Gastrointestinal Transit and Distribution of Ranitidine in the Rat[1]

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

Received March 8, 1995; accepted April 19, 1995

Purpose. Ranitidine gastrointestinal distribution was examined in the rat small intestine after oral administration to determine whether intestinal transit or secretion (exsorption) may influence the appearance of secondary peaks in ranitidine serum concentration-time profiles. ***Methods.*** Male Sprague-Dawley rats received ranitidine (50 mg/kg) by oral gavage, and the mass of ranitidine recovered in all small intestinal segments (~12 cm each) was determined 30, 60, 90, or 120 min after administration. In a separate group of anesthetized rats, the small intestine was divided into two segments of equal length that were perfused with normal saline in a single-pass manner. Rats received an escalating, zero-order IV infusion of ranitidine for 30 min, and venous blood and intestinal effluent were collected over 90 min to quantitate ranitidine exsorption. ***Results.*** Thirty min after oral administration, >50% of the recovered ranitidine mass resided in the lower half of the small intestine in all rats. Ranitidine mass in 5 of 16 rats displayed a bimodal distribution with significant amounts of ranitidine recovered from the stomach 60 to 90 min after dosing. Ranitidine exsorption was more efficient from the lower jejunum and ileum than from the duodenum and upper jejunum. However, intestinal secretion of ranitidine was minor (5% of the IV dose). ***Conclusions.*** Ranitidine absorption from the lower ileum contributes significantly to systemic ranitidine concentrations before and during the time of the first concentration maximum. Separation of the drug mass into multiple boluses may contribute to secondary peaks in ranitidine concentration-time profiles. Exsorption did not contribute significantly to ranitidine distribution in the gastrointestinal tract.

KEY WORDS: ranitidine; intestinal absorption; intestinal distribution; intestinal secretion; pharmacokinetics.

INTRODUCTION

Secondary peaks in serum concentration-time profiles have been observed after oral administration of several compounds including pafenolol (1), furosemide (2), and the H_2-receptor antagonists ranitidine (3,4), cimetidine (5), and famotidine (6). A possible mechanism of the secondary peaks is the existence of site-specific absorption along the gastrointestinal (GI) tract (7–9). Regional differences in the GI absorption of ranitidine, cimetidine, and pafenolol have been demonstrated in the rat; the terminal ileum is the optimal site of GI absorption for all three compounds (10–12). Absorption of ranitidine (12) and cimetidine (10) is more efficient from the duodenum than from the midgut. Therefore, two 'windows' of ranitidine and cimetidine absorption may exist in the rat small intestine.

When regional differences in drug absorption from the GI tract exist, drug movement through the GI tract may have a significant effect on the appearance of drug in the systemic circulation. Pharmacokinetic models incorporating site-specific GI absorption have demonstrated that delivery of drug to the site of optimal absorption significantly affects the occurrence of secondary peaks in serum concentration-time profiles (8–13). Furthermore, GI transit phenomena have been proposed to influence the occurrence of secondary peaks in cimetidine concentration-time profiles (14). Therefore, the relationship between the location of the drug absorption site(s) and the movement of drug through the GI tract can greatly influence the appearance of secondary peaks in serum concentration-time profiles.

Intestinal motility is cyclic and decreases from the upper to the lower GI tract (15). The leading edge of liquid and solid test meals traverses approximately 70% of the rat small intestine in 20 to 30 min after oral administration (16–18), and reaches the terminal ileum between 60 (17,18) and 90 (19) min after oral administration. Use of the hydrogen breath test indicated that test meals reach the cecum 88 to 180 min after oral administration to rats depending on meal composition (20,21). Furthermore, the duodenum to ileum transit time of radiolabelled polyethylene glycol instilled into the duodenum was estimated to be approximately 90 to 100 min (11). The geometric center of drug mass in the rat GI tract is used to describe the distribution of the entire drug mass rather than only the leading edge (22). Estimates of the geometric center of marker compounds in the GI tract 30 min after administration range from approximately 30% of intestinal length after duodenal instillation (18,23) to 54% (24) of intestinal length after oral gavage.

Drug secretion from the systemic circulation into the intestinal lumen (exsorption) may influence drug distribution along the GI tract and the rate of drug delivery to the optimal site of absorption. Exsorption has been demonstrated for several compounds including furosemide (25), theophylline (26), organic ions (27), and pafenolol (28). Extensive exsorption may deliver drug to distal areas of the intestine more quickly than transit of drug through the intestinal lumen. Likewise, exsorption also may result in delivery of drug to proximal areas of the intestine after the drug mass residing in the lumen has reached more distal areas (*i.e.*, enteroenteric recirculation). In addition to extensive exsorption, pafenolol also exhibits regional GI absorption characteristics in rats (28). Enteroenteric recirculation in combination with regional GI absorption characteristics may influence the appearance of secondary peaks in serum concentration-time profiles.

