Regional Gastrointestinal Absorption of Ranitidine in the Rat[1]

A. Benjamin Suttle[2] and Kim L. R. Brouwer[3]

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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_{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_{max} was significantly different between 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_{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_{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, Gramatté 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 lumenal contents.

The composition of the lumenal contents may be an important factor influencing the GI absorption of many compounds. Mixed micelles of bile acids enhanced GI absorption of heparin (18), streptomycin 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 lumenal 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

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[2] Present address: Zeneca Pharmaceutials, Wilmington, DE.

[3] To whom correspondence should be addressed at Ph.D. Division of Pharmaceutics, School of Pharmacy C.B.#7360, Beard Hall, Room 23, The University of North Carolina at Chapel Hill Chapel Hill, NC 27599-7360.

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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 lightly 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 lumenal 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 I. 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

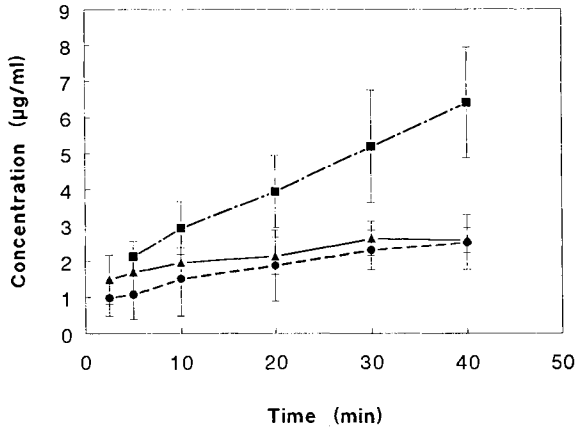

Fig. 1. Ranitidine serum concentrations after administration in pH 7 buffer into isolated gut segments (midgut, ●; duodenum, ▲; terminal ileum, ■).

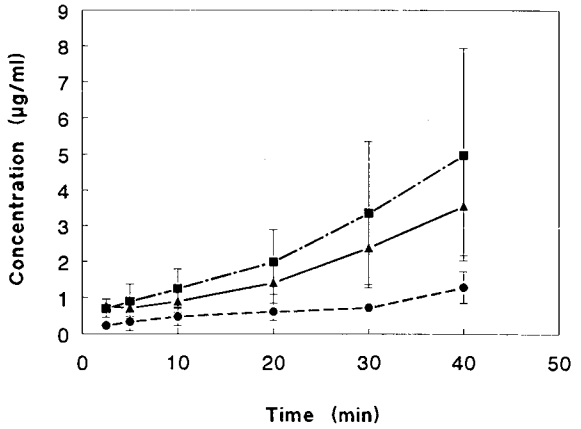

Fig. 2. Ranitidine serum concentrations after administration in pH 5 buffer into isolated gut segments (midgut, ●; duodenum, ▲; terminal ileum, ■).

present only after ranitidine administration with 50% bile. When ranitidine was administered in 50% bile, there were significant differences in AUC_{0-40} and C_{max} between all gut segments.

No significant differences in AUC_{0-40} among dosing solutions were evident after ranitidine administration into the duodenum. However, C_{max} after administration into the duodenum was significantly greater when ranitidine was administered in 50% bile compared to administration in pH 7 buffer. No significant differences in AUC_{0-40} and C_{max} were present between administration of ranitidine into the midgut with pH 7 buffer versus 50% bile. In contrast, ranitidine administration into the midgut with pH 5 buffer significantly decreased AUC_{0-40} and C_{max} compared to pH 7 buffer or 50% bile solution. AUC_{0-40} was significantly different between all dosing solutions after ranitidine administration into the terminal ileum. However, C_{max} after ranitidine administration into the terminal ileum was affected only by 50% bile.

DISCUSSION

Results of the present study suggest that region-dependent differences in the efficiency of ranitidine absorption exist in the GI tract of the rat, and that the terminal ileum is the optimal site for ranitidine absorption. This pattern of poor absorption from the middle small intestine and enhanced absorption in the lower small intestine is consistent with the results from studies of ranitidine in human subjects (15,16) and cimetidine in rats (17). Kaneniwa *et al.* (17) suggested that the enhanced GI absorption of cimetidine in the rat ileum was mediated by changes in the degree of ionization of cimetidine (pKa ~ 6.8) due to pH changes in the lumenal contents. The normal lumenal pH of the rat small intestine increases distally and ranges from approximately 6.5 in the duodenum to 7.1 in the ileum (22). Ranitidine (pK_a = 8.2) (23) is greater than 93% and 99% ionized at pH 7 and pH 5, respectively. Therefore, the enhanced absorption of ranitidine in the terminal ileum probably is related to intrinsic characteristics of the intestinal epithelia rather than the ionization state or solubility of the drug along the GI tract.

