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GR 38032F (Ondansetron), A Selective $5HT_3$ Receptor Antagonist, Slows Colonic Transit in Healthy Man

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The newly recognized class of 5-hydroxytryptamine receptors ($5HT_3$) may be involved in the induction of nausea, since their pharmacological antagonists are effective against emesis induced by chemotherapy. $5HT_3$ receptors are present on enteric neurons, and $5HT_3$ blockers may produce mild constipation; we thus hypothesized that $5HT_3$ receptors would modulate colonic motility. To determine if GR 38032F, a selective $5HT_3$ antagonist known to have antiemetic effects, influences colonic transit in health, a randomized, double-blind, placebo-controlled crossover study was performed. Using a radiopaque marker technique, colonic transit was quantified in 39 healthy volunteers (19 men, 20 nonpregnant women) 18–70 years of age. On a standard 25-g fiber diet, 16 mg of GR 38032F was given orally thrice daily. Gastrointestinal peptides (peptide YY, human pancreatic polypeptide, neurotensin, motilin, gastrin-cholecystokinin, substance P) were also measured in plasma fasting and postprandially. Mean total colonic transit time on placebo was 27.8 hr, while on GR 38032F it was 39.1 hr ($P < 0.0005$). Transit times through the left colon ($P < 0.0005$) and rectosigmoid ($P < 0.05$) were prolonged by the drug, but right colonic transit was not significantly altered. Transit times did not correlate with age or gender, but subjects with shorter transit times were significantly more affected than were those with longer transit times. The peak release of peptide YY was minimally decreased following GR 38032F ($P < 0.01$), but the peak and integrated postprandial responses of human pancreatic polypeptide, neurotensin, motilin, gastrin–cholecystokinin, and substance P were not significantly altered by the drug. We conclude that $5HT_3$ receptors may be involved in the regulation of colonic transit in healthy man.

KEY WORDS: colonic transit; gastrointestinal peptides; $5HT_3$ antagonists.

Serotonin (5-hydroxytryptamine) has been shown to cause contraction of the guinea pig ileum by direct activation of smooth muscle cells and indirectly by the release of acetycholine from intramural cholinergic neurons (1). Gaddum and Picarelli reported that the serotonin receptors located on the smooth muscle cells could be blocked by dibenzyline and that acetylcholine release from the intramural cholinergic neurons could be antagonized by morphine (2). These data suggested that pharmacologically distinct serotonin receptor subtypes existed. Later reports identified serotonin-type 1 ($5HT_1$), serotonin-type 2 ($5HT_2$), and serotonin-type 3 ($5HT_3$) receptors in various animal models (3–5); $5HT_3$ receptors have been identified in the central nervous system (5) and on postganglionic autonomic (6), enteric (7) and sensory neurons (8). A new class of drugs, the $5HT_3$ receptor antago-

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TABLE 1. EFFECT OF GR 38032F ON SEGMENTAL COLONIC TRANSIT TIMES IN HEALTHY VOLUNTEERS (N = 39)

	Colonic transit time in hours [hr, mean SEM]		
Segment	*GR 38032F*	*Placebo*	*Probability (paired t test)*
Right Colon	9.6 (1.3)	7.8 (1.6)	0.17
Left colon	15.1 (1.7)	8.6 (1.1)	0.0002
Rectosigmoid	14.3 (2.1)	11.2 (1.9)	0.049
Total	39.1 (3.2)	27.8 (3.0)	0.0002

nists, have subsequently been developed. Recent reports have suggested that these agents may act as antiemetics (9) and anxiolytics (10). Therefore, given the location of the $5HT_3$ receptors on the postsynaptic enteric nerves and the postganglionic autonomic nerves, we reasoned that $5HT_3$ receptors might regulate lower gastrointestinal tract motility. We therefore sought evidence of an effect of $5HT_3$ receptor antagonists on the colon.

We aimed to assess the effect of oral ondansetron (GR 38032F), a selective $5HT_3$ receptor antagonist, on colonic transit in normal volunteers. We also aimed to determine if $5HT_3$ receptor blockade altered the release of specific peptides that may regulate gastrointestinal motility.

MATERIALS AND METHODS

Twenty men and 20 women (age range 18–70 years) took part in a randomized, double-blind, placebo-controlled crossover trial. All were healthy volunteers who had no history of gastrointestinal disease or surgery, were not taking any medications, and had a normal bowel habit. Informed consent was obtained from all subjects, and the protocol was approved by the Institutional Review Board of Mayo Clinic.