Exsorption also may affect the GI absorption characteristics of a compound. Turnheim and Lauterbach (29) demonstrated that net GI absorption of model cations was decreased by extensive exsorption of the compounds. How-

[1] This work was presented in part at the 8th Annual Meeting of the American Association of Pharmaceutical Scientists, and was completed in partial fulfillment of requirements for the Doctor of Philosophy degree in Pharmaceutics at the University of North Carolina at Chapel Hill.

[2] Present address: Zeneca Pharmaceuticals, 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.

0724-8741/95/0900-1316$07.50/0

ever, the net absorption of these compounds increased when the systemic concentrations of the ions were sufficient to saturate the exsorption processes. Exsorption and the possible saturation of that process has been proposed to influence the apparent regional GI absorption characteristics of pafenolol and the appearance of double peaks in the serum concentration-time profile (28). Ranitidine also may be subject to saturable exsorption. Exsorption may contribute significantly to both the appearance of secondary peaks in serum concentration-time profiles and the apparent regional absorption characteristics of the drug.

The purpose of this study was to examine the GI transit rate of ranitidine in the small intestine of the rat. Furthermore, experiments were performed to determine the extent of ranitidine exsorption in rats after IV administration.

MATERIALS AND METHODS

GI Transit Experiments

Male Sprague-Dawley rats (257–360 g; $n = 16$) were anesthetized with ether the day before the study, and a silicone rubber cannula for blood sampling was implanted in the right jugular vein and exteriorized at the base of the neck. After an overnight fast, rats received ranitidine (50 mg/kg, 25 mg/ml in normal saline) by oral gavage. At 30, 60, 90, or 120 min after ranitidine administration, rats were sacrificed with 0.5 g/kg IV urethane (3–5 rats per time point). The small intestine was exposed immediately, and segments from the pylorus to the cecum (7–8 per rat) were isolated quickly with tubing clamps. The first clamp was placed approximately midway between the ligament of Treitz and the cecum, and subsequent clamps were placed ~12 cm apart at random. Approximately 2 min elapsed from the time of sacrifice until all segments were isolated. After segment isolation, each segment was ligated with surgical silk and the clamps were removed. The stomach and small intestine were removed from the peritoneum, laid flat on a metal surface, and the length of each segment was measured. Each segment was flushed with 5 ml of normal saline, and effluent was collected in pre-weighed polypropylene tubes.

Intestinal Secretion Experiments

Male Sprague-Dawley rats (255–318 g; $n = 7$) were anesthetized with i.p. ketamine (60 mg/kg) and xylazine (12 mg/kg). Body temperature was maintained at 37°C during the experiment with a heating pad linked to a temperature controller and surface temperature probe (Yellow Springs Instrument Co., Inc., Yellow Springs, OH) placed beneath the rat. The right jugular and femoral veins were cannulated with silicone rubber tubing (0.037 in. o.d.) for ranitidine administration and venous blood collection, respectively. The small intestine was exposed through a midline incision, and the bile duct was cannulated with polyethylene tubing (P.E. 10).

The small intestine from the ligament of Treitz to the cecum was divided into two segments of approximately equal length. The proximal end of each 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 each 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 around the polyethylene tubing with silk thread. The segments were flushed gently with normal saline until the effluent was clear. The intestine was placed in the abdominal cavity, and the incision was covered with saline-soaked gauze and parafilm. Previous studies indicated that intestinal extraction of ranitidine from a single-pass perfusion was low (≤22%) at a flow rate of 0.25 ml/min (30). Therefore, normal saline was perfused through the segment at a flow rate of 0.5 ml/min. Effluent was collected in pre-weighed polyethylene tubes.

After intestinal effluent flow was established, an escalating, zero-order IV infusion of ranitidine (15 mg/ml in normal saline) was administered at rates of 15 mg/h from 0–10 min, 30 mg/h from 10–20 min, and 90 mg/h from 20–30 min. At 30 min, the IV infusion was terminated. Venous blood (0.25 ml) was collected at 5, 10, 15, 20, 25, 30, 35, 45, 57.5, 72.5, 85, and 90 min after initiation of the IV infusion. Effluent intestinal perfusate was collected at 10-min intervals for 50 min and from 50–65, 65–80, and 80–90 min. After the 90-min blood and effluent perfusate samples were collected, the intestine was removed from the peritoneum and examined for viability. Only data from rats with bright pink intestinal segments, pulsatile blood flow, and noticeable peristalsis were included in subsequent analyses. After the rat was sacrificed with IV urethane (0.5 g/kg), the intestine was excised from the peritoneum, laid flat on a metal surface, and the length of the intestinal segments was measured and recorded.

