Nizatidine Enhances the Gastrocolonic Response and the Colonic Peristaltic Reflex in Humans

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ABSTRACT
Animal studies demonstrate that nizatidine, an H2-receptor inhibitor, may enhance colonic activity independent of its effect on acid secretion. The effect of nizatidine on human colonic motility is unknown. We evaluated the potential prokinetic property of nizatidine in 12 healthy subjects (10 men and 2 women, age 21–46 years). Each subject received either nizatidine (600 mg), famotidine (80 mg, a H2-receptor inhibitor used as a control), or a placebo, on separate days in randomized order at least 3 days apart. Following an overnight fast, a three-lumen catheter fitted with a stimulus balloon and two barostat bags was placed in the descending colon. The gastrocolonic response was tested by antral balloon inflation and the colonic peristaltic reflex was evaluated by colonic distension. Changes in colonic motility were assessed by volume changes in the barostat bags. Antral distension evoked volume-dependent increases in colonic motility, maximal at a 300-ml inflation, as demonstrated by a reduced bag volume. Nizatidine enhanced colonic motility in response to antral distension at 200 and 300 ml, compared with famotidine and placebo. Colonic distension evoked volume-dependent increases in colonic motility proximal to the stimulus balloon. Compared with famotidine and placebo, nizatidine enhanced the ascending and descending contractile limbs of the peristaltic reflex but did not affect relaxation distal to the balloon. In conclusion, nizatidine enhanced the gastrocolonic response and the colonic peristaltic reflex in healthy subjects. Further research on the prokinetic action of nizatidine in the colon may lead to novel treatments for idiopathic constipation.

Constipation is a common gastrointestinal disease in clinical practice. The underlying mechanisms are poorly understood and may vary between different groups of patients. Some patients with constipation result from systemic disease such as diabetes mellitus exhibit blunting of the gastrocolonic response (Battle et al., 1983). Patients with idiopathic constipation may demonstrate an abnormal colonic peristaltic reflex (Battle et al., 1983). The treatment for these conditions is usually unsatisfactory, despite some success with prokinetic agents such as cisapride, which is not without adverse effects.

Research has shown that intraduodenal acid may delay gastric emptying. Thus, H2-receptor inhibitors, such as ranitidine, cimetidine, and nizatidine, may enhance emptying by inhibiting acid secretion (Ohira et al., 1993). Recent investigations have shown that nizatidine stimulates gastric and duodenal motor activity in humans (Chey et al., 1995) and ileal activity in guinea pigs (Kounenis et al., 1987) by a mechanism independent of its effect on acid secretion. Furthermore, recent studies in dogs have demonstrated increased contractions in the ascending and descending colon after intravenous administration of nizatidine (3 mg/kg) (Ueki et al., 1999). These findings suggest that nizatidine may be useful in the treatment of constipation. However, the effect of nizatidine on human colonic motility is unknown.

We recently characterized the local and extended neural reflexes that mediate colonic motility in humans (Sims et al., 1995; Bjuransson et al., 1998). In the present study, we examined the effect of nizatidine on human colonic motility by investigating its actions on the gastrocolonic response and the colonic peristaltic reflex in healthy subjects.

Materials and Methods
Healthy Subjects. Twelve healthy volunteers—10 men and 2 women, age 21 to 46 years—were recruited by campus-wide advertisement. None had a history of chronic gastrointestinal complaints, of previous abdominal surgery, or of taking medications known to alter gastrointestinal motility. The University of Michigan Institutional Review Board approved the studies. Written informed consent was obtained from all subjects prior to participation.

Study Design. Isobaric determination of colonic motility was performed using a barostat with recording bags placed in the descending colon. The evening before the study, each subject ingested 3.8 liters of colonic lavage solution (GoLYTELY; Braintree Laboratories, Braintree, MA). Following an overnight fast, the subjects were mildly sedated with intravenous midazolam (4–10 mg, Versed; Hoffmann-La Roche, Nutley, NJ). Once sedated, the subjects were positioned on their left side and colonoscopy was performed to the cecum. A Teflon-coated guidewire was inserted through the biopsy
channel, the colonoscope was removed, and a multilumen barostat catheter made from three 14-Fr Tygon tubes was advanced over the guidewire. Placement of the catheter tip at the splenic flexure was confirmed by fluoroscopy. Two recording barostat bags and the stimulus balloon were located in series along the distal 30 cm of the catheter, each communicating with a separate lumen (Björnsson et al., 1998). The stimulus balloon, 5 cm in length, was positioned in the middle and served as the distending stimulus. Two highly compliant, polyethylene barostat bags, 8 cm in length and 400-ml maximum capacity, were positioned such that their geometric centers were 15 cm, one proximal and the other distal, from the center of the stimulus balloon. Each bag was connected to an electronic barostat (Isobar-3; G & J Electronics, Toronto, ON, Canada) to measure changes in colonic motility. A single 700-ml cylinder within the barostat controlled the inflation of the bags. The cylinder apparatus recorded pressures. Volume and pressure data from the barostat were recorded on a paper chart (Beckman Dynograph Recorder R611; Sensor Medics, Yorba Linda, CA) and stored in digitized form for later analysis. After a 2-h equilibration period to permit recovery from sedation and adaptation to the catheter, the subjects were positioned on their left side with knees and hips flexed for the recording of colonic motility.

