Digestive Diseases and Sciences, Vol. 31, No. 8 (August 1986), pp. 807–810

Cisapride Offsets Dopamine-Induced Slowing of Fasting Gastric Emptying

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The effect of cisapride, a new gastrokinetic drug, on gastroduodenal motility was tested in six healthy volunteers. In order to obtain a model for slowed gastric emptying, dopamine was infused at a rate of 8 μg/kg/min. Dopamine significantly slowed the fractional emptying rate of fasting gastric contents from 5.14 ± 0.37 to 1.45 ± 0.67 %/min. Injection of either 10 mg of cisapride or 10 mg of metoclopramide restored emptying rate to normal (5.87 ± 0.56 and 5.62 ± 0.61 %/min, respectively). When cisapride was given without dopamine background, emptying was only moderately enhanced. Reflux of bile salts was not significantly affected by either cisapride or dopamine alone. When given on a dopamine background, however, both metoclopramide and cisapride decreased bile salt reflux below control values without any active treatment. It is concluded that emptying of fasting gastric contents can be speeded by cisapride, particularly when emptying is slowed by dopamine. A clear effect on bile salt reflux cannot be demonstrated.

Gastric emptying can be speeded by metoclopramide in patients with chronic gastric stasis (1–4). Inhibition of gastric motility induced by dopamine can be reversed by this drug (5, 6). It acts both as a dopamine antagonist and an acetylcholine-releasing compound (7, 8). Cisapride is a new drug devoid of antidopaminergic properties which acts, at least in the guinea pig, via release of acetylcholine from the myenteric plexus (7, 9). In contrast to metoclopramide (8, 10), it stimulates gastrointestinal motility not only in the upper gastrointestinal tract but also in the colon (9). In the present study, it was determined whether cisapride could prevent the slowing of emptying of fasting gastric contents induced by dopamine. Metoclopramide served as a reference substance. Bile salt reflux was also measured.

Manuscript received February 21, 1985; revised manuscript received July 25, 1985; accepted November 13, 1985.

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MATERIALS AND METHODS

Experimental Procedure. The experiment was started at 8 AM after a 12-hr fast. A nasogastric tube (CH 14) with an air vent was positioned with its tip in the most dependent part of the stomach under fluoroscopic control. The subject then lay in the left supine position. A winged needle was inserted into a forearm vein. Fifteen minutes later, gastric contents were aspirated by manual suction using a 50-ml syringe. The volume of the aspirate was measured by differential weighing (Sartorius, GFR, model 1003). An equal volume of marker solution was instilled into the stomach. It consisted of polyethylene glycol 4000 (PEG, 200 g/liter) in saline prewarmed to 37°C. The time between the beginning of aspiration and the end of instillation was 3 min. Twenty-seven minutes later gastric contents were again aspirated and measured. Five milliliters were sampled and replaced by PEG solution. The mixture was reinstilled into the stomach. This procedure again took 3 min. It was repeated every 30 min until the end of 4 hr.

The concentration of PEG (11) was measured in the samples. Acidity was determined by titration with 0.05 M NaOH. Total bile salt concentration was determined using the 3-α-hydroxysteroid dehydrogenase method (12). The rates of gastric emptying, gastric secretion, and bile salt reflux were calculated as follows. The intragastric amount of PEG, acid, and bile salts, respectively, at

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a given time is the product of their concentrations and the measured gastric volume at this time. The change of the intragastric amount, G, of PEG over time is

$$dG/dt = -gG \quad (1)$$

where g is the fractional gastric emptying rate (13). The solution of the equation is

$$G_2 = G_1 e^{-gt} \quad (2)$$

where the indices 1 and 2 refer to the beginning and end of the time interval t. The change of the other intragastric quantities over time is given by the equation

$$dA/dt = -gA + a \quad (3)$$

where A represents the intragastric amount of fluid secreted by the stomach, acid, and bile salts, respectively, and a represents the rate by which A enters the stomach, ie, secretion rates of volume and acid, respectively, and bile salt reflux rate. The solution of this equation is

$$a = \frac{(A_2 - A_1 e^{-gt})g}{1 - e^{-gt}} \quad (4)$$

Appropriate corrections were made for the diminution of intragastric concentrations which are induced by replacing a sample by PEG solution.

Calculations were performed with a computer (Siemens 404/3) using user-written software. Statistical comparisons between treatments were made by analysis of variance and subsequently by Duncan's test (14). Assessment of significance of changes in the time course of a measured variable was done by the Wilcoxon rank-sum test for paired data.

Subjects Studied. Six healthy volunteers were studied four times each. On each of the four occasions, a different treatment was given at random. In one experiment they received an intravenous infusion of saline during the entire experiment and an intravenous injection of saline after the 90th minute. In the three other studies, the infusion contained 8 μg/kg/min of dopamine (a dose found to have pronounced effects without inducing nausea). The injection contained either saline or 10 mg (the usual therapeutic dose) of metoclopramide or cisapride, respectively. This injection was given in a double-blind fashion. Six other volunteers were studied without intravenous infusion, but received an intravenous injection of 10 mg of cisapride following the 90th minute. No side effects of the intravenous injection were experienced. The study protocol was approved by the local ethical committee.