Analysis

Intestinal effluent volume from both studies was measured gravimetrically assuming a density of 1 g/ml. Serum and effluent perfusate samples were analyzed for ranitidine by HPLC (31). Serum samples collected during intestinal secretion studies were diluted either 2- or 4-fold before addition of the internal standard and protein precipitation. Gut perfusate effluent samples were diluted (2- or 4-fold in intestinal secretion experiments; 100-fold in GI transit experiments) and filtered through a 0.2-μm nylon filter prior to addition of the internal standard.

GI Transit

The stomach was assigned a length of 3 cm in all rats. The total length of the upper GI tract was calculated as the sum of the stomach length and the length of the small intestine from the pylorus to the cecum. The fraction of the cumulative length of each segment ($FTotLen_i$) was defined as:

$$FTotLen_i = \frac{\text{Cumulative length of intestine at end of segment}}{\text{Total length of upper GI tract}} \quad (1)$$

The mass of ranitidine recovered in each gut segment and the cumulative mass of ranitidine recovered in the entire small intestine (Ran_i and Ran_{tot}, respectively) were measured. The geometric center of the ranitidine dose in the small intestine was calculated as:

$$GC = \sum_{i=1}^{n} \frac{Ran_i}{Ran_{tot}} * FTotLen \quad (2)$$

Exsorption

A 2-compartment model was fit to serum concentration-time profiles with PCNONLIN (Statistical Consultants, Lexington, KY). Systemic disposition parameters generated from model fits to the data were used to calculate ranitidine clearance in each rat. Then, ranitidine clearance was used to calculate the area under the concentration-time profile from zero to infinity ($AUC_{0-\infty}$). The area under the ranitidine concentration-time profile from zero to 90 min (AUC_{0-90}) was calculated with a combination of the linear and log trapezoidal rules. The administered dose was corrected for the fraction eliminated over 90 min, and the fraction of the dose recovered in the intestinal perfusate (F_{rp}) was calculated as:

$$F_{rp} = \frac{\text{Ranitidine in perfusate}}{\text{Dose} * AUC_{0-90}/AUC_{0-\infty}} \quad (3)$$

F_{rp} was normalized for the length of intestine perfused, and compared between segments with a paired Student's *t*-test.

RESULTS

GI Transit

Ranitidine metabolites were not detected in any of the samples. The mean percentage of the ranitidine dose recovered from the stomach and small intestines and the geometric center of the ranitidine mass are included in Table I. Representative ranitidine mass recovered in each segment *vs.* FTotLen plots are displayed in Figure 1. Thirty minutes after oral administration, more than 50% of the ranitidine mass recovered resided in the lower half of the small intestine in all rats. Ranitidine was recovered from the terminal ileum in all rats 60 min after administration. More than 65% of the ranitidine recovered at 90 min was recovered from the most distal 25% of the small intestine in 3 of 5 rats. The mean geometric center of 86.2% of total length indicates that the majority of the ranitidine dose present in the small intestine resided in the ileum 120 min after ranitidine administration. The mean fraction of the dose recovered from the stomach and small intestines decreased approximately 5% at each 30-min time interval. The mean geometric center increased slightly at each sample time, but remained approximately 70% until 90 min after ranitidine administration.

Only small amounts of ranitidine were recovered from the duodenum and upper jejunum at all time points throughout the study. A significant amount (>30%) of the recovered ranitidine mass remained in the stomach in 3 of 5 rats 60 min after administration, and 2 of 5 rats 90 min after administration. Quantifiable amounts of ranitidine were recovered from the upper 50% of the small intestine in only 1 of 3 rats sacrificed 120 min after dosing. Ranitidine mass in the small intestine displayed a bimodal distribution in 5 of 16 rats. Representative ranitidine mass versus FTotLen profiles that displayed a bimodal distribution are shown in Figure 2.

Table I. Mean (SD) fraction of ranitidine dose recovered from the stomach and small intestine and the geometric center of the ranitidine mass after oral administration.

	Fraction recovered (%)	Geometric center (% intestinal length)
30 min (n = 3)	64.7 (3.9)	66.5 (14.9)
60 min (n = 5)	56.2 (14.2)	71.6 (11.1)
90 min (n = 5)	50.8 (18.8)	73.5 (16.9)
120 min (n = 3)	45.5 (19.6)	86.2 (9.8)

Exsorption

The mean serum ranitidine concentration-time and intestinal secretion rate versus time profiles for 7 rats after IV infusion of ranitidine are displayed in Figure 3. Ranitidine recovery from the intestinal perfusate is shown in Table II. The mean mass of ranitidine recovered in the intestinal effluent over 90 min was 1.0 mg, which represented 5.5% of the dose excreted in 90 min. When the ranitidine mass recovered in intestinal perfusate was corrected for the length of intestine perfused, the amount recovered from the lower small intestine was significantly greater than the amount recovered from the upper small intestine ($p < 0.01$). The mean ranitidine exsorption rate from the lower small intestine paralleled serum concentrations at all times. The mean exsorption rate versus time profile from the upper small intestine reached an apparent plateau during the study. However, this plateau was a result of data variability. Only 2 of 7 individual exsorption rate versus time profiles evidenced a plateau during the study.

