Influence of Gastrointestinal Site of Drug Delivery on the Absorption Characteristics of Ranitidine

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The absorption characteristics of ranitidine after delivery to three locations in the gastrointestinal tract were compared in an open-label study of eight healthy males. Subjects received ranitidine HCl (150 mg) for injection via a nasoenteric tube directly into their stomach, jejunum, or cecum sequentially in three separate periods (24 hr apart). Plasma samples were collected at periodic time intervals for 12 hr following each dosing and analyzed for ranitidine concentration by high-pressure liquid chromatography. Mean concentrations following cecal dosing were lower ($P < 0.05$) than concentrations following gastric or jejunal dosing at each sampling time except baseline. Mean concentrations following gastric and jejunal dosing were similar except at 2 hr (gastric > jejunal). Mean pharmacokinetic parameters for cecal administration were different ($P < 0.05$) from either the gastric or the jejunal periods with the exception of T_{max}. There was no difference in any pharmacokinetic parameter after gastric or jejunal dosing. The relative bioavailability after cecal administration was less than 15% of that observed after administration into the stomach or jejunum. Additionally, Wagner–Nelson analysis indicated that the rate of ranitidine absorption was much slower following cecal administration than after gastric or jejunal dosing. Two plasma concentration peaks were observed in three of eight subjects after gastric dosing, in eight of eight subjects after jejunal dosing, and in zero of eight subjects after cecal dosing. These data demonstrate that the absorption profile of ranitidine is equivalent, in extent and duration, after delivery to the stomach or jejunum, while absorption from the cecum is significantly less. In addition, the two plasma concentration peaks commonly seen with ranitidine administration are not secondary to variations in gastric emptying as has been hypothesized.

KEY WORDS: ranitidine; drug absorption; site of absorption.

INTRODUCTION

Ranitidine is a histamine H2-receptor antagonist used for the treatment of duodenal ulcers, gastric ulcers, gastroesophageal reflux disease, and acid hypersecretory conditions. The absorption and bioavailability of ranitidine after oral administration have been examined in several clinical studies (1). In normal subjects receiving ranitidine in the fasting state, the onset of absorption is 15 to 34 min. Peak plasma drug concentrations occur 1 to 3 hr after administration. Mean oral bioavailability of ranitidine ranges from 50 to 60% but varies widely between individuals.

Two ranitidine plasma concentration peaks have been demonstrated after oral dosing (2). This effect is most pronounced in the fasting state, is blunted with food (3), and has also been noted after intravenous dosing (4). This double-peak plasma concentration profile also occurs with oral administration of cimetidine, another histamine H2-receptor antagonist (5,6). Several explanations for this second peak have been proposed.

1. The intestinal absorption of these drugs may be discontinuous, i.e., there may exist two areas of efficient absorption separated by an area of poor absorption (7).
2. Variability in the rate of gastric emptying of ranitidine from the stomach may account for varying amounts of drug available for absorption in the small intestine over time (8).
3. The drug may undergo enterohepatic recycling (1,9). Following oral or intravenous administration, ranitidine or a metabolite may accumulate in the bile with subsequent bolus release into the duodenum. The released parent compound, or the metabolite reconverted by enteric bacteria to the parent compound, would then be available for reabsorption. Alternatively, ranitidine may be sequestered in the hepatic parenchymal tissue with subsequent bolus into the systemic circulatory system secondary to an unknown stimulus.

The objective of this study was to determine and compare the absorption profile of ranitidine when delivered directly to the stomach, jejunum, and cecum. An additional objective was to assess the influence of site of drug delivery on the frequency of the occurrence of two plasma concentration peaks.

MATERIALS AND METHODS

This study was a nonrandomized, open-label comparison of the absorption characteristics of ranitidine HCl, 150 mg (Zantac, Glaxo Inc., Research Triangle Park, NC). Ranitidine for injection (25 mg/ml, 6 ml) was directly administered via a nasoenteric tube into the stomach during the first study day, into the proximal jejunum the second study day, and into the cecum the third study day. Each dosing was separated by at least 24 hr.

Subjects

Eight healthy adult male volunteers, aged 19–33 years (mean = 27 years), completed the study. Subjects weighed between 71 and 91 kg (mean weight = 80 kg) and were within 10% of their ideal body weight. No subject had a history of gastrointestinal disease or recent exposure to histamine H2-receptor antagonists. This study was approved by the Committee for the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine and subjects provided written consent prior to entry into the study.

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Diet Restrictions

Subjects were instructed to abstain from ingestion of any alcohol, drugs, or caffeine for 3 days prior to and during the study. Subjects received a low-fat, caffeine-free diet throughout the experiment. Subjects fasted overnight prior to each drug dosing. Subjects received a meal 4 hr following drug dosing, an evening meal, and a 10 PM snack.

Clinical Procedures

Period 1—Gastric Dosing

Subjects were admitted to the General Clinical Research Center of The University of North Carolina Hospitals the night prior to study initiation and fasted overnight. A four-lumen, 4.5-m-long nasoenteric tube was inserted on the morning of Day 1 of the study and advanced until the tip reached the stomach. One lumen of this tube was fitted with two pH probes, one at the level of the drug delivery port near the tip of the tube, and one 35 cm proximal to the first probe. Two of the lumens terminated in side ports 5 cm apart, the most distal of which served as the drug administration port. The tip of the tube was fitted with a tungsten weight and a balloon which could be inflated or deflated with room air via the fourth lumen. Positioning of the drug administration port in the stomach was assessed by pH monitoring (distal probe indicating acidic pH, proximal probe indicating acidic or neutral pH) and auscultation during air insufflation.

