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KDR-5169, a new gastrointestinal prokinetic agent, enhances gastric contractile and emptying activities in dogs and rats

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Abstract

KDR-5169, 4-amino-5-chloro-*N*-[1-(3-fluoro-4-methoxybenzyl)piperidin-4-yl]-2-(2-hydroxyethoxy)benzamide hydrochloride dihydrate, is a new prokinetic with a dual action, i.e., stimulation of the 5-HT_4 receptor and antagonism of the dopamine D2 receptor. In this study, we determined in vitro activities of KDR-5169 towards both receptors and demonstrated the effect of the compound on gastrointestinal motor activity in conscious dogs and rats. In dogs, intravenous KDR-5169 stimulated upper gastrointestinal motility in the fasting state and also eliminated the depressive effect of 3,4-dihydroxyphenylalanine (L-DOPA) on this motility in the postprandial state. The effect of KDR-5169 on gastric emptying was further characterized by the use of three rat gastroparesis models (dopamine D2 receptor agonist (quinpirol)-, abdominal surgery-, or combined-situation-induced). Domperidone (a dopamine D2 receptor antagonist) was effective in the quinpirol-delay and combination-delay models, and cisapride and mosapride (5-HT_4 receptor agonists) were effective in the surgery-delay model. Only KDR-5169 eliminated the delay of gastric emptying in all three models. In addition, KDR-5169 accelerated emptying to above the normal level in the combination-delay model. These results suggest that KDR-5169 would be effective in various types of gastric ileus caused by different mechanisms.

Keywords: Gastric emptying; KDR-5169; 5-HT_4 receptor; Dopamine D2 receptor

1. Introduction

Gastrointestinal motility is basically under autonomic neuronal control via parasympathetic and sympathetic nerves, while the neural regulation mainly involves the cholinergic system in the gastric myenteric plexus. Stimulation of the peripheral dopamine D2 receptors located on the postganglionic cholinergic nerves decreases acetylcholine release from parasympathetic nerves (Kusunoki et al., 1985; Schuurkes et al., 1986) and results in a decrease in upper-gut motility (Nagahata et al., 1992; Dhasmana et al., 1993; Velasco and Luchsinger, 1998). On the other hand, activation of the 5-HT_4 receptors at the pre- and post-ganglionic levels stimulates acetylcholine release in the gut (Briejer et al., 1995; Matsuyama et al., 1996) and accelerates its motor activity (Taniyama et al., 1991; Matsuyama et al., 1996).

Several gastrointestinal prokinetics are used clinically to modify gastrointestinal dopamine D2 receptor and/or 5-HT_4 receptor functions (Orihata and Sarna, 1994; Ladabaum and Hasler, 1999). For example, domperidone, a dopamine D2 receptor antagonist, has significant beneficial effects on the symptoms of dyspepsia, especially on nausea and emesis (Prakash and Wagstaff, 1998; Barone, 1999). One of the most widely used prokinetics is cisapride, which facilitates cholinergic transmission in the myenteric plexus and promotes gastrointestinal motility (Schuurkes et al., 1985; Dumuis et al., 1989; Taniyama et al., 1991). It acts mainly through activation of the 5-HT_4 receptor, although it has some affinity for dopamine D2, 5-HT_2, 5-HT_3 receptors and α-adrenoceptors (Holtmann and Talley, 1993; Briejer et al., 1995). Mosapride, a recently developed prokinetic stimulates acetylcholine release from the myenteric plexus via the 5-HT_4 receptor and has no real affinity for dopamine D2, 5-HT_1, 5-HT_2 receptors or α_1-adrenoceptor (Yoshida et al., 1993).

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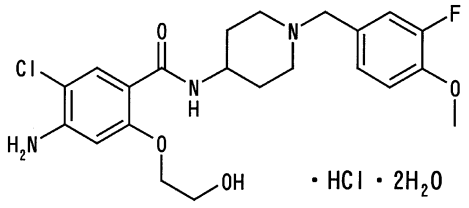

Fig. 1. Chemical structure of KDR-5169.