DISCUSSION

Previous work suggested that the rat may be a good model for investigating the mechanism(s) responsible for secondary peaks in ranitidine serum concentration-time profiles after oral administration (31). The distribution of ranitidine in the rat GI tract was investigated in the present study to obtain an accurate measurement of the GI transit characteristics of ranitidine after oral administration. Measurements of both the leading edge and the geometric center of the ranitidine dose in the small intestine 30 and 60 min after oral administration were consistent with results of previous studies investigating the GI transit of orally administered liquid markers (24). However, the geometric center of the ranitidine mass 30 min after administration in the present study (66% of intestinal length) was approximately twice the reported geometric center of radiolabelled markers administered into the duodenum [≈ 30% of intestinal length (18,23)]. In contrast to the pylorus-to-cecum transit time of 90 to 100 min reported by Lennernas *et al.* (11), results of the present study indicate that the stomach-to-cecum transit time for orally administered ranitidine is less than 60 min.

Results of the present study are not consistent with the hypothesis that the double peaks in ranitidine serum concentration-time profiles are caused by movement of drug mass through absorption 'windows' located in the upper and lower small intestine (8). The first peak in the serum ranitidine concentration-time profile occurs 1 to 2 h after oral administration to rats (31); more than 50% of the ranitidine mass resided in the lower half of the small intestine 30 min after

