Gastroprokinetic Effect of a New Benzamide Derivative Itopride and Its Action Mechanisms in Conscious Dogs

Yuji Iwanaga¹, Naoshi Miyashita¹, Takaharu Saito¹, Koji Morikawa¹ and Zen Itoh²

¹Research and Development Division, Hokuriku Seiyaku, Co., Ltd., Inokuchi 37-1-1, Katsuyama, Fukui 911, Japan
²GI Laboratories, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi 371, Japan

Received November 15, 1995   Accepted March 12, 1996

ABSTRACT—The novel benzamide derivative itopride was assayed for its effect on gastrointestinal motility in conscious dogs when it was administered intraduodenally (i.d.). Gastrointestinal motility was measured by means of chronically implanted force transducers, and itopride at a dose of 10 mg/kg, i.d. or more increased the gastric contractile force during the digestive state. Intraduodenal cisapride, domperidone and metoclopramide also stimulated gastric motility, and their threshold doses were 1, 3 and 1 mg/kg, respectively. Dopamine infusion (1 mg/kg/hr, i.v.) caused the postprandial gastric motility to disappear, but it was immediately restored by itopride at a dose of 3 mg/kg, i.d. With itopride at 1 and 3 mg/kg, i.d., acetylcholine (0.05 mg/kg/min)-induced contractions were greatly enhanced. In addition to its gastric stimulation, itopride at doses of 10–100 mg/kg, p.o. inhibited apomorphine (0.1 mg/kg, s.c.)-induced vomiting in dogs. In conclusion, intraduodenal itopride stimulates gastric motility through both anti-dopaminergic and anti-acetylcholinesterase actions. Its gastroprokinetic threshold dose was as large as 3–10 times those of cisapride, domperidone and metoclopramide. These findings suggest that itopride is an orally active gastroprokinetic with a moderate anti-emetic action.

Keywords: Conscious dog, Gastroprokinetic, Itopride, Gastric motility, Anti-emetic action

Itopride (N-[p-[2-(dimethylamino)ethoxy]benzyl]verapamil hydrochloride) is a novel gastroprokinetic for improving symptoms of discomfort in the epigastrium, such as fullness in the abdomen, nausea, emesis and anorexia due to delayed gastric emptying in non-ulcer dyspepsia. Itopride stimulated gastric motility in conscious dogs in a dose-dependent manner when it was administered intravenously (1). We have also demonstrated that intravenous administration of itopride antagonized the inhibitory effect of dopamine on gastric motility and enhanced the motor stimulating activity of acetylcholine (ACH) in a dose-dependent manner (1). In in vitro experiments, itopride was found to have an affinity to dopamine D₂-receptor (2) and to inhibit acetylcholinesterase (AChE) (1, 3). Thus it is likely that intravenously administered itopride exerted gastric stimulation through its dopamine D₂-antagonist action and anti-AChE action (1).

Itopride, when it was administered orally, stimulated gastric emptying in dogs (4) and recovered delayed gastric emptying in non-ulcer dyspepsia (5), but there was no information on the effect of itopride, which was administered orally or intraduodenally to conscious dogs, on the gastric smooth muscle contractions. Metoclopramide, domperidone and cisapride are widely used as oral gastrointestinal prokinetics, but so far as we know, there are few useful reports on their effects on gastrointestinal motility in conscious dogs, when these drugs were administered intraduodenally. In order to investigate the potency of itopride in comparison with these drugs, it is necessary to study their effects under the same experimental conditions.

The aims of this study are to estimate the motor stimulating effect of itopride administered intraduodenally in comparison with metoclopramide, domperidone and cisapride and to confirm its action mechanisms observed in our previous intravenous study (1). In addition, as apomorphine-induced vomiting is induced through dopamine D₂-receptor activation (6), the effect of itopride on apomorphine-induced vomiting was also investigated.