KDR-5169, 4-amino-5-chloro-*N*-[1-(3-fluoro-4-methoxybenzyl)piperidin-4-yl]-2-(2-hydroxyethoxy)benzamide hydrochloride dihydrate (Fig. 1), is a new benzamide-derived prokinetic with a dual action: it acts as an antagonist at the dopamine D2 receptor and as an agonist at the 5-HT_4 receptor. We now describe the profile of KDR-5169 in terms of its effects on gastrointestinal motility in dogs and rats, while comparing it with the other prokinetics mentioned above. We also discuss the involvement of dopamine D2 and 5-HT_4 receptors in various models of delayed gastric emptying.

2. Materials and methods

2.1. Animals

Male beagle dogs, weighing 9 to 12 kg, were purchased from Nihon Nosan Kogyo (Japan). Male Sprague–Dawley rats, weighing 270–330 g, and Hartley guinea pigs, weighing 300–400 g, were obtained from SLC Japan (Japan). The experiments in this study were conducted in accordance with the recommendations of the Kissei Pharmaceutical Animal Care and Use Committee and with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society.

2.2. Dopamine D2 receptor binding assay

The binding assay was performed according to the method of Rumigny et al. (1984) with some modifications. Briefly, striatal membrane was prepared from male Sprague–Dawley rats and stored at −80 °C until use. The membrane (0.2 mg protein) was incubated with 0.1 nM [^{3}H]spiperone, 0.1 μM mianserin and one of the test compounds for 30 min at 37 °C in 1 ml of incubation buffer (50 mM Tris–HCl, pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$). Bound/free separations were achieved by filtration through glass filters (Whatman GF/B) followed by four washes with 2 ml of ice-cold stop solution (50 mM Tris–HCl pH 7.4). The radioactivity on the filter was counted in a liquid scintillation counter (Packard, USA). Specific [^{3}H]spiperone binding was defined as the difference between the values obtained for [^{3}H]spiperone binding in the presence and absence of 30 μM (±)-sulpiride. IC_{50} values were obtained from the competition data by means of GraphPad PRISM computer software (GraphPad Software, USA), with K_i values then being calculated using the following equation:

$$K_i = IC_{50}/(1 + [\text{ligand}]/K_d)$$

where [ligand] = concentration of competitor ligand and K_d = dissociation constant. The K_d value was obtained from a saturation experiment done as above with the exception of [^{3}H]spiperone concentration (seven concentrations ranging from 0.018 to 1.49 nM).

2.3. 5-HT_4 receptor agonist activity

The agonist activity towards the 5-HT_4 receptor shown by the various benzamides was evaluated using a tunica muscularis mucosae preparation from the rat oesophagus (Baxter and Clarke, 1992). Concentration–effect curves were obtained by cumulative addition of agonists after the preparation was contracted with 1 μM carbachol and relaxed with cumulative doses of 5-HT. Agonist responses were confirmed by antagonism with 1 μM GR113808, 1-methy-1*H*-indole-3-carboxylic acid 1-[(2-methanesulfonylaminoethyl)-piperidin-4-yl]methyl ester, in individual preparations. EC_{50} values were obtained with the GraphPad PRISM computer software mentioned above. The intrinsic activity of each test compound was obtained by expressing its maximum effect relative to that of 5-HT.

2.4. 5-HT_4 receptor binding assay

The binding assay was performed according to the method of Grossman et al. (1993), with some modifications. Briefly, striatal membrane was prepared from male Hartley guinea pigs and stored at −80 °C until use. The membrane (0.2 mg protein) was incubated with 0.5 nM [^{3}H]GR113808 and one of the test compounds for 60 min at room temperature in 0.5 ml of incubation buffer (50 mM Tris–HCl pH 7.4). Bound/free separations were achieved by filtration through glass filters (Whatman GF/B) followed by four washes with 2 ml of stop solution (ice-cold 50 mM Tris–HCl pH 7.4). The radioactivity on the filter was counted in a liquid scintillation counter (Packard, USA). Specific [^{3}H]GR113808 binding was defined as the difference between the values obtained for [^{3}H]GR113808 binding in the presence and absence of 10 μM cisapride. K_i values were obtained as described above. For the saturation study, eight concentrations of [^{3}H]GR113808 were used to give final concentrations of 0.031–2.0 nM.

