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Omeprazole-induced slowing of gastrointestinal transit in mice can be countered with tegaserod

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Abstract

Omeprazole, besides suppressing gastric acid, causes delayed gastric emptying, which may be associated with aggravated dyspeptic symptoms. Effects of omeprazole on small intestinal transit are unknown. In this study, we evaluated in mice if (a) omeprazole affects transit of a meal through the stomach and small intestine and (b) co-treatment with the promotility agent, tegaserod, can prevent the slowing effect of omeprazole. Omeprazole (40–150 mg/kg, i.p. once daily for 5 days) delayed gastric emptying of the meal in a dose-related manner. Small intestinal transit was then evaluated at the lowest dose of omeprazole (40 mg/kg) that did not retard gastric emptying. Such transit was significantly delayed after this dose of omeprazole compared with vehicle-treated controls. When tegaserod (0.10 mg/kg) was administered concomitantly with the omeprazole, small intestinal transit of the meal was not slowed and was not different from controls. These results show that omeprazole reduces aboral transit of luminal contents through the stomach and small bowel of mice and that this delay is reversed by tegaserod.

Keywords: Omeprazole; Tegaserod; Small intestinal transit

1. Introduction

Proton pump inhibitors suppress gastric acid secretion and are currently the most effective pharmacological agents for treating patients with gastroesophageal reflux disease. Omeprazole, a substituted benzimidazole, was the first proton pump inhibitor available clinically and has been extensively studied for both efficacy and safety (Richardson et al., 1998). Of note, in several studies evaluating short-term treatment with omeprazole, the investigators reported that it caused a delay in gastric emptying of solid meals in healthy subjects (Rasmussen et al., 1991; Benini et al., 1996; Parkman et al., 1998). In some of the omeprazole studies, specimens of gastric and small intestinal contents showed increased microbial colony counts mainly of oral type flora but sometimes accompanied by excessive numbers of bacteria usually only found in distal small intestine and colon (Thorens et al., 1996; Pereira et al., 1998; Mitsui et al., 2003; Woosley, 2004). Decreased bactericidal activity of gastric contents, owing to reduced acidity caused by omeprazole, is the usual explanation for proximal gastrointestinal bacterial overgrowth during therapy with proton pump inhibitors. Another contributing factor may be the concomitant delaying effect of omeprazole on gastric emptying and a potential decrease in small intestinal motility, which is suggested by presence of organisms normally restricted to the distal bowel. Thus, reduced luminal clearance may also play a role. However, the effects of omeprazole on small bowel motility or transit are unknown. We hypothesized that omeprazole causes a delay in both gastric and small bowel emptying. Quantification of the effects of omeprazole on gastric emptying and small bowel transit is the first area

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evaluated in the current study. If such an adverse effect of omeprazole is documented, one would like to define a way to correct the abnormality since the acid-suppressing effect of the drug is clinically valuable. Therefore, the second area evaluated in this investigation was the hypothesis that one can reverse or prevent any slowing effect of omeprazole on upper gastrointestinal motility by concomitant treatment with a promotility agent. For this, we chose tegaserod, an aminoguanidine indole derivative, which is a potent partial agonist at serotonin type-4 (5-HT_4) receptors in the gastrointestinal tract. Pharmacodynamically, tegaserod has been shown to cause a strong promotile effect on both the stomach and small intestine. In vitro, tegaserod enhances peristalsis in human, rat and guinea pig intestine (Grider et al., 1998). In vivo, tegaserod accelerates gastric emptying and small bowel transit in humans (Prather et al., 2000; Camilleri, 2001; Degen et al., 2001). Accordingly, we tested whether addition of tegaserod would counteract any slowing effect of omeprazole on transit of a test meal through the upper gastrointestinal tract. The specific aims of this study were thus threefold: first, in a standard mouse model of gastrointestinal transit, to confirm that omeprazole slows gastric emptying; second, to determine the effects of omeprazole on small intestinal transit, and third, to test the hypothesis that concomitant administration of tegaserod will attenuate any adverse effect of omeprazole on gastric and small intestinal motility.

2. Materials and methods

2.1. Animals

Male Swiss albino mice (Ace Laboratories, Boyertown, PA) weighing 25–30 g were used. The animals were housed 5 per cage with free access to food and water. A standard light–dark cycle was maintained with a timer-regulated light period from 7 a.m. to 7 p.m. The experimental procedure was approved by Temple University Institutional Animal Care and Use Committee.