MATERIALS AND METHODS

Experiments on gastrointestinal motility

Preparation of animals: Fifteen adult dogs of either sex
weighing 7.7 to 14 kg were used to study the effects on gastric motor activity. Four adult male dogs weighing 10 to 10.5 kg and 3 adult dogs of either sex weighing 10 to 14 kg were used to investigate the anti-dopaminergic and anti-AChE action of itopride, respectively. Under general anesthesia (pentobarbital Na, 30 mg/kg, i.v.), a force transducer (7) was chronically implanted onto the serosa in the gastric antrum in a direction to measure circular muscle contraction. In order to study the organ specificity of the contractile response to itopride on gastrointestinal motility, 8 force transducers were chronically implanted in 3 of the dogs. The 8 sites of transducer implantation were the gastric body, gastric antrum, duodenum, jejunum, mid-intestine, ileum, ascending colon and descending colon. A silicone tube (Silastic, 602-205; Dow Corning, Midland, MI, USA) was inserted into the duodenum to use as a route for duodenal administration of test materials. The lead wires of the force transducers and the silicone tube were taken out from a skin incision between the scapulae and sutured onto the adjacent skin with silk thread. After the abdominal surgery, a 5-cm longitudinal skin incision was made in the right frontal neck to expose the right external jugular vein to insert a silicone tube (Silastic, 602-205) so that the tip was placed in the superior vena cava. This tube was used as a route for intravenous administration of dopamine or ACh. After the surgery, the dogs were fitted with a jacket to protect the lead wires and the tubes from the dog’s scratching. They were fed once a day and water was given freely. The beagle dogs used in this study were obtained from OBC (Shizuoka) and Nakajima Experimental Animals (Aichi).

Recording and measurement of contractile activity: The dogs were housed in individual experimental cages and cable leads from the amplifiers (UG-6, UG-15 and SS-1689 from Nihon Kohden, Tokyo or FS08M from Star Medical, Tokyo) were hung from the ceiling above the cage with an elastic cord and connected to the lead wires of the implanted force transducers with a small connector under the jacket. For visual inspection of the general contractile pattern, contractile activity in the gastrointestinal tract was continuously recorded on a pen-writing multi-channel recorder (WI-681GE and ME-95D from Nihon Kohden or WR3701 from Graphtec, Tokyo) so that the maximum contractions in phase III activity of each transducer were recorded on the full scale for pen deflection. At the same time, signals from the gastric antrum were input into a computer to measure motor indices, which denote the area under the contraction waves. The motor-stimulating activity was calculated by comparing the motor indices for the control with the drug-treatment data.

Experimental procedures
Effects of itopride, cisapride, domperidone and metoclopramide on gastric motility in conscious dogs: Test material or saline was given intraduodenally via the silicone tube inserted into the duodenum in the postprandial state. Motor index measurement was begun 20 min before drug administration and continued for at least 80 min. Motor indices were calculated every 20 min and were compared with the pre-drug 20-min control value as 100%.

Effect of itopride on dopamine-induced inhibition in gastric motility in conscious dogs: Anti-dopaminergic activity was studied by introducing itopride into the duodenum after gastric motor activity was suppressed by continuous intravenous infusion of dopamine at a dose of 1 mg/kg/hr. Itopride was given 20 min after the dopamine infusion was started. Motor indices were calculated every 20 min and were compared with the pre-dopamine 20 min as 100%. In a preliminary experiment, dopamine infusion (0.25-2 mg/kg/hr) inhibited gastric motility in conscious dogs in a dose-dependent manner; and at higher doses of dopamine (1 and 2 mg/kg/hr), gastric motility was mostly abolished. When gastric motility was almost completely abolished by dopamine (1 mg/kg/hr), neostigmine (10 μg/kg, i.v.) failed to restore it (data not shown), even though the dose was enough to enhance ACh-induced gastric contractions (1).

Effects of itopride and neostigmine on ACh-induced gastric contractions: For this study, ACh was used as a gastrointestinal motility stimulant that was hydrolyzed by AChE and infused intravenously for 5 min at a dose of 0.05 mg/kg/min. Test materials or saline were administered intraduodenally 15 min before ACh infusion. Motor indices were calculated during ACh infusion and were compared with the value under the background administration of saline as 100%.