2.5. Gastrointestinal motor activity in conscious dogs

Four beagle dogs were used in this part of the study. Strain gauge force transducers were sutured onto the seromuscular layer of the gastrointestinal tract according to the method of Itoh et al. (1977). The sites at which transducers were implanted were the gastric body, the pyloric antrum and

the pylorus. In the fasting state experiments, dogs were used after overnight fasting. In the postprandial state experiments, L-(3,4-dihydroxyphenylalanine (L-DOPA) was infused intravenously at 10 mg/kg/hr about 20 min after feeding of regular solid chow. Once decreased motor activity and two emetic episodes had been observed, the test drug was administered intravenously. Gastrointestinal motor activity was recorded and analysed by means of a computer-aided telemetry system (8 STAR; Star Medical, Japan).

2.6. Gastric emptying in normal rats

In conscious rats, gastric emptying of non-nutrient solid beads was measured by the method of Miyata et al. (1995) with minor modifications. After overnight fasting, rats were given orally 100 particles of silicone nitride beads (diameter: 1 mm) with 1 ml of 0.5% methylcellulose as a vehicle by way of a suitably prepared gastric syringe. KDR-5169, domperidone, mosapride or cisapride was administered orally 60 min before bead administration, also with a gastric syringe. Thirty minutes after bead administration, the rat was killed and the stomach was removed. Gastric emptying was assessed by subtracting the number of beads remaining in the stomach from the number administered and expressed as the percentage of beads expelled.

2.7. Dopamine D2 receptor agonist-induced gastroparesis model in rats

A dopamine D2 agonist, quinpirole hydrochloride, dissolved in physiological saline at 0.06 mg/ml, was administered intraperitoneally at 0.3 mg/kg immediately after bead administration (see above). Quinpirole administration led to a delay in gastric emptying, as previously reported (Dhasmana et al., 1993). The methods used for the measurement of gastric emptying and the oral administration of each drug were the same as those described above.

2.8. Postoperative ileus model in rats

Three hours before bead administration, a laparotomy approximately 3 cm long was made in the median abdomen under ether anaesthesia. The incision was closed immediately using metal clips and a surgical adhesive agent. Oral administration of drugs was performed as described above, 1 h before bead administration. Gastric emptying was measured as described above, however, gastric emptying was measured after 60 min instead of 30 min.

2.9. Surgery/quinpirole-induced gastroparesis model in rats

A model of ‘‘delayed gastric emptying by complex causes’’ was produced by a combination of a surgical operation and quinpirole administration. An abdominal incision was made and 3 h later quinpirole was administered intraperitoneally immediately after bead administration. Each prokinetic was administered orally 1 h before bead administration. Each procedure was carried out according to the methods outlined above. Gastric emptying was measured over 30 min as described above.

2.10. Statistical analysis

The results are expressed as means ± S.E.M. A one-way analysis of variance followed by Dunnett’s test was applied for multiple comparisons. For the comparison of two groups, Student’s *t*-test was used. The significance level for all tests was set at $P < 0.05$.

2.11. Drugs

KDR-5169, domperidone, cisapride, mosapride and GR113808 were all synthesized by Kissei Pharmaceutical (Hotaka, Japan). For the dog experiments, KDR-5169 was dissolved in distilled water, while domperidone and cisapride were solubilized in 1% lactic acid. Each was administered in a volume of 0.1 ml/kg. For the rat experiments, all agents were suspended in 0.5% methylcellulose and each was given orally in a volume of 5 ml/kg. L-DOPA was purchased from Sankyo Pharmaceutical (Tokyo, Japan). Quinpirole hydrochloride, mianserin, (±)-sulpiride, carbachol and 5-HT were all obtained from Sigma (USA). [^{3}H]Spiperone (3.44–4.07 TBq/mmol) and [^{3}H]GR113808 (2.22– 3.12 TBq/mmol) was from Amersham Pharmacia Biotech (USA).

3. Results

3.1. Dopamine D2 receptor affinity, 5-HT$_4$ receptor affinity and 5-HT$_4$ receptor agonist activity

Table 1 shows the dopamine D2 receptor affinities, the 5-HT$_4$ receptor affinities and the 5-HT$_4$ receptor agonist activities of the prokinetics used in this study. The K_d and B_{max} values obtained in the dopamine D2 receptor binding assay were 125 pM and 247 fmol/mg protein, respectively.

