Effect of Cisapride and Renzapride on Gastrointestinal Motility and Plasma Motilin Concentration in Dogs

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ABSTRACT
The effects of cisapride and renzapride (BRL 24924), on plasma concentration of motilin and gastroduodenal motility were studied in seven dogs with implanted force transducers in the antrum and duodenum. In the interdigestive state, the i.v. administration of cisapride (5 mg) or renzapride (5 mg) administered in phase I resulted in a prompt and marked increase in plasma motilin concentration and in gastroduodenal motility. Mean plasma motilin levels during the first 30 min after cisapride and after renzapride injection were 85.0 ± 6.5 (± S.E.) and 96.1 ± 6.3 pm, respectively. These values were significantly greater (P < .001) than those for the corresponding time period of the control cycle, 52.2 ± 5.6 and 57.4 ± 5.3 pm (mean phase III level, 120 ± 8.1 pm), respectively. The increases in the motilin level after cisapride or renzapride coincided with significant increases in contractile activities of the antrum to 43.2 ± 5.3% and 44.9 ± 4.6% and of the duodenum to 28.4 ± 3.1% and 34.2 ± 2.2% of phase III activity (100%) from that in the corresponding control period, 0.7 ± 0.4% and 0.2 ± 0.1%, respectively. The changes in both plasma motilin and motility in response to the two drugs were abolished completely by the i.v. administration of atropine. The drugs also enhanced the meal-induced contractile activities of the antrum as well as the duodenum but failed to influence the postprandial plasma motilin concentration. We conclude that cisapride and renzapride have similar effects on plasma motilin and gastroduodenal motility: 1) the two drugs increase plasma motilin levels and stimulate gastroduodenal motility in the interdigestive state, and 2) in the digestive state, both drugs enhance motility without influencing the plasma motilin levels.

Cisapride is a prokinetic drug that is derived from a benzamide compound and is reported to be effective in the treatment of some gastric, small intestinal and colonic motor disturbances (Champion, 1989; Krevsky et al., 1989; Lee et al., 1984; McHugh et al., 1992). In conscious dogs, the i.v. administration of cisapride stimulated digestive and interdigestive GI motility (Edwards et al., 1987; Muller-Lissner et al., 1986; Gullikson et al., 1993; Meulemans and Schuurkes, 1984). The mechanism of this action is not clearly known, although it has been suggested that it facilitates ACh release from the myenteric plexus (Van Nueten et al., 1984). Previously, we reported that i.v. cisapride increased GI motility via an atropine-sensitive mechanism (Lee et al., 1984).

A new substituted benzamide compound, renzapride (BRL 24924), which does not have any dopamine blocking activity, has also been reported to stimulate gastric motility (Bermudez et al., 1990; Cooper et al., 1986; Gullikson et al., 1991; Gullikson et al., 1993). It was reported that both cisapride and renzapride enhanced the contractions of the electrically stimulated ileum, but not contractions caused by exogenous ACh and therefore it was suggested that the action of both compounds was due to a stimulation of cholinergic neurons (Craig and Clark, 1990). Recently, it has been proposed that these two benzamide compounds exert their motility-stimulating actions via serotonin receptor (Gullikson et al., 1993; Meulemans and Schuurkes, 1992) by activating serotonin-4 receptors (Ford and Clarke, 1993). In the present study, we have investigated the effect of both cisapride and renzapride on the plasma motilin concentrations and gastroduodenal motility in fasting and postprandial states.

Materials and Methods
Seventh dogs (body weight 15 to 22 kg) were prepared with gastric cannulas and a set of three strain gauges sutured on the serosal walls of the antrum: two 4 cm and 2 cm proximal to the pylorus and one on the duodenal wall, 5 cm from the pylorus. Experiments were started at least 2 weeks after surgery. After an 18-hr fast, dogs were placed on the Pavlov stand, and the motility was recorded by using a Grass polygraph (Model 7PI). During the experiments, venous blood samples were obtained via an indwelling catheter in a vein of one of a fore or hind leg while the stomach cannula was left open to drain gastric juice. The stomach cannula was closed before a meal was fed.

Study design. Three different groups of studies were carried out.

1) Interdigestive state: at least two cycles of interdigestive motor activity, including phases I, II, III and IV were recorded before drug was administered. Phase I represents a quiescent period with no contractions that lasts about 30 to 60 min, phase II represents a period of random contractions that lasts about 20 to

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60 min and phase III represents a period of maximum contractions that lasts about 5 to 20 min and migrates aborally. Phase IV represents a transitional period between phase III and phase I, exhibiting random contractions similar to the phase II period and lasting 5 to 10 min. One cycle of the interdigestive motor activity lasts about 90 to 120 min in dogs (Code and Marlett, 1975). Cisapride or renzapride was administered i.v. in a bolus at a dose of 5 mg in phase I (30 min after the second phase III), and motility recording was continued for at least 2 hr more after drug administration. After i.v. administration of cisapride or renzapride, sampling of blood was made at intervals of 5 min during first 30 min and at intervals of 10 min thereafter. For the control, blood samples were obtained during the corresponding time period of the control cycle.

