Regional Gastrointestinal Absorption of Ranitidine in the Rat

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Purpose. Ranitidine absorption from isolated segments of rat small intestine (duodenum, midgut, and terminal ileum) was investigated to examine the influence of pH and 50% bile, and to determine if ranitidine is absorbed preferentially from a specific region. Methods. Ranitidine (50 mg/kg) was administered into each segment in pH 5 or pH 7 buffer, or in 50% bile. Venous blood was collected at various times for 40 min from the right jugular vein. Results. When ranitidine was administered in pH 7 buffer or in 50% bile, \(C_{\text{max}}\) and AUC\(_{0-40}\) were significantly greater after administration into the terminal ileum compared to the duodenum and midgut. AUC\(_{0-40}\) was significantly greater when ranitidine was administered in pH 5 buffer or in 50% bile into the duodenum compared to the midgut. \(C_{\text{max}}\) was significantly different between ranitidine administration into the duodenum and midgut only when ranitidine was administered in 50% bile. Ranitidine administration in pH 5 buffer significantly decreased AUC\(_{0-40}\) and \(C_{\text{max}}\) after administration into the midgut, and AUC\(_{0-40}\) after administration into the terminal ileum compared to administration with pH 7 buffer or in 50% bile. Bile had no significant effect on AUC\(_{0-40}\) after ranitidine administration into the duodenum and midgut compared to administration in pH 7 buffer. However, bile significantly increased AUC\(_{0-40}\) and \(C_{\text{max}}\) after ranitidine administration into the terminal ileum compared to administration with pH 7 and pH 5 buffer. Conclusions. Results suggest that ranitidine is absorbed from the entire small intestine. However, the terminal ileum is the optimal site of gastrointestinal absorption. Furthermore, bile enhances ranitidine absorption from the terminal ileum.

KEY WORDS: ranitidine; intestinal absorption; pharmacokinetics; bile.

INTRODUCTION

Ranitidine is a histamine H\(_2\)-receptor antagonist that exhibits secondary peaks in the oral concentration-time profile after a single dose in humans (1–4) and in rats (5). Proposed mechanisms responsible for this phenomenon include enterohepatic recirculation and delayed gastric emptying of a portion of the oral dose (6). Less than 2% of an oral dose is recovered in the bile as ranitidine in humans (7), and as ranitidine and its metabolites in rats (5). Therefore, enterohepatic recirculation of ranitidine or its metabolites does not contribute significantly to the occurrence of secondary peaks in oral concentration-time profiles in these species.

Double peaks in the concentration-time profiles after direct administration of ranitidine into the duodenum and jejunum of human subjects (8) indicated that factors other than gastric emptying are responsible for secondary peaks. Other possible mechanisms of the double-peak phenomenon include post-absorptive storage and release of drug (9), and discontinuous or site-specific gastrointestinal (GI) absorption (10–14).

Pharmacokinetic models incorporating discontinuous (10) and site-specific (12,13) GI absorption have been fit to concentration-time profiles evidencing double peaks. However, limited physiologic data are available to support the existence of discontinuous or variable GI absorption of histamine H\(_2\)-receptor antagonists as described by these pharmacokinetic models. Regional preferences in ranitidine GI absorption have been demonstrated in humans. Ranitidine was absorbed more efficiently in the lower small intestine than in the upper small intestine in one human subject (15). Recently, Grammaté and coworkers (16) demonstrated that ranitidine absorption was more efficient from the upper and lower small intestine than from the middle small intestine. Cimetidine, a histamine H\(_2\)-receptor antagonist that also exhibits double peaks in oral concentration-time profiles, has been shown to be absorbed more efficiently from isolated segments of rat ileum and duodenum than from isolated jejunum segments in situ (17). However, interpretations of regional differences in gut permeability to cimetidine were confounded by the effects of varying pH and composition of luminal contents.

The composition of the luminal contents may be an important factor influencing the GI absorption of many compounds. Mixed micelles of bile acids enhanced GI absorption of heparin (18), streptomyacin and gentamycin (19), and sulfaguanidine and sulfanilic acid (20) due to enhanced permeability of the intestinal wall in situ. In contrast, the presence of bile acids and mixed micelles of bile acids inhibited the GI absorption of quinine and imipramine in situ (20) and nadolol in situ and in vivo (21). Interaction of each drug with bile micelles was the proposed mechanism for inhibition of GI absorption. Although biliary excretion of ranitidine is minor, intact bile flow has been shown to impair ranitidine absorption in rats in vivo (5). The mechanism(s) by which bile and/or bile flow alter the GI absorption of ranitidine has not been elucidated.

The present study was undertaken to determine if region-dependent absorption of ranitidine occurs in the rat small intestine. Furthermore, the influence of the composition of the luminal contents (pH and the presence of bile) on the GI absorption of ranitidine was investigated.

METHODS

All chemicals used in this study were of reagent grade. Ranitidine HCl was provided by Glaxo Research Institute (Research Triangle Park, NC). Blank bile was collected from naive male Sprague-Dawley rats anesthetized with urethane (1 g/kg i.p.). Bile was collected for one hour after bile duct cannulation, and frozen. On the day of each experiment, blank bile from several rats was thawed, pooled, and diluted to 50% with purified water.