Table 1
Dopamine D2 receptor affinities, 5-HT$_4$ receptor affinities and agonist activities of compounds used in this study

	KDR-5169	Domperidone	Cisapride	Mosapride
Dopamine D2 receptor affinity (K_i, nM)	6.2	0.11	70	>10000
5-HT$_4$ receptor affinity (K_i, nM)	81	4100	49	97
5-HT$_4$ receptor agonist activity (EC_{50}, nM)	61 (i.a. = 0.71)	ND	24 (i.a. = 0.55)	200 (i.a. = 0.71)

The abbreviation i.a. means intrinsic activity (expressed as the ratio of the maximum responses of each test compound to that of 5-HT). ND, not determined.

The K_i value obtained for domperidone (0.11 nM) was comparable to those reported previously (0.5 and 0.3 nM; El Tayar et al., 1998 and Waddington et al., 1986, respectively). In terms of dopamine D2 affinity, KDR-5169 was 56 times weaker than domperidone, but 11 times more potent than cisapride. As for the 5-HT_4 receptor binding assay, the K_d and B_{max} values were 47 pM and 160 fmol/mg protein, respectively. The K_i values of KDR-5169, cisapride and mosapride obtained for the 5-HT_4 receptor were in a similar affinity range (81, 49 and 97 nM, respectively), while that of domperidone was in a lower affinity range (4100 nM). In terms of 5-HT_4 receptor agonist activity, KDR-5169 was 2.5 times weaker than cisapride, but 3.3 times more potent than mosapride. This rank order was same as that for 5-HT_4 receptor affinity. The 5-HT_4 receptor agonist activity of domperidone was not determined because its 5-HT_4 receptor affinity was much lower than the other compounds.

3.2. Gastrointestinal motor activity in conscious dogs

Fig. 2 shows typical gastro-pyloric responses to prokinetics in a conscious dog. Intravenous administration of

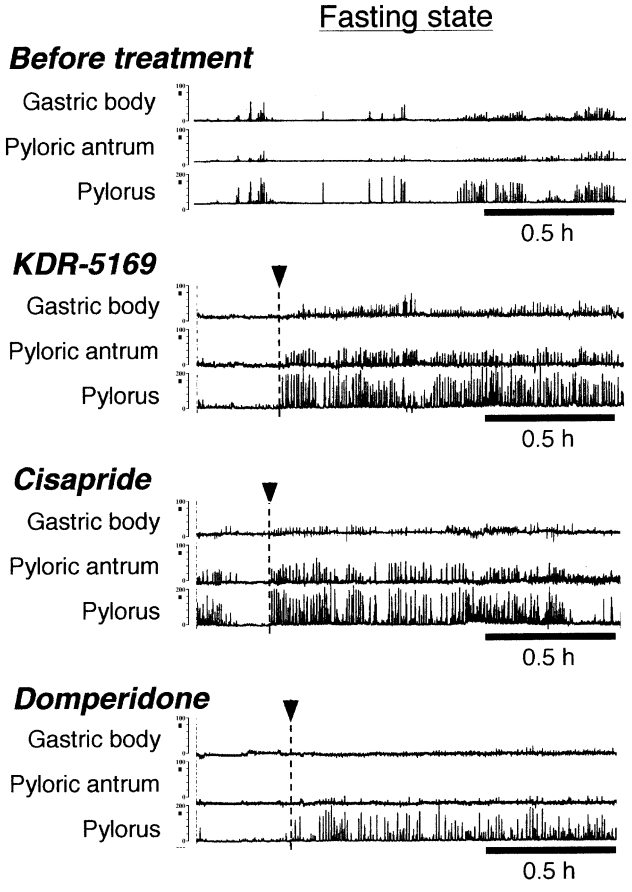

Fig. 2. Typical tracings of upper gastrointestinal motor activity before and after administration of KDR-5169 (0.3 mg/kg), cisapride (0.3 mg/kg) and domperidone (1.0 mg/kg) in conscious dog in the fasting state. Each drug was administered intravenously. Each dotted line with arrowhead indicates the time of drug administration.