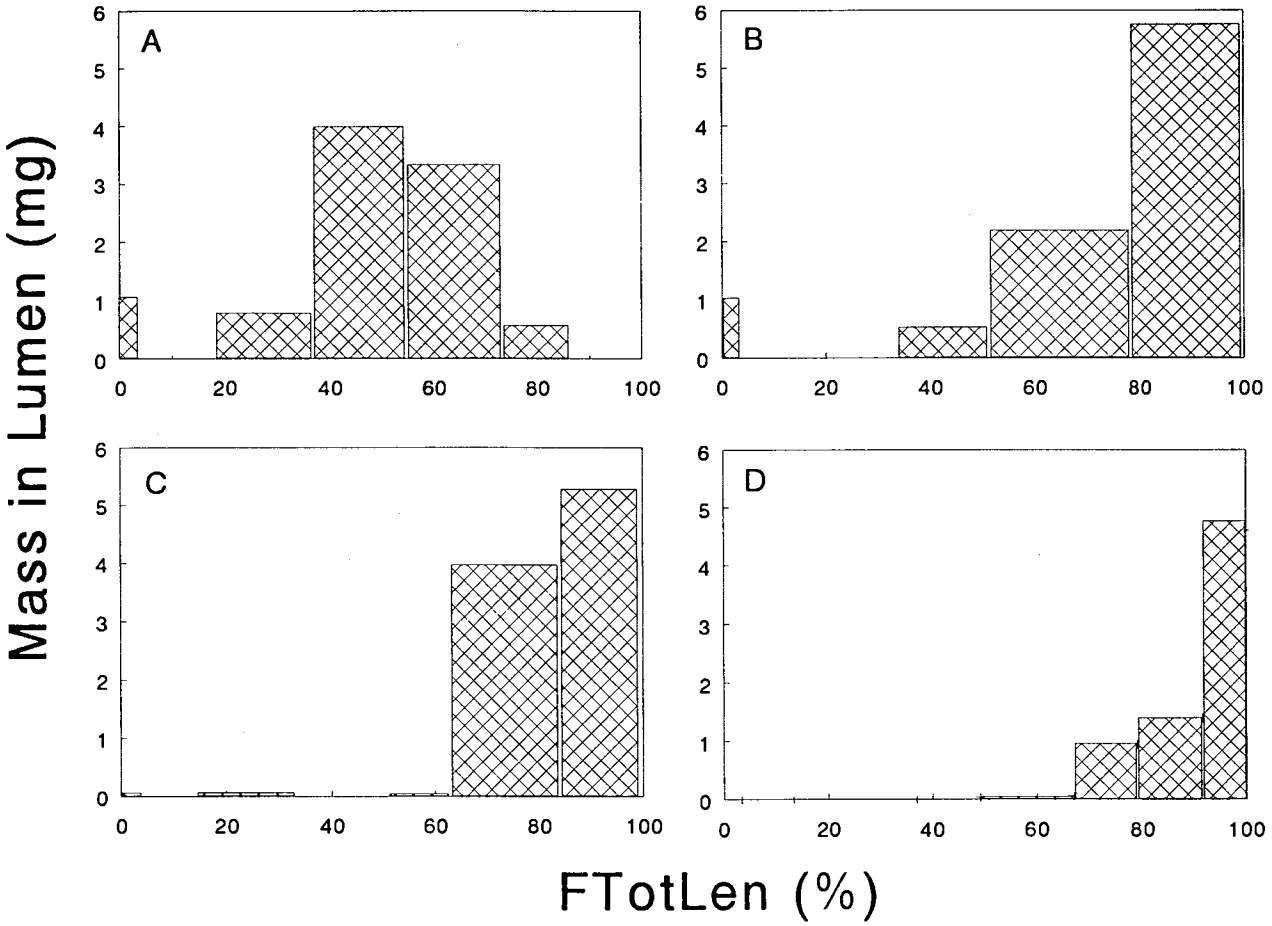

Fig. 1. Mass of ranitidine in intestinal lumen (mg) *vs.* FTotLen (%) of small intestinal segment in representative rats receiving ranitidine. Bar width represents length of the intestinal segment: A, 30 min after oral administration; B, 60 min after oral administration; C, 90 min after oral administration; D, 120 min after oral administration.

oral administration. Furthermore, significant ranitidine mass (> 40% of recovered mass) reached the distal 20% of the small intestine in all 5 rats 60 min after administration. The terminal ileum is the optimal site of ranitidine absorption (12). Therefore, passage of the ranitidine mass through a window of absorption and into an area of relatively poor absorption in the upper small intestine cannot account for appearance of the first serum ranitidine concentration maximum. Results of the present study suggest that absorption of ranitidine from the lower ileum contributes significantly to systemic ranitidine concentrations prior to and during the time of the first concentration maximum.

Distribution of ranitidine along the GI tract may influence the occurrence of secondary peaks in serum concentration-time profiles since the distribution of the ranitidine mass along the GI tract was bimodal in 5 of 16 rats. Furthermore, significant amounts of ranitidine were recovered from the stomach in 3 of 5 rats 60 min after administration and 2 of 5 rats 90 min after dosing. These results suggest that ranitidine may travel through the GI tract in separate boluses rather than as a single mass. A bimodal distribution along the GI tract for an orally administered marker also was observed by Galligan and Burkes (23). If the optimal site of drug absorption is in a distal portion of the small intestine, boluses of drug may reach that site at different times, and result in secondary peaks in the concentration-time profiles. This mechanism is consistent with observations that gastric motility influences the occurrence of secondary peaks in serum concentration-time profiles (14). It also is feasible that the drug mass may separate into more than one bolus after exiting the stomach. This could explain the occurrence of secondary peaks in serum concentration-time profiles observed after direct intestinal administration of ranitidine in humans (32).

The present data indicate that ranitidine exsorption has a minor effect on the distribution of ranitidine in the GI tract and the oral absorption of ranitidine. Approximately 1 mg of a 22.5-mg IV dose of ranitidine was recovered in intestinal perfusate throughout the 90-min study period. An escalating, zero-order infusion during a 30-min period was used in the study to characterize the exsorption of ranitidine over a wide range of ranitidine serum concentrations (5–70 μg/ml). There was no evidence that the exsorption mechanism was saturable over the range of ranitidine serum concentrations achieved in this study. However, if the exsorption mechanism was saturated during the present study, the maximal intestinal secretion rate of 1 mg/90 min would not have a significant effect on ranitidine distribution in the GI tract.