RESULTS

Effect of Dopamine. Dopamine inhibited gastric secretion of both volume and acid by about 50%. It slowed gastric emptying by about 70%. Therefore the total volume present in the stomach was higher during the infusion of dopamine than during the infusion of saline (see Table 1; Figure 1).

Effects of Metoclopramide and Cisapride. Gastric secretion was not affected by these compounds (Table 1). When given without dopamine background, cisapride was also without effect on secretion. Injection of metoclopramide or cisapride during dopamine infusion lead to a sharp increase of fractional gastric emptying rate to twice normal values and to a concomitant drop in intragastric volume (all $P < 0.05$, Figures 1 and 2). Subsequently, emptying rates were similar to control values. Overall, the effect of dopamine was completely offset by either of the two drugs. When given without dopamine background, cisapride induced a peak emptying rate (Figure 3). Overall, the emptying rate was increased from 3.67 ± 0.21 %/min precisapride to 5.85 ± 0.32 postcisapride ($P < 0.05$).

Bile Salt Reflux. Dopamine was without significant effect on both bile salt reflux rate and gastric bile salt concentration (Table 1). When metoclopramide or cisapride were injected during dopamine infusion, bile salt reflux rates were significantly lower than in studies without any active treatment. Gastric bile salt concentrations, however, did not significantly differ due to dilution in different gastric volumes (Table 1). The intravenous injection of cisapride alone did not significantly affect bile salt reflux. It was 0.46 ± 0.20 μmol/min precisapride and 0.34 ± 0.10 postcisapride.

TABLE 1. RESULTS IN SIX SUBJECTS STUDIED FOUR TIMES EACH

	PP*	DP	DM	DC	F†	P†
Secretion rates						
Volume (ml/min)	1.44 ± 0.33	0.81 ± 0.15a‡	0.69 ± 0.14a	0.63 ± 0.14a	3.66	<0.05
Acid (μmol/min)	63.2 ± 19.4	20.3 ± 5.6a	28.5 ± 8.7	19.2 ± 5.4a	6.56	<0.01
Emptying rates (%/min)	5.14 ± 0.37	1.45 ± 0.67b	5.87 ± 0.56c	5.62 ± 0.61c	10.14	<0.01
Gastric volume (ml)	33.3 ± 8.5	102.2 ± 29.0a	13.4 ± 2.1c	13.6 ± 2.3c	9.89	<0.01
Bile salt						
Reflux rate (μmol/min)	0.52 ± 0.06	0.28 ± 0.06	0.21 ± 0.06a	0.19 ± 0.04a	5.28	<0.01
Concentration (μmol/l)	447 ± 106	286 ± 54	318 ± 29	344 ± 62	1.34	NS

*PP, DP, DM, DC: first letter = intravenous infusion, second letter = intravenous injection, P = placebo, D = dopamine, M = metoclopramide, C = cisapride. Means from 90th minute onwards ± SEM.
†By analysis of variance.
‡a = $P < 0.05$ vs PP, b = $P < 0.01$ vs PP, c = $P < 0.01$ vs DP.

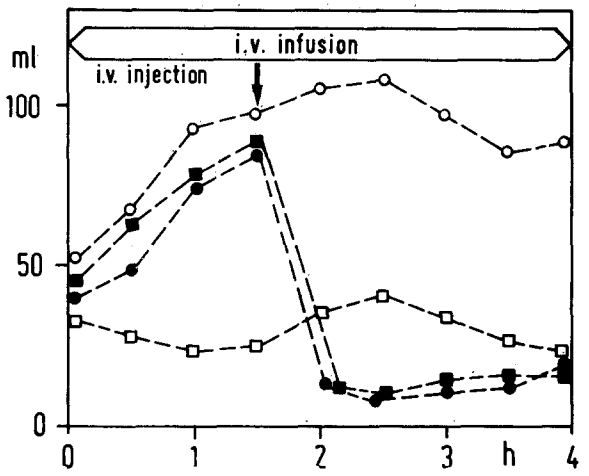

Fig 1. Time course of mean intragastric volumes. PP, DP, DM, DC: first letter = intravenous infusion, second letter = intravenous injection; P = placebo, D = dopamine, M = metoclopramide, C = cisapride; □———□ = PP, ○———○ = DP, ■———■ = DM, ●———● = DC. Infusion of dopamine increases gastric volume above control level. Subsequent injection of metoclopramide or cisapride reduces volume below control level; the drop of volume is significant ($P < 0.05$).

DISCUSSION

In the present study, the effect of dopamine and two gastrokinetic compounds on fluid movements of the fasting stomach was evaluated. Dopamine, which has been claimed to be the neurotransmitter for gastric relaxation (6), may provide a model for pathologically slow gastric emptying. In this model, gastrokinetic drugs can be tested for their ability to speed gastric emptying towards normal.