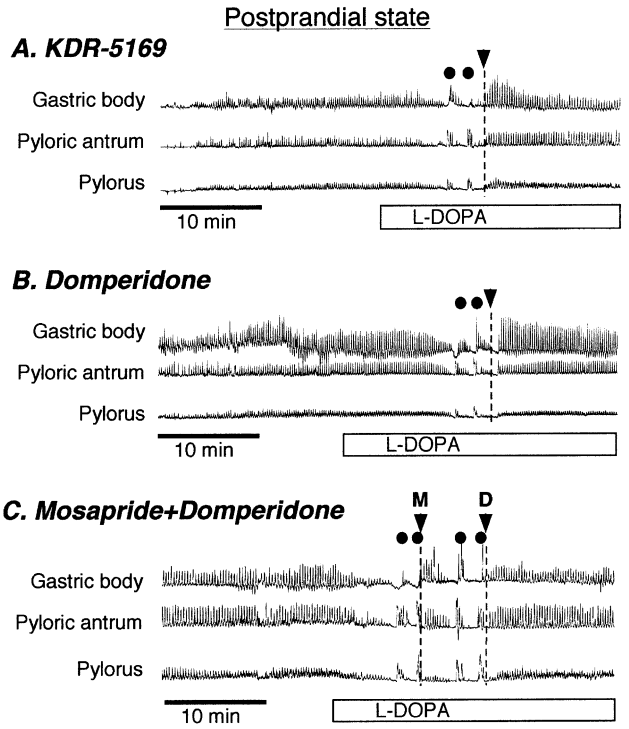

Fig. 3. Reversal of L-DOPA-induced inhibition of gastric motor activity in dogs in the postprandial state by KDR-5169 and domperidone. About 20 min after regular solid chow was fed, L-DOPA was infused intravenously at 10 mg/kg/h. Once decreased motor activity and two emetic episodes had been observed, the test drug was administered intravenously. Closed circles indicate occurrence of vomiting. Dotted line with arrowhead indicates the time of drug administration at doses of: (A) KDR-5169, 1.0 mg/kg; (B) domperidone, 0.1 mg/kg; (C) mosapride (M), 1.0 mg/kg; and (D) domperidone, 0.3 mg/kg.

KDR-5169 (0.3 mg/kg) and cisapride (0.3 mg/kg) in the fasting state induced contractile activity in the gastrointestinal tract. The effects clearly continued for more than 1 h, whereas the migrating motor complexes observed in the pretreatment period were <20 min long. These effects were considered not to be secondary to changes in blood pressure because in our preliminary experiments blood pressure was not significantly altered in anaesthetised dogs at the doses used (data not shown). The contractile response of the pylorus to 1.0 mg/kg domperidone was weak as compared to the contractile response to 0.3 mg/kg KDR-5169 and 0.3 mg/kg cisapride. The data shown here were obtained in the same dog and the other 3 dogs responded to these prokinetics in a similar way.

In the postprandial state, a continuous L-DOPA infusion suppressed gastrointestinal motor activity and induced repeated emesis. These effects were observed within 10 min of the start of L-DOPA infusion (Fig. 3). Both intravenous KDR-5169 (1 mg/kg) and domperidone (0.1 mg/kg) restored the activity and prevented further emesis (Fig. 3A and B). Under the same conditions, mosapride (1 mg/kg) caused transient induction of contractile activity. However, following this repeated emesis was observed again at the dose

tested. Both emesis and suppressed motility recovered completely on subsequent administration of 0.3 mg/kg domperidone (Fig. 3C).

3.3. Gastric emptying in normal rats

In order to estimate the basal potency of each of the prokinetics in terms of effects on gastric emptying, the rate of expulsion of non-nutrient solid beads from the stomach was measured in normal rats pretreated orally with one of the compounds. As shown in Fig. 4A, KDR-5169 enhanced gastric emptying at 3 mg/kg, with the maximum response being seen at 10 and 30 mg/kg. Mosapride (3, 10 and 30 mg/kg) and cisapride (1, 3 and 10 mg/kg) also increased it, and reached a significant level from 10 and 3 mg/kg, respectively. However, domperidone (1, 3 and 10 mg/kg) had no such effect over the dose range tested (Fig. 4A).

