantly inhibited by morphine (0.3 mg/kg, s.c.), consistent with previous data (16, 17). HSR-803 (10-100 mg/kg, p.o.) improved the morphine-induced delay in a dose-dependent manner and the effect of HSR-803 at doses of 30 and 100 mg/kg, p.o. was significant (Fig. 6). Metoclopramide at 3 mg/kg, p.o. significantly restored the small intestinal transit inhibited by morphine, but at higher doses, metoclopramide (10 and 30 mg/kg, p.o.) had no effect like domperidone (Fig. 6).

DISCUSSION

HSR-803 is a newly synthesized gastroprokinetic agent, which has been reported to stimulate gastrointestinal motility in conscious dogs (1). In the present study, we assayed the influence of HSR-803 on gastrointestinal propulsion to evaluate its effect on non-ulcer dyspepsia. Because non-ulcer dyspepsia is mainly due to delayed gastric emptying, we have measured the gastric emptying in dogs and rats as appropriate experimental models. In addition, we also estimated its effect on small intestinal transit, because this model is widely used in studying the effect of drugs on gastrointestinal functions.

In the present study, we measured the dog gastric emptying by the acetaminophen method. Acetaminophen is one of the markers widely used in measuring gastric emptying, because it is safe and is not absorbed from the stomach. It has been reported that almost all the acetaminophen infused into the small intestine was absorbed and the absorbance be-
gan within several minutes (18). Accordingly, it is thought that the plasma acetaminophen concentration correlates with the amount of acetaminophen emptied from the stomach. In our dog experiment, the plasma concentration of the capsuled acetaminophen peaked 3 times more slowly than that of the acetaminophen solution, and the peak plasma concentration of the former was one third that of the latter (6.9 ± 1.2 and 20.0 ± 5.4 μg/ml, respectively). The gastric emptying of a meal is strongly influenced by the type of meal; a solid meal is emptied slowly from the stomach, but a liquid meal is quickly emptied (19). Thus these data showed that the present gastric emptying reflected solid or semisolid meal emptying.

Under this condition, we demonstrated that the plasma acetaminophen concentration of the dogs given HSR-803 was significantly higher than that of the control animals, suggesting that HSR-803 increased gastric emptying probably by gastric motility stimulation. However, for a more exact estimation, it would be necessary to determine whether HSR-803 influences the process of acetaminophen absorption in the intestinal mucosa or not.

In the second series of experiments, the gastric emptying of phenol red was very fast, because the phenol red was dissolved in 1.5% CMC solution just as the liquid meal was. We therefore used this experiment to estimate the improving effect of drugs on delayed gastric emptying. Dopamine and dopamine receptor agonist are known to inhibit gastric contractions (20–22) and to delay gastric emptying (9, 23, 24), and dopamine is likely to be one of the inhibitory neurotransmitters (20, 25). In the in vitro study, dopamine acted at a dopamine receptor on the postganglionic cholinergic neuron in the stomach to inhibit the ACh release from the neuron (26). Because HSR-803, domperidone and metoclopramide stimulate the gastric contraction depressed by dopamine in conscious dogs (1, 27), all 3 drugs were expected to restore gastric emptying delayed by dopamine. However, only HSR-803 and metoclopramide significantly counteracted the delay caused by dopamine, but the more potent D2 antagonist domperidone did not. The reason why only HSR-803 and metoclopramide counteracted the delay under this condition is not clear, but there are the following possibilities: 1) Gastric emptying is known to be depressed by atropine, suggesting that ACh is the main mediator. HSR-803 has an anti-AChE action 10 times more potent than that of domperidone (1), and metoclopramide was recently reported to increase ACh release by stimulating non-classical 5-hydroxytryptamine receptors in the myenteric plexus (28). Thus the restoration of gastric emptying by HSR-803 may be due to the ACh release by the D2 blocking action and the ACh accumulation by the anti-AChE action. In the case of metoclopramide, the restoration may be due to the ACh release by the D2 blocking and the 5-hydroxytryptamine receptor activation. 2) Domperidone is reported to inhibit electrically evoked smooth muscle contractions (29, 30). Under our conditions, the inhibitory effect on smooth muscle may cancel the stimulatory effect produced by the D2 blocking action. In any case, it is impossible to exclude that the D2 blocking action may have influenced the delay in the gastric emptying induced by dopamine, even though domperidone had no effect in our study, because there are some reports showing that dopamine antagonists reversed the dopamine agonists-induced delayed emptying (9, 23, 24).

If the stimulation by HSR-803 of gastric emptying was only due to its D2 blocking action, it was expected that HSR-803 had no effect on gastric emptying delayed by agents other than dopamine. In the morphine experiment, HSR-803 significantly counteracted delayed gastric emptying, suggesting that HSR-803 exerted actions other than the D2 blocking action on gastric emptying. In this experiment, we observed that metoclopramide further depressed gastric emptying, suggesting that the actions of HSR-803 were different from those of metoclopramide.

In mice, HSR-803 increased small intestinal transit in a dose-dependent manner, and the effect of HSR-803 was abolished by atropine.
This suggests that the HSR-803-induced increase was due to the cholinergic stimulation. Previously we reported that HSR-803 enhanced gastric contractions induced by ACh in conscious dogs and had anti-AChE activity in vitro (1). These results may therefore mean that the stimulation by HSR-803 of small intestinal transit was partly due to the AChE inhibition. On the other hand, we observed that atropine did not inhibit small intestinal transit by itself. Many mediators other than ACh, such as 5-hydroxytryptamine and substance P, are known to regulate the intestinal migration as final mediators. In vitro, spontaneous contractions of intestine are not always depressed by atropine. Also, the charcoal meal used as a marker was fluid and could be propelled by a small pressure difference. It was therefore likely that these circumstances hid the effect of atropine. Stimulation of small intestinal transit was also induced by metoclopramide, but not by domperidone or cisapride. Domperidone was reported to have either no effect or only an inhibitory effect on small intestinal transit (31). In the case of cisapride, it was reported that cisapride did not affect small or large bowel transit even though it promoted gastric emptying (11).

It is known that morphine inhibits small intestinal transit through peripheral opiate receptors (32). Recently it was reported that reflex peristalsis of the ileum was endogenously controlled by opiate receptors (33). Endogenous opioids may therefore be one of the causes of gastrointestinal disorders. HSR-803 offset the delay induced by morphine as in the case of gastric emptying, suggesting that HSR-803 was useful in treating gastrointestinal disorders. But the stimulatory effect of HSR-803 does not seem to be due to an anti-morphine action, because HSR-803 affected not only the morphine-treated models but also the normal model and the other inhibitor-treated model. It is also unlikely that the effect was only due to its D2 blocking action.

In conclusion, HSR-803 enhanced gastrointestinal propulsion in both the normal model and delayed model, suggesting that HSR-803 is a promising gastroprokinetic agent for treating non-ulcer dyspepsia. The action of HSR-803 was likely to be exerted through cholinergic stimulation induced by its anti-AChE action and D2 blocking action.

Acknowledgments
We are grateful to Mr. T. Aratani and Mrs. E. Kasakawa, researchers at the Central Research Laboratories, Hokuriku Seiyaku Co., Ltd. for their technical assistance.

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