2) Atropine background: similar experiments were repeated under the influence of atropine sulfate at 5 µg/kg given i.v., followed by continuous infusion at 20 µg/kg/kg. Atropine was started at least 20 min before a testing drug was administered.

3) Digestive state: 30 min after the end of duodenal phase III, dogs ate a standard meal containing 150 g of cooked ground beef, 100 ml of milk and one slice of white bread. A testing drug was given i.v. 30 min after the meal. Blood samples were obtained at 5-min intervals for 30 min. The blood samples collected in heparinized tubes were placed immediately in ice, and at the end of the experiment, plasma was separated by refrigerated centrifugation at 3000 rpm for 10 min. Plasma samples containing 1 mM ethylendiamine tetra-acetic acid, 1.5 mg/ml of bovine trypsin inhibitor, 100 mg/ml of soybean trypsin inhibitor and 9.9 × 10−6 M D-Phe-L-Arg-CH2Cl2, a potent, specific, irreversible inhibitor of kallikreins were kept frozen at −20°C for future radioimmunooassay of motilin (Tai and Chey, 1978). Cisapride was supplied by Janssen Research Foundation, Piscataway, NJ, and renzapride by Beecham Pharmaceuticals, Surrey, England.

Measurement of plasma motilin and motility analysis. The plasma motilin concentration was determined at 5 to 10-min intervals, and gastroduodenal contraction was analyzed at 10-min intervals. The results of motility changes observed during first 30 min were expressed as percent contraction of phase III, during which maximum contractions (100%) occurred. In order to evaluate the effect of drug on motilin release and gastroduodenal contractile activity, the mean plasma motilin concentrations we determined and the contractile activity analyzed for 30 min after drug administrations were compared with those during the corresponding time period of the control cycle. Because the actions of both drugs were immediate, the initial effect was probably due to the direct action of either drug.

Analysis of data. The results were expressed as means ± S.E., and a linear model was used for comparison (Neter et al., 1985). P values of less than .05 were considered statistically significant.

Results

During the interdigestive state, the i.v. administration of cisapride or renzapride resulted in prompt and marked increases in contractile activities of the antrum and duodenum (fig. 1). Mean contractile activities of the antrum and duodenum during the first 30 min after cisapride or renzapride administration were 43.2 ± 5.3 or 44.9 ± 4.6% and 28.4 ± 3.1% or 34.2 ± 2.2% of phase III contractile activity, respectively, values that were significantly higher (P < .001) than those of the corresponding control period, 0.7 ± 0.4% and 0.2 ± 0.1% (fig. 2). The contractile activity lasted for more than 2 hr—as long as the recording continued. The increase in the motility coincided with significant increases in plasma motilin levels from 52.2 ± 5.6 pM to 85.9 ± 6.5 pM after cisapride and from 57.4 ± 5.3 pM to 96.1 ± 6.3 pM after renzapride, respectively (P < .01) (fig. 2).

The increased motility induced by either cisapride or renzapride was completely suppressed by atropine. Also, the increase in plasma motilin concentration was completely abolished by atropine pretreatment (fig. 3). A meal ingestion converted the motility to a digestive pattern immediately, which was enhanced by the i.v. administration of cisapride or renzapride (fig. 4). After cisapride, the increased motility after a meal, 12.5 ± 3.2% and 11.1 ± 4.2% observed in the antrum and duodenum, respectively, was enhanced further to 46.4 ± 3.0% and 24.8 ± 6.0% of phase III, respectively (P < .01). Similarly, renzapride significantly augmented (P < .01) the digestive motility from 12.3 ± 3.2% and 13.1 ± 3.5% to 41.6 ± 4.0% and 26.5 ± 5.0% of phase III in the antrum and duodenum, respectively (fig. 5). However, the drugs failed to influence the plasma motilin concentration (fig. 5). Mean postprandial plasma motilin levels during the first 30 min after cisapride and renzapride injections were 73.1 ± 4.2 pM and 70.9 ± 3.6 pM, respectively, values that were no different from those—76.4 ± 4.8 pM and 69.6 ± 3.4 pM, respectively—during the 30-min period before the administration of either of the two drugs.

Discussion

In the present study, we observed a significant increase in gastroduodenal motility when cisapride or renzapride was administered i.v., a result that confirms the previous publi-
cations (Bermudez et al., 1990; Cooper et al., 1986; Fraser et al., 1993; Gullikson et al., 1993; Sanger, 1987). In addition, significant increases in the plasma motilin concentration were observed after cisapride or renzapride administration. Thus we confirmed our previous observation that cisapride increased plasma motilin levels (Lee and Chey, 1984), although others failed to observe any changes in plasma motilin level (Kawagishi et al., 1993; Suzuki et al., 1984). The reason for this discrepancy between our observations and those of others is not known.