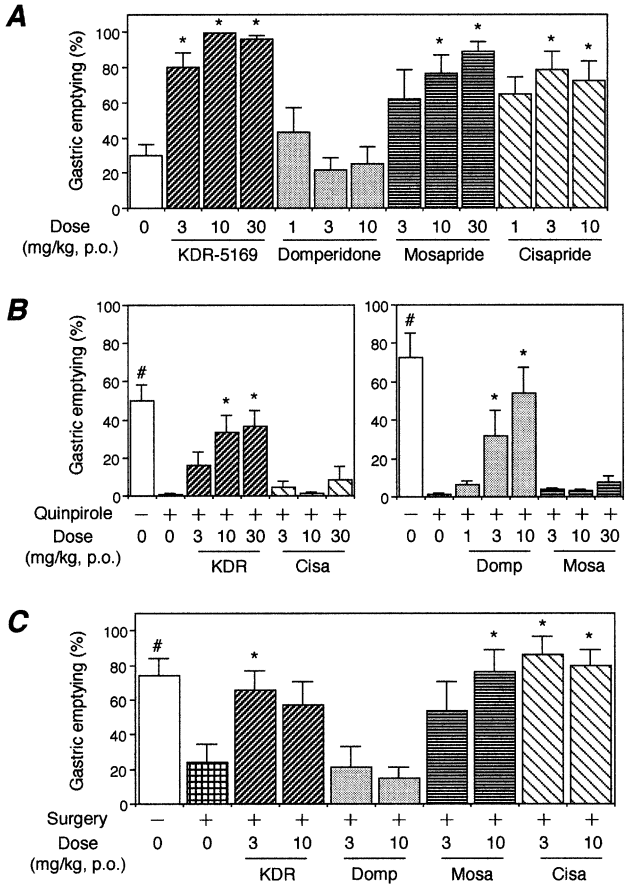

Fig. 4. Effects of prokinetics on gastric emptying in rats. Each prokinetic was administered orally 60 min before bead administration. (A) Gastric emptying in normal rats. Gastric emptying was assessed over a 30-min period. Values are the means ± S.E.M. of 6–7 experiments. (B) Gastric emptying in a quinpirole-delay model in rats. Quinpirole (0.3 mg/kg) was administered intraperitoneally immediately after bead administration. Gastric emptying was assessed over a 30-min period. Values are the means ± S.E.M. of 7–8 experiments. (C) Gastric emptying in a surgery-delayed model in rats. Three hours before bead administration, laparotomy was made and immediately closed. Gastric emptying was assessed over a 60-min period. Values are the means ± S.E.M. of 5–7 experiments. * $P<0.05$ vs. untreated control in A (Dunnett's multiple-comparison test) or $P<0.05$ vs. treated control (quinpirole (+) or surgery (+)/drug (0) group) in B and C (Dunnett's multiple-comparison test), and $^{\#}P<0.05$ vs. treated control in B and C (Student's *t*-test).