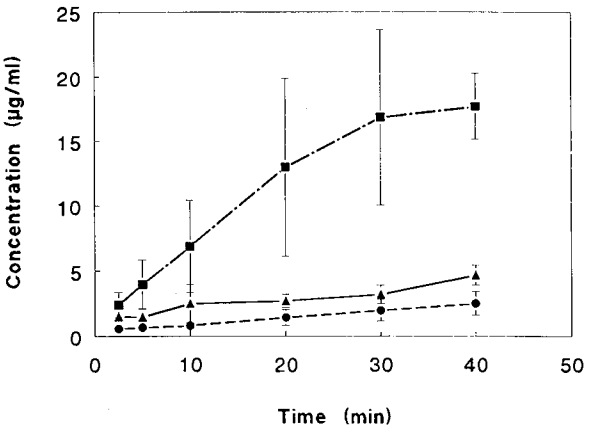

Fig. 3. Ranitidine serum concentrations after administration in 50% bile into isolated gut segments (midgut, ●; duodenum, ▲; terminal ileum, ■).

Table I. Ranitidine AUC_{0-40} and C_{max} Values after Administration into Isolated Segments of the Rat Small Intestine in pH 5 Buffer, pH 7 Buffer, and 50% Bile in Water (pH 7)*

Segment	pH 5	pH 7	50% Bile pH 7
AUC_{0-40} (μg · min/ml)			
Duodenum	66.31^{b}	80.50^{b}	109.72^{b}
	(25.85)	(17.17)	(22.06)
Midgut	24.97^{a}	$71.71^{b,c}$	55.15^{c}
	(8.42)	(22.27)	(17.54)
Terminal Ileum	92.30^{b}	155.95^{a}	404.91^{d}
	(47.69)	(31.66)	(121.75)
C_{max} (μg/ml)			
Duodenum	$3.56^{e,g,h}$	2.75^{e}	4.85^{g}
	(1.39)	(0.83)	(0.79)
Midgut	1.28^{h}	2.77^{e}	2.51^{e}
	(0.43)	(0.74)	(0.90)
Terminal Ileum	4.98^{g}	6.41^{g}	19.14^{f}
	(2.96)	(1.38)	(4.84)

$^{a-h}$ Means within treatment and segment with different letters are significantly different ($p < 0.03$).
* Numbers in parentheses are standard deviations (±SD).

The finding that ranitidine absorption from the rat GI tract was most efficient from the terminal ileum may be indicative of the mechanism(s) of ranitidine absorption. The permeability of the small intestine to hydrophilic markers decreases from the duodenum to the ileum (24,25). Electrical resistance across the intestinal epithelia increases from the jejunum to the terminal ileum in animals (26) indicating increased resistance to passive ion flow in the distal regions of the small intestine. Therefore, results of the present study suggest that factors other than simple passive diffusion contribute to the absorption of ranitidine from the rat GI tract.

Studies utilizing Caco-2 cell monolayers indicated that ranitidine absorption from the GI tract is mediated predominately by passive diffusion through paracellular pathways (27). However, extrapolation of results from studies utilizing Caco-2 monolayers to results from *in situ* rat intestines is difficult. When the permeability coefficients of polyethylene glycols of various molecular weights were compared, the Caco-2 cell monolayers were much less permeable to these compounds than excised rat ileum. Moreover, the perme-

ability profiles of the Caco-2 monolayers were much more similar to profiles from the rat colon (28). Regional differences in ranitidine absorption efficiencies in the small intestine, as demonstrated in the present work, indicate that morphological differences between segments of the small intestine significantly influence ranitidine absorption. Therefore, a homogeneous *in vitro* cell line may not be an appropriate model for the investigation of the mechanisms of ranitidine absorption.

The pattern of regional differences in GI absorption of ranitidine observed in this study may influence the occurrence of secondary peaks in oral concentration-time profiles. Although results of the present study demonstrate that ranitidine absorption occurs in all regions of the rat small intestine, these results are consistent with models of discontinuous and site-specific GI absorption. Previous studies (10,13,14) in which such models were fit to concentration-time profiles exhibiting secondary peaks indicated that the terminal absorption process was more efficient than proximal absorption processes. Furthermore, the differences in C_{max} and AUC_{0-40} after ranitidine administration in 50% bile (ileum > duodenum > midgut for both parameters) are consistent with the pattern of site-specific absorption proposed by Funaki *et al.* (12) as the mechanism of secondary peaks in cimetidine oral concentration-time profiles.