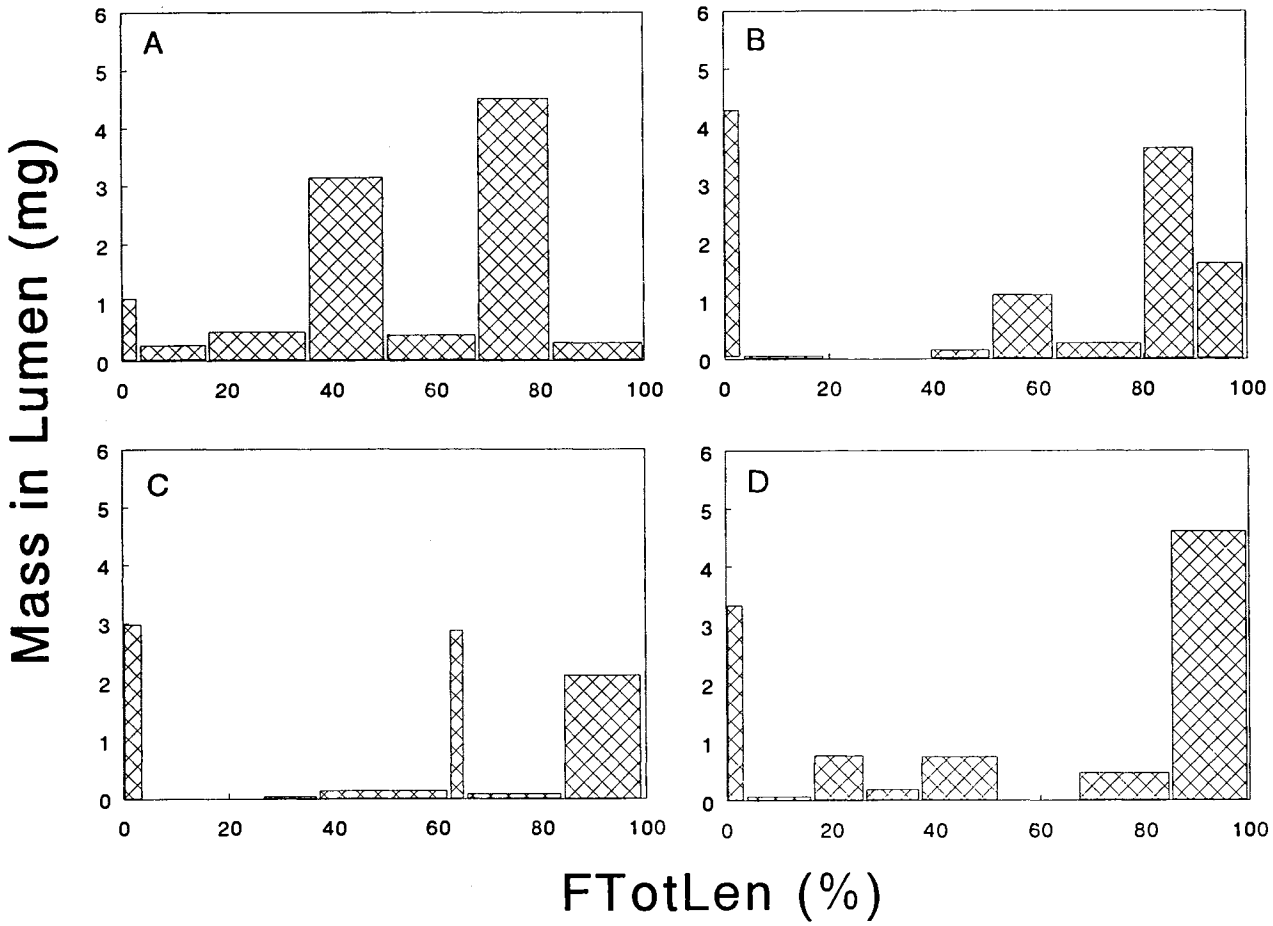

Fig. 2. Mass of ranitidine in intestinal lumen (mg)*vs.* FTotLen (%) of small intestinal segment in representative rats exhibiting bimodal distributions. Bar width represents length of the intestinal segment. Rats were sacrificed: A, 30 min after oral administration; B, 60 min after oral administration; C and D, 90 min after oral administration.

Simulations suggest that the second of two serial absorption processes must contribute at least 20% of the fraction absorbed to produce a secondary peak in the serum concentration-time profile (8). Secondary peaks were observed in serum concentration-time profiles after administration of 50 mg/kg ranitidine in rats (31). A maximal exsorption rate of 1 mg/90 min would result in secretion into the small intestine of only 7% of a 15-mg ranitidine dose administered to a 300-g rat.

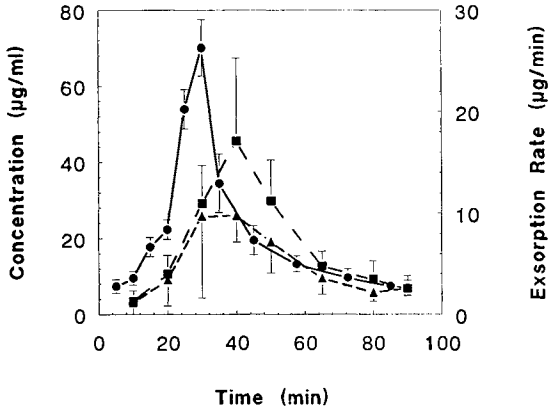

Fig. 3. Mean (±SD) serum ranitidine concentration-time and exsorption rate *vs.* time profiles in rats receiving an escalating IV infusion of ranitidine (15 mg/h from 0–10 min; 30 mg/h from 10–20 min; 90 mg/h from 20–30 min): —●—, serum concentrations (µg/ml); —■—, exsorption rate from the lower intestine (µg/min); —▲—, exsorption rate from the upper small intestine (µg/min).

In humans, regional differences exist in ranitidine intestinal exsorption as well as absorption. Gramatté *et al.* (33)

Table II. Ranitidine recovered in effluent intestinal perfusate after IV administration.