Dopamine decreased fasting gastric secretion and motility in our study and in previous studies (5, 6, 15–18). It probably affects secretion via β-receptors (15) but motility via specific dopamine receptors (6, 17, 18). Since metoclopramide has antidopaminergic activity (8, 10), the reversal of depressed emptying but not of secretion can easily be explained. Cisapride, however, is devoid of antidopaminergic properties (9). In the guinea pig (7) and in the dog (Van Nueten, personal communication) it releases acetylcholine from the myenteric plexus which innervates the gastrointestinal muscle layers but not the secretory cells of the mucosa. An effect of cisapride on secretion is therefore neither to be expected nor has it been observed (Table 1) (19). The reversal of dopamine-induced inhibition of gastric emptying by cisapride shows that antidopaminergic specificity is not mandatory for such an effect.

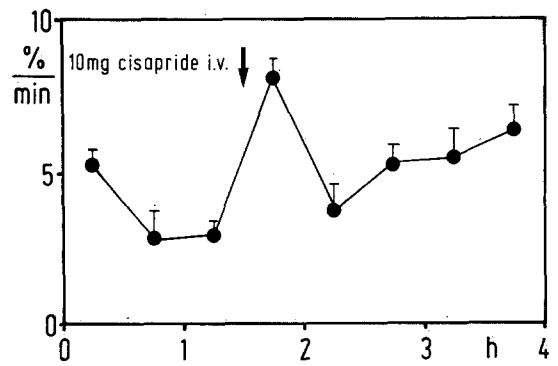

Fig 2. Time course of mean fractional gastric emptying rates. □———□ = PP, ○———○ = DP, ■———■ = DM, ●———● = DC. The increase following injection of metoclopramide and cisapride, respectively, is statistically significant ($P < 0.05$).

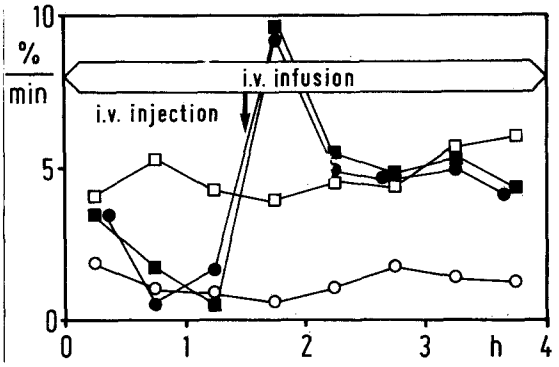

Fig 3. Time course of fractional gastric emptying rate of subjects treated with intravenous injection of 10 mg cisapride only; means ± SEM. The increase after intravenous injection is statistically significant ($P < 0.05$).

Speeding of gastric emptying by metoclopramide has been shown in patients with chronic gastric retention (1–4) but not in subjects with normal gastric emptying (2, 20). Improvement of slowed gastric emptying in patients has also been shown with cisapride (20). In the present study, a moderate but clear effect of cisapride on fasting gastric emptying was shown in healthy people following an intravenous bolus injection of the compound (Figure 3). This does not imply, however, that similar results would occur after oral medication or during emptying of a caloric meal.

What are the possible advantages of cisapride over the presently available prokinetic drugs? Due to its action on the entire gut, it may be useful in diseases involving both the upper and the lower gastrointestinal tract such as diabetic neuropathy, scleroderma, and intestinal pseudoobstruction. Secondly, it may be able to overcome the gastrointestinal side effects of dopamine agonists without

interference with their intended action. Finally, the central-nervous side effects of metoclopramide (extrapyramidal symptoms) (8) will not occur.

Dopamine exerted no statistically significant effect on bile salt reflux. Cisapride given alone was also ineffective. In contrast, when given on a dopamine background, both metoclopramide and cisapride significantly reduced the bile salt reflux rate as compared to control studies without any treatment (Table 1). This did not, however, result in lower gastric bile salt concentration. An attempt to explain these results deals with a general problem of the bile salt reflux rate. This rate depends on two quantities, namely, biliary output into the duodenum and duodenogastric reflux (22). The observed effects would be obtained if dopamine would decrease biliary output to a similar extent or slightly more than the increase in duodenogastric reflux and also if metoclopramide and cisapride would stimulate duodenal propulsive motility slightly more than biliary output. At present, this explanation remains however, hypothetical. In addition, it does not provide an answer to the question as to whether chronic treatment with one of the gastrokinetic compounds would affect bile salt reflux rate or gastric bile salt concentration. Furthermore, the clinical usefulness of the bile reflux-reducing properties of a compound is not clear because the role of bile reflux in gastric ulcer pathogenesis (23) is uncertain (13).

In conclusion, gastric emptying can be slowed by dopamine. This may serve as a model for gastric retention. The dopamine effect can be reversed by drugs devoid of antidopaminergic actions. At present, the effect of metoclopramide and cisapride on bile salt reflux cannot be consistently explained.

ACKNOWLEDGMENTS

We are indebted to Mrs. G. Zimmermann for secretarial assistance; to Mrs. E. Beranek and A. König, MD, for help in the statistical evaluation; and to Deutsche Forschungsgemeinschaft (Mu 629/1-3) for financial support.

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