Anti-emetic activity of gastropokinetics
Experimental procedure: Thirteen adult dogs of either sex weighing 8.5-11.5 kg were used to study anti-emetic effects of itopride, metoclopramide and domperidone (first group), and 10 adult dogs of either sex weighing 10-12 kg were used in the study of itopride, cisapride and domperidone (second group). After overnight fasting, test materials were orally administered to the dogs 45 min before feeding. Fifteen minutes after feeding, apomorphine (0.1 mg/kg, s.c.) was applied and then observation for vomiting was continued for 30 min. In the first group, itopride and metoclopramide dissolved in water and domperidone suspended in 0.5% carboxymethylcellulose were administered via a gastric probe at a volume of 1 ml/kg. In the second group, gelatin capsules (Torpac size: #12; Torpac, Fairfield, NJ, USA) filled
Fig. 1. Effect of itopride on gastrointestinal contractile activity during the digestive state in a conscious dog. Itopride at a dose of 10 mg/kg was administered intraduodenally through a Silastic tube implanted in the duodenum. As the bottom figure shows, itopride significantly increased the amplitude of contractions in the gastric antrum about 5 min after the intraduodenal administration. The portion in the upper figure enclosed by the rectangle is the same as that shown in the lower figure and the other portions show the immediate previous and subsequent changes recorded for 4 hr.
with test materials or empty capsules were administered orally. The time needed for apomorphine to induce vomiting (onset) and the number of vomitings were recorded. The beagle dogs used in this study were obtained from Nihon Nosan Kogyo (Hyogo), Laboratory Research Enterprises (Kalamazoo, MI, USA) and OBC.

Analyses of data
The experiments on the motor stimulating activity alone and the anti-AChE activity were conducted three times in each of the 3–5 dogs, and the results are expressed as the mean ± S.E. Dopamine infusion sometimes induced emesis in dogs, resulting in the disturbance of gastric motility. The experiment on the anti-dopaminergic activity was therefore performed once in each dog. Student’s t-test was used for statistical analysis, and P values less than 0.05 were considered to be significantly different.

Drugs
Itopride, cisapride and domperidone were synthesized at the laboratory of Hokuriku Seiyaku Co., Ltd. Metoclopramide and apomorphine hydrochloride were purchased from Sigma Chemical Co., St. Louis, MO, USA. Dopamine hydrochloride (Nacalai Tesque, Kyoto), acetylcholine chloride (Ovisot; Daiichi Pharmaceutical Co., Ltd., Tokyo) and neostigmine methylsulfate (Vagostigmin; Shionogi Pharmaceutical Co., Ltd., Osaka) were purchased. In the experiments on gastric motility, itopride and metoclopramide were dissolved in saline to the required concentration. Cisapride and domperidone were dissolved in 5% lactic acid. The solution was adjusted to pH 5 and diluted with distilled water to the required concentration.

RESULTS
Effects of itopride, cisapride, domperidone and metoclopramide on gastric motility in conscious dogs
Itopride at a dose of 3 mg/kg, i.d. did not affect gastrointestinal motility. With itopride at 10 mg/kg, i.d., as shown in Fig. 1, the contractile force of the gastric antrum was increased immediately. A simultaneous increase in the contractile force of the duodenum was also observed, but it was transient (Fig. 1). Contractions in the jejunum through the colon were not affected by itopride, with the result that intraduodenal itopride selectively stimulated gastric motility as intravenous itopride did (1) (Fig. 1). Table 1 summarizes the effects of itopride, cisapride, domperidone and metoclopramide on gastric motility in conscious dogs, when they were given intraduodenally during the digestive state. Saline as a control and itopride at a dose of 3 mg/kg, i.d. produced no significant change in gastric motor activity. Itopride at a dose of 10 mg/kg, i.d. produced a significant increase in gastric motor activity in the period 0–20 min after itopride administration. The increase in the motor index was observed in the 20–40 min period, but it was not significant. When the dose of itopride was increased to 30 mg/kg, i.d., the gastric motor activity was about doubled, and the enhancement by itopride was continued for 60 min. Figure 2 shows the dose-response relationship for itopride, and itopride at doses of 3–30 mg/kg, i.d. stimulated gastric motility in a dose-dependent manner.