The mechanoreceptor component of the gastrocolonic response and the colonic peristaltic reflex were assessed on the same day, 2 h after each subject received either 600 mg of nizatidine (Eli Lilly and Company, Indianapolis, IN), 80 mg of famotidine (Merck & Co., Whitehouse Station, NJ), which served as a control for acid inhibition, or placebo, on separate days in randomized order at least 3 days apart. The dose of 80 mg of famotidine was chosen based on its equivalent ability to suppress similar amounts of acid secretion as observed with 600 mg of nizatidine. Blood pressure, pulse, oxygen saturation, and respiration rate were monitored for 2 h following the administration of nizatidine or famotidine.

Gastrocolonic Response Assessment: Gastric Mechanoreceptor Activation. Before assessment of the gastrocolonic response, each subject was intubated with a modified 18-Fr nasogastric tube, the end of which was fitted with a standard latex condom for balloon distension of the stomach. The balloon, 9.5 cm in length, was sutured to both ends of the catheter to ensure radial but not longitudinal distension on inflation. After intubation, placement in the distal antrum was confirmed by fluoroscopy. For measurement of the gastrocolonic response, the proximal colonic recording barostat bag was set at an operating pressure of 2 mm Hg above the minimal distending pressure necessary to detect respiratory variations on the chart recorder volume tracing. After a 30-min basal recording period, the mechanoreceptor component of the gastrocolonic response was evoked by antral balloon distension with air to volumes of 100, 200, and 300 ml at a rate of 300 ml/min in a stepwise fashion, using previously validated methods (Sims et al., 1995; Björnsson et al., 1998). The antral balloon remained filled for 5 min, during which time changes in colonic motility were assessed by changes in the proximal colonic barostat bag volume. After each antral distension, a 30-min deflation period allowed colonic motility to return to baseline. The magnitude of the gastrocolonic response was measured as the mean volume decrease during the inflation period compared with the 5-min period prior to antral balloon inflation. The latency to development of the gastrocolonic response was defined as the time in seconds from the onset of antral balloon inflation to the point at which the decrease in the colonic bag volume represented 10% of the maximal volume decrease obtained during the 5-min preinflation period. The maximal volume decrease was determined by the lowest volume level obtained from the analysis of volume values obtained in 1-s intervals in standard spreadsheet format (Excel, Microsoft, Redmond, WA).

Colonic Peristaltic Reflex Assessment. The orad component of the peristaltic reflex was assessed by the proximal barostat bag, whereas the distal bag assessed the caudal response. All assessments were made after inflation of the middle stimulus balloon. Each recording barostat bag was inflated to an operating pressure of 2 mm Hg above the minimal distending pressure. The peristaltic reflex was evoked by inflating the middle stimulus balloon with air at a rate of 30 ml/s to volumes of 30, 60, and 90 ml. Stimulus inflations were maintained for 30 s and were followed by 5-min intervening periods of deflation to allow colonic motility to return to baseline. The magnitude of the contractile or relaxant response was measured by the difference between the minimal or maximal volume during the inflation period compared with the mean volume recorded during a 30-s preinflation baseline period. A positive ascending or descending contraction was defined as a recording barostat bag volume decrease of at least 1 ml occurring during the 30-s inflation. The latency of the ascending or descending contraction was defined as the time from the onset of the stimulus inflation to the point at which the decrease in the proximal or distal barostat bag volume represented 10% of the maximal volume decrease. A positive descending relaxation was defined as a recording barostat bag volume increase of at least 1 ml in the first 15 s of the inflation. The latency of the descending relaxation was defined as the time from onset of stimulus inflation to the point at which the increase in distal barostat bag volume represented 10% of the maximal volume increase. Minimal and maximal volume values were obtained by spreadsheet analysis of data acquired in 1-s intervals.