Subjects were prescribed a standard 25-g fiber diet, to begin two days prior to being randomized to receive either GR 38032F (16 mg three times a day) or placebo. A dose of 16 mg three times a day was chosen because it was the maximum dosage that could be used, based on the available safety data (11). To measure colonic transit, 20 radiopaque markers were ingested under supervision on three consecutive days. On the fourth day, a single abdominal x-ray film was obtained, and transit times of the right colon, left colon, rectosigmoid, and entire colon were assessed using a previously validated, single-film method (12, 13). Diary cards, which recorded bowel habit and any side effects of the drug, were completed daily.

After a washout period of one week or more, the study was repeated exactly as before, but with subjects crossing over between active drug and placebo. One male subject was excluded from the study, since the drug and placebo were taken concurrently. This left 39 subjects for analysis. A full blood count, urea, creatinine, electrolytes, and liver function tests were performed before entry to and during the study.

Twenty subjects were randomly selected, for additional analysis; 10 were younger than 40 years of age (five males, five females) and 10 were 40 years of age or older (five males, five females). Blood samples were collected for the measurement of gastrointestinal peptide hormones, fasting and for 120 min after a standard breakfast (25% of total daily calories: 30 cal/kg body weight; 20% protein, 30% fat, 50% carbohydrate) on the morning of the fourth day. The following peptides were measured: peptide YY, human pancreatic polypeptide, neurotensin, motilin, and gastrin–cholecystokinin. In addition, substance P was measured in four subjects following drug and placebo.

Each of the three segmental transit times in the colon and total colonic transit times (the sum of all segments) was tested for the presence of an order effect. The postprandial hormone response was summarized by first transforming individual values at each time point to a log scale for analysis. The areas under the log concentration–time curve and the peak (log) response were then analyzed. In the absence of a significant order effect, the overall differences in transit times and hormone responses (drug vs. placebo) were analyzed using the paired t test.

Total transit times and the integrated and peak postprandial responses of the hormones were also analyzed using a linear regression model: $Y = \alpha + \beta * X +$ other covariates (baseline values, age, sex), where Y is the response on drug and X is the response on placebo. This more general form of the paired t test adjusts for the possible influence of covariates and tests for a nonzero intercept (α) and whether the slope (β) deviates from 1. The usual paired t test compares the intercept to zero but assumes the slope to be 1 and does not adjust for covariates. All P values calculated were two tailed.

RESULTS

Total colonic transit times were significantly delayed by GR 38032F when compared with placebo treatment (Table 1). This effect was most marked in the left colon. Age and gender did not significantly correlate with changes in transit times in reference to the drug. No significant order effects were de-

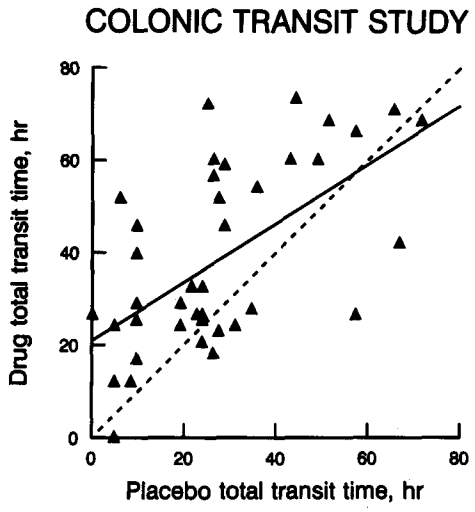

Fig 1. Regression of total colonic transit time following GR 38032F against total colonic transit time following placebo. Each triangle identifies a subject. The solid line is the regression; the broken line is the line of identity [$y = x$].

tected. The reported mean number of stools per day on GR 38032F was 1.7 (range 0.3–4) compared with 1.8 on placebo (range 0.8–4).

The regression of total colonic transit time when taking GR 38032F against total transit time when taking placebo gave an intercept greater than zero and a slope less than 1 (Figure 1). This indicates that subjects with short transit times on placebo were affected more by the drug than were subjects with long transit times on placebo ($P < 0.05$).