Cisapride at a dose of 0.3 mg/kg, i.d. did not affect gastric motility (Table 1). With cisapride at 1 and 3 mg/kg, i.d., no significant enhancement in gastric motility was observed in the early period (0–20 min), but in the late period (20–60 min), cisapride produced significant enhancement (Table 1). The maximal response was observed in the 20–40 min period; and during this period cisapride, stimulated gastric motility in a dose-dependent manner (Fig. 2). The lowest dose of domperidone did not affect gastric motility (Table 1). With domperidone at 3 mg/kg, i.d., the enhancement in gastric motility appeared in the 20–40 min period and disappeared thereafter (Table 1). Domperidone at a dose of 10 mg/kg, i.d. produced significant suppression in gastric motility in the early period (0–20 min) and then enhanced gastric motility (Table 1). As shown in Fig. 2, domperidone also stimulated gastric motility dose-dependently. Metoclopramide at doses of 1–10 mg/kg, i.d. enhanced gastric motility immediately (Table 1). Both the duration of the enhancement and the increase in gastric motility were affected by metoclopramide in a dose-dependent manner (Table 1, Fig. 2). The gastric stimulation of itopride and metoclopramide appeared immediately, but the appearance of the effects of cisapride and domperidone was late (Table 1). With respect to the threshold dose of the 4 drugs, the order of potency was as follows: cisapride = metoclopramide (1 mg/kg, i.d.) > domperidone (3 mg/kg, i.d.) > itopride (10 mg/kg, i.d.) (Table 1, Fig. 2).

Effect of itopride on dopamine-induced inhibition in gastric motility in conscious dogs
Figure 3 shows typical tracings of the effect of itopride (3 mg/kg, i.d.) on dopamine-induced inhibition of contractions in the gastric antrum in a conscious dog. Dopamine infusion at a dose of 1 mg/kg/hr immediately suppressed the postprandial gastric contractions. This suppression continued for 40–50 min, but thereafter gastric contractions sometimes recovered partly in the control experiments. As seen in the lower recording, itopride immediately recovered the gastric contractions inhibited by dopamine. Itopride antagonized the dopamine-induced
Table 1. The effects of itopride, cisapride, domperidone and metoclopramide on gastric motility during the digestive state in conscious dogs

| Dose (mg/kg, i.d.) | % of control motor index |
|-------------------|-------------------------|
|                   | 20–0 | 0–20  | 20–40 | 40–60 (min) |
| Itopride 0        | 100  | 102.2±19.3 | 121.0±26.6 | 116.5±22.5 |
| 3                 | 100  | 121.3±13.5 | 107.3±11.4 | 94.7±12.8  |
| 10                | 100  | 178.0±16.7**| 166.9±13.8 | 123.7±13.1 |
| 30                | 100  | 223.5±38.9* | 262.3±31.3**| 218.4±45.1 |
| Cisapride 0       | 100  | 110.6±7.3  | 107.8±9.2  | 106.6±8.9  |
| 0.3               | 100  | 110.0±7.3  | 132.1±10.0 | 114.6±8.4  |
| 1                 | 100  | 116.8±8.6  | 144.1±6.7**| 139.8±7.7**|
| 3                 | 100  | 130.7±10.2 | 167.3±14.4**| 148.1±11.6**|
| Domperidone 0     | 100  | 101.1±5.9  | 102.0±4.8  | 98.2±6.0   |
| 1                 | 100  | 101.0±5.4  | 100.1±7.4  | 101.9±6.1  |
| 3                 | 100  | 108.4±6.3  | 142.7±10.4*| 118.3±10.9 |
| 10                | 100  | 68.0±11.7**| 163.9±13.9*| 173.3±11.7*|
| Metoclopramide 0  | 100  | 104.8±7.8  | 107.1±9.9  | 103.8±12.6 |
| 0.3               | 100  | 116.8±6.9  | 119.7±5.5  | 112.5±6.9  |
| 1                 | 100  | 128.6±7.8* | 137.4±11.7 | 112.1±8.3  |
| 3                 | 100  | 191.2±19.5*| 177.1±17.0**| 137.3±11.8 |
| 10                | 100  | 258.8±25.3*| 271.4±32.9*| 217.5±25.8*|

Each value is the mean±S.E. for 3 trials in each of 3–5 dogs. *P<0.05, **P<0.01 vs 0 mg/kg (saline).

Fig. 2. Effects of itopride, cisapride, domperidone and metoclopramide on gastric motility in conscious dogs during the digestive state. All drugs were administered intraduodenally. Increases in the motor index are expressed as a percentage of the pre-drug administration motor index. Each column and vertical bar represent the mean±S.E. obtained from 3 observations in each of 3–5 dogs. *P<0.05, **P<0.01 vs 0 mg/kg (saline).
inhibition in gastric motility in a dose-dependent manner (Fig. 4). The recovery produced by 3 mg/kg itopride was significant, and that by 10 mg/kg was complete (Fig. 4).