It has been previously shown that there is an intimate relationship between cyclic increase in fasting plasma motilin concentration and the interdigestive motor complex of the antrum and proximal small intestine (Chey et al., 1978; Itoh et al., 1978; Lee et al., 1978). The increases in both plasma motilin level and contractile activity of the antrum and duodenum induced by cisapride or renzapride were almost completely blocked after atropine infusion, which suggests that the actions of these two drugs on the release of motilin and on the motility are mediated by local release of ACh (Craig and Clarke, 1990; Kilbinger et al., 1995). A similar observation was made in the interdigestive state in dogs as well as humans (You et al., 1980) in which cyclic increases in plasma motilin concentration coinciding with phase III motor activity of the duodenum were completely abolished by i.v. atropine (Chey et al., 1978; Lee et al., 1983).

In the postprandial state, neither of the two drugs raised the plasma concentration of motilin, although both significantly increased gastroduodenal motility. As shown previously, the cyclic increase in plasma motilin is interrupted by ingestion of a meal in dogs (Chung et al., 1992; Lee et al., 1980). The elevation of motilin may be suppressed during the postprandial period by increased releases of gut and pancreatic hormones such as pancreatic polypeptide (Adrian et al., 1980; Hall et al., 1983), insulin (Jenssen et al., 1984) and somatostatin (Poitras et al., 1980), which are known to suppress motilin release. In duodenectomized dogs, cyclic patterns of motility were preserved without any motilin fluctuations (Mallertheiner et al., 1989), which suggests that a factor or factors in the duodenum contribute to the cyclic coupling of motility and motilin. More recently, Chung et al. (1992) reported that postprandial patterns of motility and motilin was converted to the fasting patterns when vagal tone was blocked by cooling. Thus in dogs, dissociation between the increase in plasma motilin and gastroduodenal motility in the postprandial state could be mediated by multiple factors, including hormonal as well as neuronal factors. Further studies will be needed.

Although the mechanisms of the action of cisapride and renzapride have not been clearly defined, it has been implicated that cisapride may act on motility by facilitating the
release of ACh at nerve endings in the myenteric plexus (Pfeuffer-Friederich and Kilbinger, 1984; Van Nueten et al., 1984). In the guinea pig ileum strip, a transient increase, induced by cisapride, in the release of ACh was abolished in the presence of serotonin (Pfeuffer-Friederich and Kilbinger, 1984). The facilitating effect of serotonin on ACh release was reduced by cisapride also (Pfeuffer-Friederich and Kilbinger, 1984). Thus cisapride was claimed to be a weak agonist of both excitatory and inhibitory serotonin receptors (Pfeuffer-Friederich and Kilbinger, 1984) or a serotonin receptor blocker (Van Nueten et al., 1984). Renzapride also increased electrically evoked cholinergically mediated contractions, probably by increasing ACh release (Sanger, 1987). This action of renzapride was claimed to be a weak agonist of both excitatory and inhibitory serotonin receptors (Pfeuffer-Friederich and Kilbinger, 1984) or a serotonin receptor blocker (Van Nueten et al., 1984). Renzapride also increased electrically evoked cholinergically mediated contractions, probably by increasing ACh release (Sanger, 1987). This action of renzapride was prevented by a high concentration of serotonin, but not by hexamethonium, phentolamine, propranolol or methysergide (Sanger, 1987). It has also been suggested that these new benzamide compounds exert their motility-stimulating actions via an agonistic effect on serotonin-4 receptor (Craig and Clarke, 1990; Craig and Clarke, 1991; Ford and Clarke, 1993; Gullikson et al., 1993; Meulemans and Schuurkes, 1992; Taniyama et al., 1991) or a nonserotonergic mechanism (deKidd and Schuurkes, 1993). Because some of the enterochromaffin cells contain motilin as well as serotonin (Kishimoto et al., 1981), the serotonin-4 receptor agonistic actions of the two benzamides may have a regulatory role on the release of motilin from the enterochromaffin cells.

It was recently discovered that the mechanism of GI prokinetic action of metoclopramide, another benzamide, is through the activation of serotonin-4 receptors (Ford and Clarke, 1993), not via dopamine blocking action. So far, three different investigators have examined the effect of metoclopramide on motilin release in the human (Achem-Karam et al., 1985; Grandjouan et al., 1989; Rees et al., 1982). All three investigators agreed on its prokinetic action on the GI tract, but only Achem-Karam et al. (1985) reported that it stimulated motilin release. The reason for these conflicting results is not clear. Further investigation will be needed.

The stimulatory effect of renzapride on gastroduodenal motility suggests that, like cisapride (Kawagishi et al., 1993; Krevsky et al., 1989; McHugh et al., 1992), it may have useful clinical application to improve motility disorders associated with gastroparesis and/or disturbed gastroduodenal coordination. Renzapride may join such well-established prokinetic drugs as cisapride and metoclopramide.

In conclusion, both cisapride and renzapride increased plasma motilin levels and gastroduodenal motility simultaneously in the interdigestive state, whereas in the postprandial state, although both increase gastroduodenal motility, neither one influenced the plasma concentration of motilin. Like cisapride, renzapride may exert similar stimulatory effects on gastroduodenal motility in humans. Thus it may become a useful prokinetic agent.
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