Statistical Analysis. Results are expressed as means ± S.E.M. Basal colonic motility, gastrocolonic response latencies, and peristaltic reflex latencies were compared using the paired two-tailed Student’s t test. The magnitude of the mechanoreceptor-mediated gastrocolonic response and that of the peristaltic reflex were compared using the Student’s t test. P < 0.05 defined statistical significance.

Results

All subjects tolerated the studies well. No significant changes in blood pressure, pulses, oxygen saturation, or respiratory rate were noted.

Basal Colonic Tone. All subjects tolerated placement of the barostat catheter well and did not perceive inflation of the recording barostat bags in the colon. The mean operating pressure was 12.1 ± 1.0 mm Hg with minimal interindividual differences. Under control conditions, the mean basal barostat bag volumes were similar (P > 0.05) after nizatidine (105 ± 13 ml), famotidine (102 ± 12 ml), and placebo (108 ± 16 ml).

Gastrocolonic Response Assessment: Gastric Mechanoreceptor Activation. Inflation of the antral balloon resulted in reproducible decreases in the colonic recording barostat bag volume with a latency of onset of 60 to 90 s, indicative of increased colonic motor activity in all subjects (Fig. 1). Antral distension evoked volume-dependent increases in colonic motor activity with a maximal effect observed at an inflation volume of 300 ml (Fig. 2, P < 0.05). After nizatidine administration, changes in colonic motor activity in response to antral distention at 200 and 300 ml were markedly enhanced (Fig. 2, P < 0.05). In contrast, there were no differences in increases in colonic tone between placebo and famotidine at all three volumes of antral distention (Fig. 2, P < 0.05).

Peristaltic Reflex Assessment. Inflation of the stimulus balloon in the descending colon resulted in reproducible increases in colonic motor activity orad to the stimulus (i.e., an ascending contraction; Fig. 3A) and a biphasic response caudal to the stimulus, consisting of an initial decrease in motor activity followed by an increase in motor activity (i.e., the descending responses; Fig. 3B).
Ascending Contraction. Inflation of the colonic stimulus balloon produced increases in colonic motor activity orad to the stimulus with a mean latency of $9 \pm 0.3$ s. The inflation produced volume-dependent decreases in the orad recording barostat bag volume, which were further enhanced by nizatidine (Fig. 4, $P < 0.05$). The volume reduction was significantly larger after nizatidine administration at distending volumes of 60 and 90 ml (Fig. 4, $P < 0.05$). In contrast, there were no significant differences between famotidine and placebo at all distending volumes.

Descending Responses. Inflation of the colonic stimulus balloon produced a biphasic response in the caudad recording barostat bag: an initial relaxation (mean latency $7 \pm 2$ s) followed by contractions (mean latency $20 \pm 3$ s). Following placebo infusion, the maximal descending relaxation was observed after a 30-ml inflation of the stimulus balloon, which produced volume increases in the caudad recording barostat bag of $5 \pm 2$ ml (Fig. 5). Administration of famotidine or nizatidine did not have any significant effects on the descending relaxation evoked by colonic distension at 30, 60, and 90 ml (Fig. 5).

Stimulus balloon inflation produced volume-dependent descending contractions after the relaxation phase. Maximal volume reduction of the caudad recording barostat bag volume was $70 \pm 15$ ml, measured after the 90-ml stimulus inflation. Famotidine did not alter the magnitude of increases and subsequent decreases in the caudad recording barostat bag volume in response to stimulus balloon inflation (Fig. 6). In contrast, nizatidine evoked significantly larger reductions in recording bag volume compared with famotidine and placebo at each distending volume (Fig. 6, $P < 0.05$).

Discussion

Studies in experimental animals have shown that nizatidine, an $H_2$-receptor inhibitor, may enhance stomach and small bowel motility (Ueki et al., 1993, 1999; Zarling, 1999),
and accelerate gastric solid emptying to a degree similar to that observed with cisapride in rats (Ueki et al., 1999; Zarling, 1999). Similar results were observed in humans. In a crossover study, Harasawa and Miwa (1993) reported that a 150-mg oral dose of nizatidine accelerated the gastric emptying rate in patients with gastric ulcer. This effect was observed as early as 45 min after administration of the medication. Chey and colleagues (1995) also reported that nizatidine (150 mg) given orally shortened the duration of the migrating motor complex, which was prolonged in patients with gastroesophageal reflux.