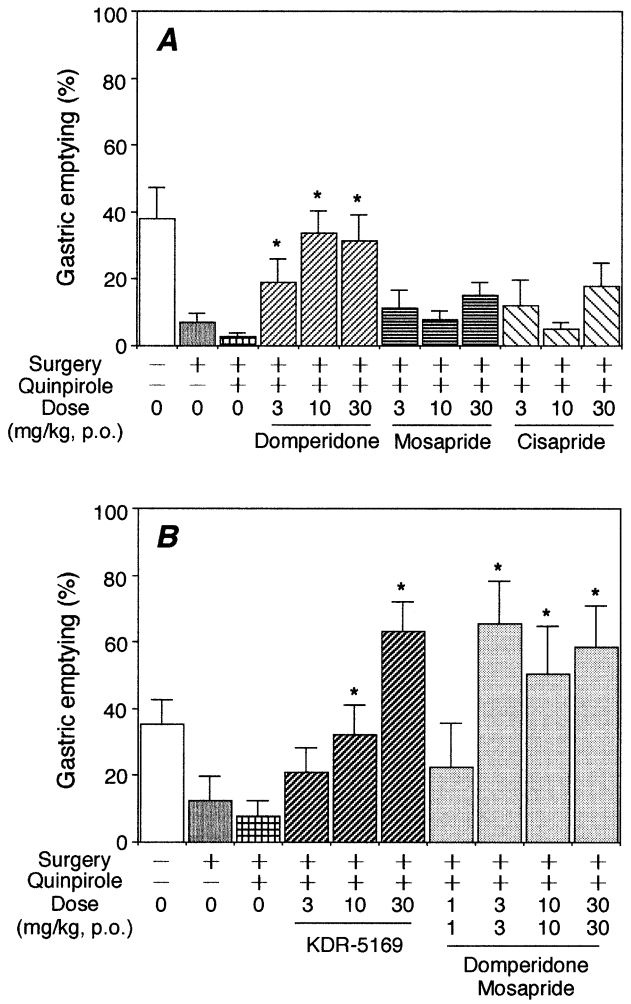

Fig. 5. Effects of prokinetics on gastric emptying in surgery/quinpirole-induced gastroparesis model in rats. An abdominal incision was made 3 h prior to bead administration, and quinpirole (0.3 mg/kg) was intraperitoneally administered immediately after bead administration. Gastric emptying was assessed over a 30-min period. Values are the means ± S.E.M. of 7–11 experiments. * $P<0.05$ vs. surgery (+)/quinpirole (+)/drug (0) group.

3.4. Dopamine D2 receptor agonist-induced gastroparesis model in rats

As a model for the gastroparesis induced by stimulation of dopaminergic neurons, rats were treated with quinpirole, a dopamine D2 receptor agonist. In the preliminary study, the effect of quinpirole lasted no longer than 30 to 60 min, so we assessed gastric emptying in this model over a 30-min period. In quinpirole-treated rats, gastric emptying was markedly decreased for 30 min after the treatment (from 49.9 ± 8.3% to 0.9 ± 0.3% or 72.4 ± 12.4 to 1.3 ± 0.3%) (Fig. 4B). The emptying rates of the untreated control were different between experiments because the rate could easily be altered

by experimental environments such as faint noise, a slight difference in temperature, signs of neighboring other species, etc. In this delayed gastric emptying model, either KDR-5169 (3, 10 and 30 mg/kg) or domperidone (1, 3 and 10 mg/kg) restored the rate in a dose-dependent fashion, whereas neither mosapride (3, 10 and 30 mg/kg) nor cisapride (3, 10 and 30 mg/kg) had a significant effect even at the highest doses tested (Fig. 4B).

3.5. Postoperative-ileus model in rats

The delayed gastric emptying associated with laparotomy is widely used as a model of stress-induced gastroparesis (Martinez et al., 1997; Resnick et al., 1997a,b; Taché et al., 1999). In our preliminary study, we observed a significant depression of gastric emptying for 3 h after surgery, with the delay showing a gradual recovery over the subsequent 24 h. Consequently, we chose 3 h as the measurement period. In this model, all three agonists of the 5-HT_4 receptor (KDR-5169, mosapride and cisapride) restored gastric emptying to the normal level, but domperidone showed no such effect (Fig. 4C).

3.6. Surgery/quinpirole-induced gastroparesis model in rats

To allow us to examine the effects of prokinetics in a more complex situation, we combined two of the above mentioned gastroparesis models. In this combined model, domperidone unexpectedly reduced the delay at 3 mg/kg, with almost normal emptying being achieved at 10 and 30 mg/kg. However, mosapride and cisapride did not significantly affect the delay (Fig. 5A). KDR-5169 dose dependently eliminated the delay and, even at the highest dose used, accelerated emptying to above the normal level. A similar elimination of delay and acceleration effect were seen when a combination of mosapride and domperidone was given (Fig. 5B).

4. Discussion

It is well known that activation of the dopamine D2 receptor on the gastrointestinal tract results in the inhibition of gastrointestinal motility in both humans and animals. In the present study, it was also shown that L-DOPA decreased gastrointestinal motor activity in dogs and that quinpirole suppressed gastric emptying in rats as reported by others (Shuto et al., 1980; Dhasmana et al., 1993). These effects of the two dopamine-related compounds were completely eliminated by administration of domperidone, a dopamine D2 receptor antagonist, while mosapride, a selective 5-HT_4 receptor agonist, did not eliminate the effects of L-DOPA and quinpirole at the doses tested in the present study. It has been reported that quinpirole has agonist activity towards the dopamine D3 receptor as well as towards the dopamine D2 receptor (Dhasmana et al., 1993). However, since domperidone binds preferentially to the dopamine D2 receptor (> 30-fold vs. the dopamine D3 receptor, Sokoloff et al., 1990), the above effects of L-DOPA and quinpirole can be assumed to be exerted mainly through the peripheral dopamine D2 receptor. In addition, we suggest that the elimination of L-DOPA or quinpirole effects by KDR-5169 result from its blocking of the dopamine D2 receptor, probably in the periphery. The validity of this suggestion is confirmed by the results that intravenous KDR-5169 hardly reached the brain in rats and produced virtually no behavioral side effects in mice even when administered orally (in both cases, much like domperidone) (data not shown).