---

**Fig. 3.** Anti-dopaminergic effect of itopride on gastric contractions in a conscious dog. In the upper recording, the inhibitory effect of dopamine is shown. Dopamine infusion (1 mg/kg/hr) induced immediate inhibition in the gastric antrum. The lower recording shows the significant recovery of gastric contractions after itopride (3 mg/kg) was administered intraduodenally. Contractile response to itopride is seen to be almost equal to the amplitude before dopamine infusion.

---

**Fig. 4.** Dose-related recovery of dopamine-inhibited contractions in the gastric antrum during the digestive state. Infusion of dopamine (1 mg/kg/hr) inhibited the postprandial gastric contractions significantly. Itopride antagonized the dopamine-induced inhibition in a dose-dependent manner. Each column and vertical bar represent the mean ± S.E. obtained in 4 dogs. □: control (−Dopamine), □: +Dopamine, ■: Dopamine + Itopride. *P<0.01 vs control (−Dopamine); *P<0.05, **P<0.01 vs +Dopamine.
Effects of itopride and neostigmine on ACh-induced gastric contractions

First, a control experiment with saline was performed, in which ACh was infused intravenously for 5 min to induce gastric contractions. After this control experiment was finished, ACh was infused in a similar way with a background administration of itopride at doses of 1 and 3 mg/kg, i.d. A similar experiment was carried out with neostigmine instead of itopride. Figure 5 shows the results of quantitative analysis of itopride and neostigmine effects obtained in the gastric antrum. Itopride at a dose of 1 mg/kg, i.d. significantly increased the motor index of ACh, and the enhancement due to itopride was almost equal to that due to neostigmine (0.3 mg/kg, i.d.). When the dose of itopride was increased to 3 mg/kg, i.d., the enhancement caused by itopride was further increased (Fig. 5).

Anti-emetic activity of gastroprokinetics

In Table 2, the anti-emetic effects of itopride, domperidone and metoclopramide are summarized. Apomorphine (0.1 mg/kg, s.c.) induced vomiting in all control dogs, and the first episodes of emesis induced by apomorphine appeared 4.1 ± 0.7 min after the apomorphine injection. The mean number of vomitings was 7.7 ± 0.8 in the control dogs. Itopride (10 mg/kg, p.o.) appreciably elongated the onset time to 5.2 ± 1.0 min and decreased the number of vomitings by half (Table 2). When itopride was increased to 100 mg/kg, p.o., apomorphine did not induce vomiting at all. Both dopamine D₂-antagonists, domperidone and metoclopramide, significantly inhibited apomorphine-induced emesis at a dose of 0.03 mg/kg, p.o. and 0.3 mg/kg, p.o., respectively (Table 2). Table 3 shows the anti-emetic effects of itopride, cisapride and domperidone. The effect of itopride, which was capsuled and given orally, was almost equal to that in Table 2. Itopride (10 mg/kg, p.o.) elongated the onset time and decreased the number of vomitings (Table 3). With itopride at 30 mg/kg, p.o., apomorphine-induced emesis was considerably weakened and itopride at a dose of 100 mg/kg, p.o. abolished episodes of emesis completely (Table 3). In contrast to itopride, up to 10 mg/kg, p.o., cisapride did not inhibit apomorphine-induced emesis (Table 3). Domperidone is hardly as soluble in water as cisapride, but capsuled domperidone (0.1 mg/kg) had an anti-emetic effect equal to that in Table 2 (Table 3).

DISCUSSION

Itopride is a newly synthesized benzamide derivative for clinical use as an oral gastroprokinetic agent. In particular, itopride is expected to promote gastric emptying by stimulating gastric motility in a patient with non-ulcer dyspepsia who has gastric discomfort due to delayed gastric emptying. We therefore estimated the effect of itopride administered intraduodenally on the postprandial gastric motility in conscious dogs and compared its motor stimulating activity with those of other gastroprokinetics.