The prokinetic property of nizatidine seems to be independent of its effects on acid secretion. Although suppression of gastric acid secretion removes the feedback mechanism that slows gastric emptying in the small intestine (Cooke, 1974; Houghton et al., 1990), other H₂ blockers such as ranitidine, cimetidine, and famotidine in equivalent therapeutic doses for acid suppression do not exhibit prokinetic effects (Zarling, 1999). Recent studies indicate that the prokinetic action of nizatidine is due to its anticholinesterase activity (Kounenis et al., 1988; Parkman et al., 1998). Using an in vitro preparation of acetylcholinesterase from human erythrocytes, Ueki and colleagues (1993) demonstrated that nizatidine inhibited this enzyme in a non-competitive fashion. These investigators also showed that the gastroprokinetic activity of nizatidine could be antagonized by atropine. Further studies on guinea pig antral smooth muscle demonstrated that nizatidine dose dependently increases the amplitude and frequency of spontaneous phasic contractions, which are abolished by atropine (Parkman et al., 1998). Taken together, these observations suggest that nizatidine stimulates gastric motility via a cholinergic-dependent pathway. It is interesting to note the effects of nizatidine on gastrointestinal motility were similar to that of neostigmine (Ueki et al., 1993), even though its acetylcholinesterase activity was less potent than neostigmine. It would be worthwhile to investigate the effect of neostigmine in humans. However, because of its known side effects, it was not studied in the current studies.

In the present study, we evaluated the prokinetic action of nizatidine in the human colon. We examined the effects of nizatidine on neural responses mediating colonic motility at two levels: 1) long neural arcs mediating colonic motility, which involve neural structures extrinsic to the...
wall of the colon; and 2) local reflex arcs, such as the peristaltic reflex, which are mediated by enteric nerves within the colonic wall itself.

The gastrocolonic response is the contractile response that occurs throughout the colon after the ingestion of a meal. It consists predominantly of an early phase of increased colonic motor activity in the first 10 to 30 min postprandially, followed by a second phase more than an hour after completion of the meal (Weber and Ducrotte, 1987). The immediate colonic contractile phase is mediated by activation of gastric wall mechanoreceptors and can be reproduced by distension of a gastric balloon, as was performed in the current study. This phase is followed by an intestinal phase in which colonic motility is stimulated by duodenal delivery of nutrients (Wiley et al., 1988). The early gastric phase is completely abolished by atropine, indicating mediation by extrinsic cholinergic neural pathways, whereas the intestinal phase is only partially blocked by atropine, suggesting the involvement of a more complex set of mediators. Thus, because it is mediated solely by extrinsic cholinergic neural pathways, we chose to evaluate only the gastric phase of the gastrocolonic response. In our studies, the typical gastrocolonic response showed an increase in phasic colonic motor activity and a decrease in baseline barostat bag volume, indicative of increased tone. In calculating the average bag volumes, we did not attempt to factor out the phasic activity, but rather calculated the overall average for the interval. These values, therefore, actually represent a combination of phasic and tonic activity. Our studies showed that nizatidine significantly enhanced the colonic response to gastric distension at 200 and 300 ml. This is not surprising as nizatidine possesses antiacetylcholinesterase properties, and the gastric phase of the gastrocolonic response is mediated by a cholinergic pathway.

Nizatidine also enhances the colonic peristaltic reflex, a reflex characterized by an ascending contraction proximal to a distending stimulus and a descending relaxation distal to the stimulus, which has been suggested to mediate aboral propulsion of feces in the colon. This reflex involves a complex interaction of intrinsic neural pathways (Grider and Makhlouf, 1990). The primary mediators of the ascending response appear to be the acetylcholine and the tachykinins, whereas vasoactive intestinal polypeptide and nitric oxide mediate the descending component (Grider and Makhlouf, 1986; Grider, 1989a,b, 1992). Hence, it is not unexpected that nizatidine with its antiacetylcholinesterase properties (Ueki et al., 1993; Parkman et al., 1998) enhances the peristaltic contractions in response to balloon distension, but has no effect on the caudal relaxation.

In conclusion, nizatidine appears to exert prokinetic action in the human colon. The agent augments the neural circuits for both the extended gastrocolonic reflex and the local colonic peristaltic reflex, which use acetylcholine as a neurotransmitter. In this manner, nizatidine may facilitate the movement of fecal matter in the colon and enhance colonic transit. Further research in this area may lead to novel treatments for idiopathic constipation.

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