In the fasting state in dogs, KDR-5169 enhanced gastrointestinal motor activity, the effect being clearly seen in the pyloric antrum and pylorus. This profile was similar to that seen in the present study for cisapride, but unlike that of domperidone. Even though domperidone had some effect on the activity at 1.0 mg/kg, the K_i values obtained for domperidone (0.11 nM) and KDR-5169 (6.2 nM) showed that the dose needed for dopamine D2 receptor antagonism was lower for KDR-5169 (0.3 mg/kg) than for domperidone. Moreover, gastric emptying in normal rats was increased by KDR-5169, just as it was by mosapride and cisapride, but not with domperidone. Thus, in the fasting state in dogs and in normal rats without exogenous dopamine-related compounds, the stimulating effect of KDR-5169 on gastrointestinal motility might be due to the 5-HT_4 receptor stimulation rather than to dopamine D2 receptor antagonism.

Postoperative ileus is a common complication after surgical operations (Resnick et al., 1997a,b). It is generally considered to result from a number of mechanisms, including activation of sympathetic hyperactivity and many neural and hormonal factors as well as electrolyte imbalance (Coimbra and Plourde, 1996; Resnick et al., 1997a; De Winter et al., 1999). Cisapride has been reported to be effective in a postoperative gastroparesis model in rats (De Winter et al., 1999), as was demonstrated in the present study. In addition, KDR-5169 and mosapride also reduced or eliminated the delay, whereas domperidone did not. These results indicate that the delay does not involve peripheral dopamine D2 receptor activation in this model, and that 5-HT_4 receptor activation can overcome the delay.

In order to assess the properties of prokinetics in a more complex situation, we combined the two gastroparesis models. In the combined model of surgery plus quinpirole delay in rats, mosapride and cisapride did not eliminate the delay in gastric emptying; however, to our surprise, domperidone did. It could be hypothesized that in the combined gastroparesis model a dopamine D2 receptor-related mechanism became dominant, and a 5-HT_4 receptor-related mechanism became silent. However, the reason why these phenomena appeared is not clear. Further studies will clearly be needed to answer this question. KDR-5169 could not only eliminate the delay, but also enhance gastric emptying beyond the normal level in the combined model, a dual effect also seen with a combination of domperidone and mosapride. The enhancement of gastric

emptying beyond the normal level may be due to 5-HT_4 receptor stimulation after reversal of the gastroparesis by dopamine D2 receptor antagonism. Tatsuta et al. (1992) reported that, in the clinical situation, combined administration of cisapride and domperidone leads to significantly faster gastric emptying than does cisapride plus placebo in patients with chronic idiopathic dyspepsia. Taking these results together with those obtained in the present study, we suggest that a combination of peripheral dopamine D2 receptor blockade and 5-HT_4 receptor stimulation ought to be useful in the treatment of non-ulcer (functional) forms of gastroparesis of complex cause (such as chronic idiopathic dyspepsia or functional dyspepsia).

In conclusion, our study showed that KDR-5169 not only stimulated upper gastrointestinal motor activity in dogs, but also restored the depressed gastric motility caused by several agents in both dogs and rats. These effects would seem to result from 5-HT_4 receptor agonist activity and/or dopamine D2 receptor antagonist activity. KDR-5169 restored normal activity in all the gastroparesis models tested, whereas domperidone, cisapride and mosapride only had an effect in specific models. Furthermore, KDR-5169 enhanced gastric emptying beyond the normal level in the combination-delay model in rats. It is, therefore, suggested that KDR-5169 would be effective in various types of gastric ileus caused by different mechanisms.

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