Because the optimal site of ranitidine absorption is in the lower small intestine, a lag time exists between the time ranitidine exits the stomach and reaches the area of most efficient absorption. Oral-to-cecal transit times of solutions have been estimated to be 3 to 5 h in humans (29). This transit time coincides with the time of the secondary peak in ranitidine oral concentration-time profiles in humans (1–4). The time of the secondary peak maximum observed after oral administration of ranitidine to rats ($\approx$ 2–3 h) (5) also coincides with the oral-to-cecal transit time of polyethylene glycol measured in rats (30). Therefore, the secondary peaks and plateaus observed in ranitidine oral concentration-time profiles may be influenced by the rate at which drug reaches a distal and efficient absorption site in the small intestine.

Results of the present study suggest that 50% bile had no significant effect on ranitidine absorption from the isolated duodenum and midgut, and enhanced absorption from the terminal ileum. These results apparently are in contrast to *in vivo* data in rats which indicated that intact bile flow inhibited GI absorption of ranitidine (5). The proposed mechanism for the decreased GI absorption of nadolol in rats in the presence of bile is the formation of a stable, poorly absorbed drug-bile micelle rather than altered permeability of the intestinal wall (31). Total bile acid concentration of rat bile is approximately 38 to 47 mM; taurocholic acid accounts for approximately 60% of the bile acid present (32). The critical micelle concentration (CMC) for taurocholic acid at room temperature is 10 mM and 6 mM in water and 0.15 M Na^+, respectively (33). Therefore, the concentration of taurocholic acid was probably above the CMC in the bile dosing solutions, and drug-bile micelle interactions should have taken place in the bile dosing solutions. Alternatively, inhibition of ranitidine GI absorption may not involve a simple drug-micelle interaction.

The apparent discrepancy in the influence of bile on ranitidine absorption may have resulted from differences in the concentration of bile in the isolated gut segments *in situ* versus the concentration of bile in the intestinal lumen *in vivo*. The concentration of bile acids in the intestinal lumen varies along the length of the intestine due to the dilution of bile by lumenal contents, bile acid absorption, and water flux. Bile acid concentrations in the duodenum near the duodenal papilla may be much greater than 50% bile. Active absorption of bile acids in the terminal ileum (34) may result in very low bile acid concentrations in the distal small intestine. Therefore, a single bile dilution may not be physiologically relevant for all areas of the small intestine. Inhibition of absorption may not occur in the upper small intestine unless bile acid concentrations in the gut approach those of bile. In contrast, the enhanced absorption of ranitidine in the terminal ileum may have been the result of altered membrane permeability caused by artificially high bile acid concentrations.

The effect of intact bile flow on the GI absorption of ranitidine may be indirect. Bile and bicarbonate secreted into the intestinal lumen increase the pH of gastric contents emptied into the duodenum (35). The pH of gastric contents of the rat is 3.3 to 5 (22). In the absence of bile flow, the lumenal pH in portions of the upper small intestine may approach 5. This change in pH may alter intestinal membrane permeability to ranitidine. Therefore, pH 5 buffer was selected to simulate possible pH conditions in the upper small intestine of rats with interrupted bile flow and pH 7 buffer was selected to approximate normal intestinal pH. Results of this study indicated that a lower pH had no effect on ranitidine absorption from the duodenum, where a change in pH due to interrupted bile flow is most likely to occur. Changes in pH had the greatest effect on ranitidine absorption from the midgut, although absorption was inhibited at pH 5 compared to pH 7. The inhibition of ranitidine absorption at pH 5 indicates that upper small intestinal pH changes in rats with interrupted bile flow did not account directly for the increased ranitidine absorption observed *in vivo* (5).

Coadministration of food has been reported to diminish the occurrence of secondary peaks in cimetidine (36) and ranitidine (37) concentration-time profiles in humans. Food administration may affect ranitidine absorption by multiple mechanisms. Bile release into the small intestine stimulated by food administration may alter ranitidine GI absorption. The change in GI absorption may affect the occurrence of double peaks in the concentration-time profiles. Furthermore, food administration interrupts the pattern of fasting GI motility in man (38). The change in GI motility may alter the rate of drug delivery to the optimal site of GI absorption in the lower small intestine. However, the exact mechanisms of the effect of food on the double peak phenomenon have not been elucidated.

In summary, regional differences in GI absorption of ranitidine were investigated in an *in situ* rat model. The effects of lumenal pH and bile on the GI absorption of ranitidine also were examined. Results indicate the presence of regional differences in GI absorption of ranitidine in the rat. Furthermore, ranitidine was absorbed most efficiently from the terminal ileum; absorption may involve processes other than passive diffusion. The pattern of regional differences in GI absorption observed may contribute significantly to the occurrence of double peaks in ranitidine concentration-time

profiles. The presence of 50% bile had no effect on ranitidine absorption from the isolated duodenum or midgut, but enhanced ranitidine absorption from the terminal ileum.

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