Itopride given intraduodenally stimulated the postprandial rhythmic contractions in the gastric antrum in a dose-dependent manner. The enhancement in gastric motility appeared immediately after itopride administration; itopride at a dose of 10 mg/kg, i.d. increased the gastric motor index to about double, and the effect was almost equal to that of itopride at a dose of 3 mg/kg, i.v. (1), suggesting that itopride was rapidly absorbed from the intestine. As itopride is extremely soluble in water, it was expected to dissolve rapidly in the stomach and to be immediately absorbed, resulting in immediate pharmacological effects. Itopride at doses of 10 and 30 mg/kg, i.d. stimulated gastric motility, which was coincident with that of itopride at a dose of 3 mg/kg, i.v. (1), suggesting that itopride was rapidly absorbed from the intestine. As itopride is extremely soluble in water, it was expected to dissolve rapidly in the stomach and to be immediately absorbed, resulting in immediate pharmacological effects. Itopride at doses of 10 and 30 mg/kg, i.d. stimulated gastric motility, which was coincident with that of itopride at a dose of 3 mg/kg, i.v. (1), suggesting that itopride was rapidly absorbed from the intestine. As itopride is extremely soluble in water, it was expected to dissolve rapidly in the stomach and to be immediately absorbed, resulting in immediate pharmacological effects.

![Fig. 5. Effect of itopride on ACh (0.05 mg/kg/min)-induced gastric contractions in conscious dogs during the digestive state in comparison with that of neostigmine. Neostigmine at a dose of 0.3 mg/kg, i.d. significantly enhanced ACh-induced contractions in the digestive state. Itopride significantly enhanced ACh-induced contractions at 1.0 and 3.0 mg/kg, i.d. The effect of itopride (1 mg/kg) was almost equal to that of neostigmine (0.3 mg/kg). ■: Control, □: Itopride, △: Neostigmine. *P<0.05, **P<0.01 vs saline control.](image-url)
Itopride is considered to exert gastric stimulation through its dopamine D2 antagonist action and anti-AChE action, which is supported by the effect of intravenous itopride (1) and the in vitro experiments (1-3). It is known that dopamine strongly inhibits gastric contractile activity (9-11). In addition dopamine is known to inhibit ACh release from postganglionic neurons by dopamine D2-receptor activation in the stomach (12, 13). Dopamine D2-receptor antagonists, domperidone and metoclopramide, given intravenously have been reported to restore the gastric motor activity inhibited by dopamine in conscious dogs (9), and intravenous itopride also did so (1). In our present study, itopride administered intraduodenally was found to restore the gastric motility inhibited by dopamine in a dose-dependent manner. In our preliminary experiment, intravenous neostigmine failed to restore it, indicating that the anti-AChE action of itopride was not responsible for the restoration by itopride. Itopride stimulated gastric motility at a dose of 10 mg/kg, i.d. Because itopride at a dose of 3 mg/kg, i.d. or more was found to have anti-dopaminergic activity, the dose ratio of gastric stimulation to anti-dopaminergic activity in this intraduodenal experiment was coincident with that in the intravenous experiment (1). In addition, itopride at a dose of 1 mg/kg, i.d. or more enhanced the ACh-induced gastric contractions, as we expected. In the in vitro experiments, itopride showed affinity for the dopamine D2-receptor, with a pKd of 5.60 (14) and inhibited AChE activity with an IC50 of 2.04 μM (3), showing that the potencies of both actions of itopride are almost equal. It was therefore confirmed that intraduodenal itopride exerted its gastric stimulation through both an anti-dopaminergic action and an anti-AChE action as intravenous itopride did.

Dopamine D2-antagonists domperidone and metoclopramide are potent anti-emetic agents. These