Rat	Total ranitidine (mg)	Ranitidine recovered F_{rp} (%)	Upper GI (µg/cm)	Lower GI (µg/cm)
1	0.93	4.64	13.79	19.77
2	1.02	5.33	14.91	22.50
3	1.12	6.70	16.34	28.48
4	1.15	5.88	17.96	32.23
5	1.04	5.38	14.92	18.91
6	1.05	5.80	17.53	19.80
7	0.95	5.01	15.63	22.33
Mean	1.04	5.53	15.87	23.43[a]
SD	0.08	0.67	1.50	5.03

[a] Lower GI significantly greater than Upper GI ($p < 0.01$).

recently reported that ranitidine absorption rates were greatest in the regions of the duodeno-jejunal junction and the distal jejunum/ileum; secretion of ranitidine into the gut lumen was observed in the mid-jejunum. Results of the present study in rats suggest that ranitidine is exsorbed preferentially into the second segment of the small intestine (lower jejunum and ileum). Previous studies indicated that the terminal ileum is the optimal site of ranitidine absorption from the small intestine (12). Since ranitidine exsorption does not appear to be saturable in the relevant concentration range, the apparent increased absorption efficiency of ranitidine from the terminal ileum was a result of more efficient transfer of ranitidine from the intestinal lumen to the systemic circulation rather than less efficient ranitidine exsorption in the lower small intestine. These results suggest that the lower small intestine is more permeable to ranitidine in both the lumenal-to-blood and blood-to-lumen directions than the upper small intestine. Alternatively, if ranitidine absorption is carrier-mediated in this region, these data may suggest that the transporter is bi-directional. Additional studies are needed to examine the mechanism(s) of ranitidine absorption.

In summary, the GI transit characteristics of orally administered ranitidine and the effect of ranitidine exsorption on the distribution and absorption of ranitidine in the GI tract were investigated in the rat. Results of the present study indicated that the residence time of ranitidine in the upper small intestine is very short after oral administration. Therefore, absorption 'windows' in the upper and lower small intestine probably are not responsible for the appearance of double peaks in ranitidine serum concentration-time profiles in rats. However, bimodal distribution of ranitidine along the GI tract influences drug delivery to the optimal site of absorption in the terminal ileum and may cause secondary peaks. Exsorption of ranitidine is most efficient in the lower small intestine, but is relatively minor. The presence of enteroenteric recirculation does not account for the appearance of secondary peaks in ranitidine concentration-time profiles.