2.2. Compounds tested

Omeprazole was purchased from Sigma (St. Louis, MO). Tegaserod hydrogen maleate was provided by Novartis Pharmaceuticals (East Hanover, NJ). Both compounds were suspended in 1% Tween 80 in saline. Preliminary experiments determined that Tween 80 was the most suitable suspending agent as it did not itself affect gastrointestinal transit in the animal model used. The suspension was injected i.p. in a dose volume of 0.25 ml/25 g mouse. The amount of tegaserod refers to the free base.

2.3. Dosing schedule

Four groups of 18–20 (gastric emptying) and 15 (small intestinal transit) mice were used. The animals received one i.p. injection each day for 5 consecutive days according to the schedule outlined below. The doses of tegaserod and omeprazole were based on published animal research data for omeprazole (e.g., Carlsson et al., 1986) and that provided by Novartis Pharmaceuticals for tegaserod.

(a) Vehicle
(b) Tegaserod (0.10 mg/kg)
(c) Omeprazole (40 mg/kg up to 150 mg/kg for gastric emptying and only 40 mg/kg for intestinal transit)
(d) Tegaserod (0.10 mg/kg)+omeprazole (40 mg/kg)

2.4. Quantification of transit

2.4.1. Gastric emptying

Food was withheld from the mice at 18 h before the final dose of omeprazole or vehicle. At 1 h after the final injection, each animal received a weighed and measured amount (0.50 ml) of a carbohydrate- and protein-rich semisolid meal via gavage (Osinski et al., 2002) and was then killed by cervical dislocation 1 h later. The abdomen was immediately opened, the stomach excised, and weighed both before and after removal of gastric contents. Results are expressed as percentage of food remaining in the stomach 1 h after feeding.

2.4.2. Small intestinal transit

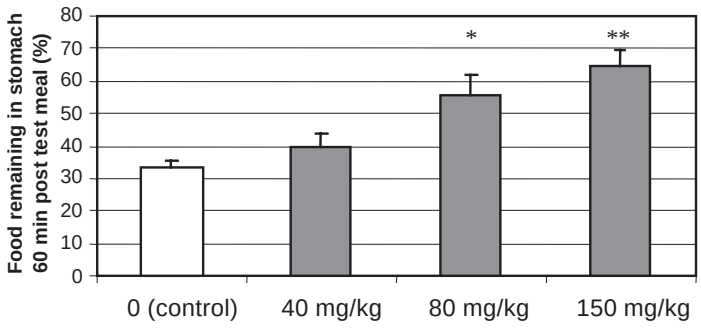
For measurement of small intestinal transit as described by Vogel (2002), the food was also withdrawn from the mice 18 h before the last drug injection. Immediately following the injection, the mice received an opaque liquid meal (0.50 ml/25 g mouse) by stomach tube. This test meal consisted of charcoal, wheat flour and water in a 1:2:6 weight–volume ratio. Thirty minutes later each mouse was killed by cervical dislocation. The abdomen was immediately opened, the small intestine excised and its length measured on a transillumination stage. The distance traveled by the opaque meal along the intestine from the pyloric sphincter during the 30 min was measured and calculated as a percentage of the total small intestinal length. Results of the treatments were compared using an analysis of covariance model with the total length of the small intestine and treatment as covariates.

3. Results

By general inspection, all active drug-treated and placebo-treated mice appeared behaviorally normal through the full duration of the experiment. There was no evidence of diarrhea and drug treatment did not result in any deaths. Under the conditions of this study, omeprazole produced a dose-dependent delay in gastric emptying, which is shown in Fig. 1.

However, the lowest omeprazole dose of 40 mg/kg did not cause a statistically significant change from placebo in gastric emptying measured as percentage of food remaining in the stomach 1 h post test meal (T_{60}). Accordingly, this dose of omeprazole was used to assess small bowel transit since it did not significantly alter entry of gastric contents into the duodenum compared to placebo omeprazole, i.e., vehicle injection.

Daily dosing of mice with omeprazole at 40 mg/kg for 5 days significantly decreased the percentage of the small intestine



Mean percent of food remaining in the stomach at T_{60} + S.E.M. in groups of 18–20 mice after 5 daily doses of the treatment indicated. Gastric emptying of mice treated with omeprazole 40 mg/kg was not different from that of control animals (P = 0.3231).

* P = 0.0058 compared with control group.