Responses of the gastrointestinal peptides to the drug are summarized in Table 2. The peak postprandial value of peptide YY was significantly altered by GR 38032F; those with lower peak values on placebo had higher values after the drug, while those with higher values on placebo changed little (slope <1, $P < 0.01$). No other significant differences were detected. Substance P was not detectable in plasma after the drug or after placebo.

Of the 20 subjects in whom peptides were measured, 15 had slower total colonic transit times on drug than placebo. We failed to detect an association between change in transit times and change in peptide levels, indicating that those who had slowed transit and those who did not had similar peptide responses.

There were no changes in routine laboratory tests that could be attributed to GR 38032F. Only one subject complained of constipation and mild crampy lower abdominal discomfort, and one subject developed intercurrent pneumonia while taking GR 38032F. No other side effects were reported.

DISCUSSION

Our results suggest that 5HT$_3$ receptors can influence colonic transit in man. In the present study, we assessed sufficient numbers of patients so that differences in total colonic transit or in individual segmental transit times could be identified; moreover, any possible effects of age or sex could be quantified. Furthermore, the crossover design meant that each subject acted as his or her own control, thereby increasing the power of the study. We also tested for an order effect; if such were present, any measurements of transit might be contaminated with the residual effects of the treatment given first. Since no significant order effects were detected, comparisons of drug and placebo within subjects was valid (14).

To our knowledge, there are no published studies of 5HT$_3$ antagonists and colonic function, although 5HT$_3$ antagonists may be associated with constipation (11), which implies an effect on the large bowel. The physiological roles of receptors for 5HT$_3$ are

TABLE 2. GASTROINTESTINAL PEPTIDE RESPONSES AFTER ORAL GR 38032F FOR 3 DAYS (16 MG THREE TIMES A DAY) AND PLACEBO ($N = 20$) MEDIAN (INTERQUARTILE RANGE: 25–75%)

	Postprandial integrated responses (ng/ml) over 120 min		*Peak response (pg/ml)*		*Time to peak response (min)*	
Peptides	*Drug*	*Placebo*	*Drug*	*Placebo*	*Drug*	*Placebo*
Peptide YY	4.1 (3–5)	4.4 (4–6)	88 (75–96)*	96 (80–127)	90 (30–143)	105 (60–120)
Human pancreatic polypeptide	13.5 (8–17)	11.0 (6–20)	334 (192–402)	272 (157–447)	30 (15–75)	15 (15–75)
Neurotensin	8.5 (6–12)	8.1 (6–11)	175 (124–218)	171 (130–211)	60 (30–120)	90 (60–143)
Gastrin-CCK	5.1 (4–8)	5.0 (4–8)	105 (79–151)	114 (88–148)	60 (30–113)	45 (30–83)
Motilin	9.6 (8–14)	9.9 (8–14)	217 (138–283)	206 (158–269)	15 (15–98)	15 (15–30)

*Linear regression analysis indicated an effect of drug ($P < 0.01$)

undefined, but $5HT_3$ antagonists are effective in the prophylaxis of emesis induced by chemotherapy (9), and they may have direct effects on the upper gut, although information is conflicting (15, 16). In this study the most striking slowing of colonic transit was noted in the left colon; thus, we postulate that the left colon may have the highest density of $5HT_3$ receptors in the large bowel.

The effects of GR 38032F on the release of peptides are less readily explained. Peptide YY is localized exclusively in the ileocolonic region (17), and the colon and rectum are the major source of circulating levels in man (18). The mechanism of GR 38032F's inhibition of peptide YY peak release postprandially is not established but is presumably mediated by $5HT_3$ receptors. We have also reported that although small intestinal transit and mouth-to-cecum transit were unaffected by a single intravenous dose of GR 38032F, the release of peptide YY was reduced (19). The clinical importance of this finding is likely to be minor, however, as the absolute reduction in peptide YY levels was so small.

Substance P and serotonin are both contained within the intestinal mucosa and also coexist within the same synaptic vesicles in the brain (20, 21). For this reason, we measured substance P levels in plasma following $5HT_3$ receptor blockade; although substance P was not detectable, we have not excluded an alteration in local release of this peptide (ie, a paracrine effect).

The present study suggests that this $5HT_3$ antagonist can modify colonic transit, although it has no effect on gastric emptying or small bowel transit (19). These data have been confirmed in abstract form by others (22); however, the underlying mechanisms and clinical significance must await further investigation.

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