REFERENCES

1. C. G. Regardh, A. Geggelund, K. Kylberg-Hansen, and P. Lundborg. Pharmacokinetics of pafenolol after iv and oral administration of three separate doses of different strengths to man. *Biopharm. Drug Dispos.* 11:607–618 (1990).
2. M. M. Hammarlund, L. K. Paalzow, and B. Odlind. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. *Eur. J. Clin. Pharmacol.* 26:197–207 (1984).
3. C. Shim and J. Hong. Inter- and intrasubject variations of ranitidine pharmacokinetics after oral administration to normal male subjects. *J. Pharm. Sci.* 78:990–994 (1989).
4. D. C. Garg, D. J. Weidler, and F. N. Eshelman. Ranitidine bioavailability and kinetics in normal male subjects. *Clin. Pharmacol. Ther.* 33:445–452 (1983).
5. S. S. Walkenstein, J. W. Dubb, W. C. Randolph, W. J. Westlake, R. M. Stote, and A. P. Intoccia. Bioavailability of cimetidine in man. *Gastroenterology* 74:360–365 (1978).
6. H. Kroemer and U. Klotz: Pharmacokinetics of famotidine in man. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 25:458–463 (1987).
7. T. Funaki, S. Furuta, and N. Kaneniwa. Discontinuous absorption property of cimetidine. *Int. J. Pharm.* 31:119–123 (1986).
8. A. B. Suttle, G. M. Pollack, and K. L. R. Brouwer. Use of a pharmacokinetic model incorporating discontinuous gastrointestinal absorption to examine the occurrence of double peaks in oral concentration-time profiles. *Pharm. Res.* 9:350–356 (1992).
9. J. J. Zimmerman. Use of Metzler's nonlin program for fitting discontinuous absorption profiles. *J. Pharm. Sci.* 72:138–142 (1983).
10. N. Kaneniwa, T. Funaki, S. Furuta, and N. Watari. Study of the absorption site of cimetidine. *J. Pharmacobio-Dyn.* 9:321–326 (1986).
11. H. Lennernas and C. Regardh. Regional gastrointestinal absorption of the beta-blocker pafenolol in the rat and intestinal transit rate determined by movement of ^{14}C-polyethylene glycol (PEG) 4000. *Pharm. Res.* 10:130–135 (1993).
12. A. B. Suttle and K. L. R. Brouwer. Regional gastrointestinal absorption of ranitidine in the rat. *Pharm. Res.* 12:1311–1315 (1995).
13. B. P. Imbimbo, S. Daniotti, A. Vidi, D. Foshci, F. Saporiti, and L. Ferrante. Discontinuous oral absorption of cimetropium bromide, a new antispasmodic drug. *J. Pharm. Sci.* 75:680–684 (1986).
14. R. L. Oberle and G. L. Amidon. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J. Pharmacokinet. Biopharm.* 15:529–544 (1987).
15. D. N. Granger, J. A. Barrowman, and P. R. Kvietys. *Clinical Gastrointestinal Physiology,* W. B. Saunders, Philadelphia, 1985.
16. S. N. S. Murthy and G. Ganiban. Effect of the secretin family of peptides on gastric emptying and small intestinal transit in rats. *Peptides* 9:583–588 (1988).
17. P. Silkoff, F. Karmeli, E. Goldin, A. Ewenson, C. Gilon, M. Chorev, R. Laufer, Z. Selinger, and D. Rachmilewitz. Effect of substance p on rat gastrointestinal transit. *Dig. Dis. Sci.* 33:74–77 (1988).
18. J. A. Reilly, Jr, E. M. M. Quigley, C. F. Forst, and L. F. Rikers. Small intestinal transit in the portal hypertensive rat. *Gastroenterology* 100:670–674 (1991).
19. D. Kruger, R. Grossklaus, M. Herold, S. Lorenz, and L. Klingebiel. Gastrointestinal transit and digestibility of maltitol, sucrose and sorbitol in rats: a multicompartmental model and recovery study. *Experientia* 48:733–740 (1992).
20. N. J. Brown, R. D. E. Rumsey, and N. W. Read. Adaptation of hydrogen analysis to measure stomach to caecum transit time in the rat. *Gut* 28:849–854 (1987).
21. J. Chesta, E. S. Debnam, S. K. S. Srai, and O. Epstein. Delayed stomach to caecum transit time in the diabetic rat. Possible role of hyperglucagonaemia. *Gut* 3:660–662 (1990).
22. M. S. Miller, J. J. Galligan, and T. F. Burks. Accurate measurement of intestinal transit in the rat. *J. Pharmacol. Meth.* 6:211–217 (1981).
23. J. J. Galligan and T. F. Burks. Cholinergic neurons mediate intestinal propulsion in the rat. *J. Pharmacol. Exp. Ther.* 238:594–598 (1986).
24. T. S. Gaginelle, R. J. Bertko, and J. F. Kachur. Effect of dextromethorphan and levomethorphan on gastric emptying and intestinal transit in the rat. *J. Pharmacol. Exp. Ther.* 240:388–391 (1987).
25. K. Arimori and M. Nakano. Transport of furosemide into the intestinal lumen and the lack of effect of gastrointestinal dialysis by charcoal in rats with acute renal failure. *J. Pharmacobio-Dyn.* 11:1–8 (1988).
26. K. Arimori and M. Nakano. Transport of theophylline from blood to the intestinal lumen following i.v. administration to rats. *J. Pharmacobio-Dyn.* 8:324–327 (1985).
27. F. Lauterbach. Intestinal secretion of organic ions. In M. Gilles-Baillien and R. Giles (eds.), *Intestinal Transport,* Springer-Verlag, New York, 1983, pp. 76–86.
28. H. Lennernas and C. G. Regardh. Dose-dependent intestinal absorption and significant intestinal excretion (exsorption) of

the beta-blocker pafenolol in the rat. *Pharm. Res.* **10**:727–731 (1993).
29. K. Turnheim and F. Lauterbach. Interaction between intestinal absorption and secretion of monoquaternary ammonium compounds in guinea pigs-a concept for the absorption kinetics of organic cations. *J. Pharmacol. Exp. Ther.* **212**:418–424 (1980).
30. A. B. Suttle and K. L. R. Brouwer. Regional absorption of ranitidine from *in situ* rat intestine. *Pharm. Res.* **9**:S347 (1992).
31. A. B. Suttle and K. L. R. Brouwer. Bile flow but not enterohepatic recirculation influences the pharmacokinetics of ranitidine in rats. *Drug Metab. Dispos.* **22**:224–232 (1994).
32. M. F. Williams, G. E. Dukes, W. Heizer, Y. H. Han, D. J. Hermann, T. Lampkin, and L. J. Hak. Influence of gastrointestinal site of drug delivery on the absorption characteristics of ranitidine. *Pharm. Res.* **9**:1190–1194 (1992).
33. T. Gramatté, E. El Desoky, and U. Klotz. Site-dependent small intestinal absorption of ranitidine. *Eur. J. Clin. Pharmacol.* **46**:253–259 (1994).