---

**Table 2. The effects of itopride, domperidone and metoclopramide on apomorphine-induced vomiting in conscious dogs**

| Treatment   | Dose (mg/kg, p.o.) | Vomiting animal Test animal | Onset (min) | Number of vomitings |
|-------------|-------------------|-----------------------------|-------------|---------------------|
| Control     | 0                 | 13/13                       | 4.1±0.7     | 7.7±0.8             |
| Itopride    | 10                | 5/5                         | 5.2±1.0     | 4.4±0.7*            |
|            | 30                | 4/4                         | 8.7±4.9     | 3.3±1.3*            |
|            | 100               | 0/5                         | >30*        | 0*                  |
| Domperidone | 0.03              | 4/4                         | 3.3±0.5     | 3.3±0.9*            |
|            | 0.1               | 2/4                         | 20.8±5.3*   | 0.8±0.5**           |
|            | 0.3               | 2/5                         | 21.1±5.6*   | 0.6±0.4*            |
|            | 1                 | 1/4                         | 23.7±6.3    | 0.5±0.5**           |
| Metoclopramide | 0.3           | 5/5                         | 8.9±1.2**   | 2.0±0.4**           |
|            | 1                 | 1/4                         | 27.1±2.9*   | 0.3±0.3*            |
|            | 3                 | 0/4                         | >30*        | 0*                  |

Apomorphine: 0.1 mg/kg, s.c. *P<0.05, **P<0.01 vs Control (distilled water).

**Table 3. The effects of itopride, cisapride and domperidone on apomorphine-induced vomiting in conscious dogs**

| Treatment   | Dose (mg/kg, p.o.) | Vomiting animal Test animal | Onset (min) | Number of vomitings |
|-------------|-------------------|-----------------------------|-------------|---------------------|
| Control     | 0                 | 10/10                      | 3.8±0.6     | 7.3±0.9             |
| Itopride    | 10                | 10/10                      | 5.2±0.8*    | 5.4±1.0**           |
|            | 30                | 5/10                       | 19.6±3.5**  | 0.6±0.2*            |
|            | 100               | 0/10                       | >30**       | 0**                 |
| Cisapride   | 1                 | 10/10                      | 3.4±0.2     | 8.4±1.2             |
|            | 3                 | 10/10                      | 4.5±0.6     | 6.4±1.1             |
|            | 10                | 9/10                       | 7.7±2.6     | 6.5±1.8             |
| Domperidone | 0.1               | 4/10                       | 21.9±3.6**  | 1.5±0.8**           |

Apomorphine: 0.1 mg/kg, s.c. *P<0.05, **P<0.01 vs Control (empty capsules).
improving symptoms due to delayed gastric emptying. The anti-emetnic action on apomorphine-induced emesis therefore supports the theory of dopamine D2-receptor antagonist activity, and an anti-emetnic action is useful for improving symptoms of discomfort in non-ulcer dyspepsia. In the present study, itopride was found to inhibit apomorphine-induced emesis at doses that were required to stimulate gastric motility, supporting that itopride had dopamine D2-receptor antagonist action. Incidentally, domperidone was found to stimulate gastric motility at a dose that was 100 times as large as that required to inhibit emesis. In the experiments on itopride, the gastric stimulation and the inhibition of emesis were both observed at a dose of 10 mg/kg or more. It is likely that the anti-AChE action of itopride potentiated the gastric stimulation produced by the anti-dopaminergic action.

Cisapride is considered to stimulate gastric motility through 5-HT4 receptor activation (15, 16), but was reported to have relatively large affinity to dopamine D2-receptor (17). In the experiment on apomorphine-induced emesis, cisapride showed no sign of anti-emetnic action up to 10 mg/kg, p.o., which was 10 times as large a dose as that required to stimulate gastric motility. Our results coincide with those reported by Megens et al. (18). It is therefore likely that the dopamine D2-receptor antagonist action was not responsible for the gastric stimulating effect of cisapride, and at the clinical doses, cisapride may not inhibit the emesis that is caused by dopamine D2-receptor activation.

In conclusion, the intraduodenal administration of itopride stimulated gastric motility in a dose-dependent manner in conscious dogs, and its gastroprokinetic threshold dose was as large as 3–10 times those of cisapride, domperidone and metoclopramide. It was confirmed that the combined inhibition of dopamine D2-receptor activation and AChE activity is responsible for this gastric motor stimulation and itopride is an orally active gastroprokinetic drug with a moderate anti-emetnic action for improving symptoms due to delayed gastric emptying.