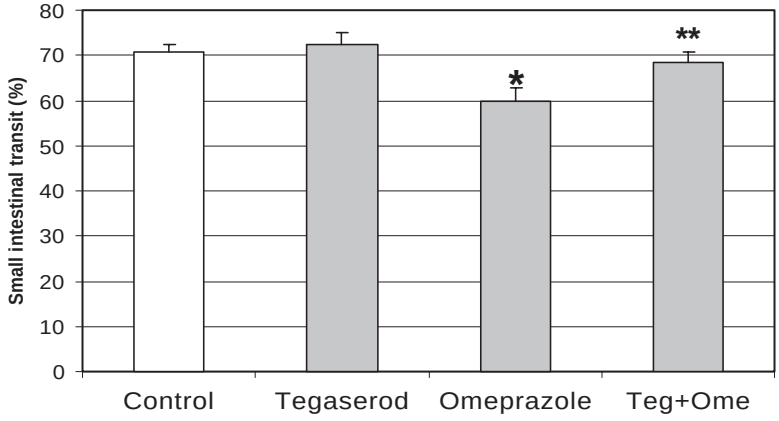
** P < 0.001 compared with control group.

Fig. 1. Effect of omeprazole on gastric emptying in mice.

traveled by the test meal compared to that obtained in mice receiving injections with the vehicle only (59.89±2.92% vs. 70.59±1.86%; mean±S.E.M.; $P=0.002$) (Fig. 2). Travel along the small intestine was not significantly affected in animals receiving tegaserod alone (72.51±2.4%). Combined treatment with tegaserod+omeprazole caused a significant increase in the percentage of the small intestine traveled compared with the omeprazole alone-treated group (68.57±2.13% vs. 59.89±2.92%; $P=0.0108$). The enhanced transit was such that the distance traveled in the combined treatment group was not statistically different from that of the vehicle control group.

4. Discussion

Treatment of mice with omeprazole once-daily for 5 consecutive days caused delayed passage of a test meal out



Mean percent of small intestine traveled + S.E.M. by a charcoal meal in groups of 15 mice after 5 daily doses of the treatment indicated.

* P = 0.002 compared with control group.

** P = 0.0108 compared with omeprazole-treated group.

Fig. 2. Small intestinal transit in mice treated with omeprazole, tegaserod, and their combination.

of the stomach and less distance aborally along the small intestine in relation to the extent of meal transit observed in vehicle control animals. These results confirm that omeprazole can impair gastric emptying in this rodent model for assessing gut transit. Utilizing a dose of omeprazole that did not affect the rate of gastric emptying, we found that transit of the test meal down the small intestine was also delayed by omeprazole. Thus, a dose of omeprazole, which was too low to adversely affect gastric emptying, did cause slow small intestinal transit. These results suggest that doses of omeprazole, which delay gastric emptying in humans, are also likely to produce slowing of aboral transit of luminal contents in the small bowel.

The exact cause for the delay in upper gastrointestinal tract emptying observed during omeprazole treatment is not certain. However, the same explanations for this effect invoked by investigators who report delayed gastric emptying in humans treated with omeprazole can be considered. The reasons are based largely on potential consequences of omeprazole-induced suppression of gastric acid. These include:

1) inadequate hydrolysis of food causing persistence of particles in the stomach that are too large to be passed quickly through the pyloric sphincter;
2) increased intraluminal pH leading to enhanced secretion of gastrin, which antagonizes gastric emptying, and,
3) decreased fluid secretion into the stomach, which increases viscosity and possibly delays emptying of gastric contents (Parkman et al., 1998). Collectively, these three events may retard the passage of a meal through the pylorus and reduce availability for small intestinal transit. These changes, as well as alterations in other mechanisms that modify small bowel motility, such as release of various gastrointestinal hormones (Harmar, 2004; Hornby and Prouty, 2004; Tebbe et al., 2004) could also contribute to the observed slowing of small bowel transit. Further specific investigations are needed to define the role for potential contributors such as gut hormones.

A key finding in this work is the demonstration that tegaserod, a potent partial agonist of serotonin 5-HT_4 receptors located in the gastrointestinal tract, prevents the upper gastrointestinal transit-slowing effect of omeprazole and returns to normal aboral movement of luminal contents along the small intestine. Tegaserod is well established clinically. It is approved in the USA and many countries worldwide for treating men and women with chronic constipation as well as women with irritable bowel syndrome whose main symptom is constipation. The possibility therefore deserves consideration as to whether or not concomitant administration of tegaserod with proton pump inhibitors such as omeprazole will prevent potentially adverse gastrointestinal tract consequences, such as bacterial overgrowth and certain gastrointestinal dysmotility or dyspeptic symptoms described in patients chronically treated with proton pump inhibitors (Thorens et al., 1996; Nelson et al., 2000; Richter et al., 2000).

In summary, our data show that omeprazole can delay upper gastrointestinal transit of food in mice and that this effect is reversed by tegaserod. Clinical investigations now seem warranted to establish if this therapeutic combination can prevent a similar effect of omeprazole in humans and prevent development of any associated symptoms and conditions.

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