Ranitidine HCl (30 mg/ml) was prepared in the following
dosing solutions: 50 mM phosphate buffer (pH 7), 50 mM phosphate buffer (pH 5), and 50% bile (pH 7). Blank 50 mM phosphate buffer was prepared and the pH was titrated to the pH of the dosing solution used in each experiment. After pH titration, the osmolality of all solutions introduced into the intestinal lumen was measured with a vapor pressure osmometer (Wescor, Inc., Logan, UT) and adjusted to 300 ± 15 mmol/kg with NaCl. After the pH and osmolality of ranitidine in bile dosing solutions were adjusted, the solution was sonicated in a water bath at 37°C for 5 min. All solutions were warmed to 37°C prior to introduction into the intestinal lumen.

Male Sprague-Dawley rats (250–350 g) were fasted with free access to water overnight prior to the experiment. Rats were anesthetized with i.p. ketamine (60 mg/kg) and xylazine (12 mg/kg), and were warmed on a heating pad during the experiment. The right jugular vein was cannulated with silicone rubber tubing (0.037 in. o.d.) for venous blood collection. The small intestine was exposed through a midline incision, and the bile duct was cannulated with polyethylene tubing (P.E. 10). The small intestine was divided into 3 segments (=12 cm in length) and defined as duodenum: pylorus to 2 cm distal to the ligament of Treitz; mid-gut: =30 cm distal to the ligament of Treitz; terminal ileum: adjacent to cecum. The lengths of the intestine were estimated with a pre-measured piece of cotton thread, and one segment was cannulated in each rat. The proximal end of the segment was punctured with a 20-gauge needle, and a silicone rubber cannula with a polyethylene collar was inserted. The intestine was ligated around the polyethylene collar with silk thread. A small incision was made in the terminal end of the segment, and a flared piece of polyethylene tubing (P.E. 240) was inserted into the intestinal lumen. The distal end of the segment was ligated tightly around the polyethylene tubing with silk thread. The segment was flushed gently with blank buffer until the effluent was clear, then air (3 ml) was injected into the segment to remove residual buffer. Dosing solution was flushed quickly through the segment and collected in pre-weighed polypropylene tubes. Residual dosing solution was removed by gentle manual manipulation, the distal polyethylene cannula was removed, and the distal end of the segment was ligated. Ranitidine was dosed through the proximal cannula, the cannula was occluded with nylon filament, and the luminal contents were mixed by gentle manual manipulation. The ranitidine dose was 50 mg/kg administered in 1.67 ml dosing solution/kg body weight. The intestine was placed in the abdominal cavity, and the incision was covered with saline-soaked gauze. Venous blood was collected at 2.5, 5, 10, 20, 30, and 40 min after ranitidine dosing.

After the 40-min blood sample, the intestine was removed from the peritoneum and examined for color, pulsatile blood flow, and the presence of peristalsis. The rat was sacrificed with IV urethane, and the intestine was excised from the peritoneum. The intestines were laid flat on a metal surface, and the length of the intestinal segment was measured and recorded. Only data from rats with intestinal segments with a bright pink color, pulsatile blood flow, and noticeable peristalsis were used in data analysis. One small intestine segment was isolated in each rat, and ranitidine was dosed in 5 rats per segment with each dosing solution (n = 45 rats).

Ranitidine serum concentrations were analyzed by HPLC (5). The area under the serum concentration-time profile from 0 to 40 min (AUC_{0→40}) was calculated by the linear trapezoidal method. The maximum serum concentration (C_{max}) was determined by visual inspection of the concentration-time profile. Statistical analysis was performed by analysis of variance procedures (ANOVA) on PCSAS (SAS Institute, Cary, NC) with segment, dosing solution, and a segment by dosing solution interaction term as main effects. Univariate analysis indicated that the AUC_{0→40} data were not normally distributed. Therefore, AUC_{0→40} data were converted to logarithm values for statistical analysis. AUC_{0→40} and C_{max} were compared among dosing solutions within segments, and among segments within dosing solution with Duncan's correction for multiple comparisons.

RESULTS

Concentration-time profiles after ranitidine administration into isolated gut segments in pH 7 buffer, pH 5 buffer, and 50% bile are displayed in Figures 1, 2, and 3, respectively. Ranitidine metabolites were not detectable in the serum of any rats. AUC_{0→40} and C_{max} data are displayed in Table 1. Analysis of the data indicated the presence of a significant effect of intestinal length on AUC_{0→40} and C_{max} due to data obtained after administration of ranitidine in 50% bile into a 17-cm terminal ileum segment in one rat. When the AUC_{0→40} and C_{max} from that rat were normalized to 12 cm length, the significant length effect was no longer present. Therefore, the normalized AUC_{0→40} and C_{max} from that rat were used in data analysis, and the length effect was dropped from the ANOVA model.

AUC_{0→40} and C_{max} values were greatest after ranitidine administration into the terminal ileum under all dosing conditions. When ranitidine was administered in pH 7 buffer or in 50% bile, AUC_{0→40} and C_{max} were significantly greater after administration into the terminal ileum than after administration into the duodenum or midgut. AUC_{0→40} was significantly greater after ranitidine administration into the duodenum than into the midgut when administered in pH 5 buffer or in 50% bile. A significant difference in C_{max} between administration into the duodenum and midgut was