REFERENCES

1. Iwanaga Y, Miyashita N, Morikawa K, Mizumoto A, Kondo Y and Itoh Z: A novel water-soluble dopamine-2 antagonist with anticholinesterase activity in gastrointestinal motor activity: comparison with domperidone and neostigmine. Gastroenterology 99, 401–408 (1990)
2. Sakaguchi J, Nishino H, Ogawa N, Iwanaga Y, Yasuda S, Kato H and Ito Y: Synthesis, gastrointestinal prokinetic activity and structure-activity relationships of novel N-[2-(dialkylamino)ethoxy]benzamide derivatives. Chem Pharm Bull (Tokyo) 40, 202–211 (1992)
3. Iwanaga Y, Kimura T, Miyashita N, Morikawa K, Nagata O, Itoh Z and Kondo Y: Characterization of acetylcholinesterase-inhibition by itopride. Jpn J Pharmacol 66, 317–322 (1994)
4. Iwanaga Y, Miyashita N, Mizutani F, Morikawa K, Kato H, Ito Y and Itoh Z: Stimulatory effect of N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride (HSR-803) on normal and delayed gastrointestinal propulsion. Jpn J Pharmacol 56, 261–269 (1991)
5. Harasawa S and Miwa T: Effect of itopride hydrochloride on gastric emptying in chronic gastritis patients. Jpn Pharmacol Ther 21, 4189–4195 (1993) (in Japanese)
6. Mitchellson F: Pharmacological agents affecting emesis. Drugs 43, 295–315 (1992)
7. Itoh Z, Honda R, Takeuchi S, Aizawa I and Takayanagi R: An extraluminal force transducer for recording contractile activity of the gastrointestinal smooth muscle in conscious dogs: its construction and implantation. Gastroenterol Jpn 12, 275–283 (1977)
8. Schuurkes JAJ, Akkermans LMA and Van Nueten JM: Stimulating effects of cisapride on antroduodenal motility in the conscious dog. In Gastrointestinal Motility, Edited by Roman C, pp 95–102, MTP Press, Lancaster (1983)
9. Itoh Z, Aizawa I and Nakamura T: Effect of dopamine and its agonists on contractile activity of the lower esophageal sphincter and the stomach. Jpn J Smooth Muscle Res 16, 99–107 (1980)
10. Lanfranchi GA, Marzio L, Cortini C, Trento L and Labo G: Effect of dopamine on gastric motility in man: evidence for specific receptors. In Gastrointestinal Motility in Health and Disease, Edited by Duthie HL, pp 161–172, MTP Press, Lancaster (1978)
11. Bech K, Hovendal CP and Andersen D: Effect of dopamine on pentagastrin-stimulated gastric antral motility in dogs with gastric fistula. Scand J Gastroenterol 17, 103–107 (1982)
12. Kusunoki M, Taniyama K and Tanaka C: Dopamine regulation of [3H]acetylcholine release from guinea pig stomach. J Pharmacol Exp Ther 234, 713–719 (1985)
13. Takahashi T, Kurosawa S, Wiley JW and Owyang C: Mechanism for the gastrointestinal action of domperidone; in vitro studies in guinea pigs. Gastroenterology 101, 703–710 (1991)
14. Miyashita N, Iwanaga Y, Kato K, Morikawa K, Kato H, Ito Y and Itoh Z: Pharmacological studies of HSR-803, a novel gastrointestinal prokinetic agent. Jpn J Pharmacol 52, Supp I, 274P (1990)
15. Craig DA and Clarke DE: Pharmacological characterization of a neuronal receptor for 5-hydroxytryptamine in guinea pig ileum with properties similar to the 5-hydroxytryptamine4 receptor. J Pharmacol Exp Ther 252, 1378–1386 (1990)
16. Elsworth CJB, Bunce KT and Humphrey PPA: Identification of putative 5-HT3 receptor in guinea pig ascending colon. Eur J Pharmacol 196, 149–153 (1991)
17. Schuurkes JAJ, Megens AAHP, Niemegeers CJE, Leyersen JE and Van Nueten JM: A comparative study of the cholinergic vs the anti-dopaminergic properties of benzamides with gastrointestinal prokinetic activity. In Cellular Physiology and Clinical Studies of Gastrointestinal Smooth Muscle, Edited by Szurszewski JH, pp 231–247, Elsevier Science Publishers, Amsterdam (1987)
18. Megens AAHP, Awtouters FHL and Niemegeers CJE: General pharmacology of the four gastrointestinal motility stimulants bethanechol, metoclopramide, trimetobutine, and cisapride. Arzneimittelforschung 41, 631–634 (1991)