The ranitidine dose was administered undiluted at 8:00 AM and was immediately followed by flushing the lumen with 10 ml of normal saline. This volume was sufficient to assure that all of the drug was flushed from the tubing (lumen volume, 2 ml). The subject remained in a semireclining position for 4 hr postdosing. Blood samples (8 ml) were collected into heparinized tubes prior to drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hr postdosing. Blood samples were immediately centrifuged and plasma was separated and frozen at −20°C until analysis.

Four hours after drug administration, the tube was allowed to advance 35 cm, with the goal to have the distal administration port in the proximal jejunum (approximately 10 cm beyond the ligament of Treitz). Location of the tube was assessed by pH monitoring (both probes neutral) and radiographs if necessary.

Period 2—Jejunal Dosing

On the morning of Day 2, with the two pH probes both recording the relatively alkaline pH of the small bowel, the tube was slowly withdrawn until the proximal pH probe displayed an acidic reading. This indicated that the proximal probe was in the stomach and that the distal probe and drug administration port were 35 cm distal to the stomach and in the proximal jejunum. Ranitidine dose was again administered via the nasoenteric tube and the tube flushed. Blood samples were collected as before.

Four hours after drug administration, the balloon at the tip of the tube was inflated with 15 cm^3 of air. Inflation of the balloon allowed the propulsive effects of gastrointestinal peristalsis to facilitate successful movement of the tube tip into the cecum within 18 hr.

In the evening of Day 2, a radiograph was obtained to assess progression of the tube tip. If the position of the balloon was determined to be in the terminal ileum or cecum at that time, the balloon was deflated and the tube secured to prevent further movement. If the balloon was not in or near the desired position, the balloon was left inflated, either partially or wholly, until the next morning.

Period 3—Cecal Dosing

During the morning of Day 3, a radiograph or fluoroscopy was used to assure correct positioning of the tube tip in the cecum. When the drug administration port was at the desired position in the cecum, the drug was administered, the tube was flushed, and blood samples were obtained as previously described. At midday, the tube was withdrawn. All subjects were discharged from the Clinical Research Unit after the last blood samples were obtained (12 hr postdosing).

Assay Procedure

Frozen plasma samples were thawed and extracted with a solid-phase extraction system described by Karnes *et al.* (10). Extracted samples were then analyzed by high-performance liquid chromatography using ultraviolet detection at 320 nm. A reversed-phase analytical column (Spherisorb ODS-1,5 mm, 2.5 cm × 4.6-mm ID, Chromanetics Scientific Products) maintained at a constant temperature of 48°C was used to separate ranitidine and the internal standard (AH-20480, Glaxo Inc.). The mobile phase consisted of 7.5 m*M* sodium-1-pentane sulfonate in 65% methanol, 5% tetrahydrofuran, and 30% 0.05 *M* sodium dibasic phosphate buffer at pH 6. The lower limit of quantitation was 10 ng/ml. The day-to-day coefficients of variation on three control samples (10, 100, and 400 ng/ml) were 8.2, 3.8, and 2.8% respectively.

Pharmacokinetic Analysis

The individual subject's ranitidine plasma concentration–time curves for each treatment period were analyzed by model-independent methods. The area under the plasma concentration–time curve to the last time point (AUCT) was calculated using the linear trapezoidal rule and extrapolated to infinity (AUCI) by adding the ratio of the last observed concentration to the elimination-rate constant (K_{el}) as determined by linear regression of the log-transformed concentration–time data in the terminal portion of the curve. Oral clearance (Cl/*F*) was determined as the dose divided by the AUCI. The mean residence time (MRT) was determined by dividing the area under the moment curve extrapolated to infinity by AUCI. Maximum plasma concentration (C_{MAX}) and time of occurrence of maximum concentration (T_{MAX}) were estimated by visual inspection. The individual subject's cumulative fraction of the absorbed dose (F_a) at each sampling time for each dosing period was determined by the Wagner–Nelson method (11).

Statistical Analysis

Plasma concentration data were tested for normal distribution using univariate analysis, followed by a two-way

analysis of variance with a post hoc Duncan's test to evaluate the differences in plasma concentration between administration site at each sampling time. Pharmacokinetic parameters were analyzed by Wilcoxon sign rank test with a Bonferroni correction for multiple comparisons.

RESULTS

All eight subjects completed the study without difficulty. Adverse experiences were mild and limited to local irritation in the nasopharynx from the nasoenteric tube.

Mean (±SD) plasma ranitidine concentrations for each sampling time at each administration site are summarized in Table I and illustrated in Fig. 1. A significant difference ($P < 0.05$) existed between plasma ranitidine concentrations resulting from cecal administration and those resulting from gastric or jejunal administration at each time interval except baseline. Drug delivery to the stomach and jejunum resulted in similar concentrations at all sampling times except at 2 hr.

The mean (±SD) values of the pharmacokinetic parameters after drug administration to each of three anatomical sites are summarized in Table II. A significant difference was demonstrated for all pharmacokinetic parameters between the cecal administration data and either the gastric or the jejunal administration data with the exception of MRT and T_{MAX}. No difference could be demonstrated in any parameter between gastric and jejunal drug delivery.

Wagner–Nelson analysis of the cumulative fraction of the absorbed ranitidine dose at each sampling time indicated that the mean time for absorption of 90% of the dose eventually absorbed was between 2 and 2.5 hr after gastric or jejunal administration. This is compared to greater than 5 hr after the drug was delivered into the large intestine ($P = 0.0001$) (Fig. 2).

The plasma concentration vs time profile for each individual subject demonstrated double peaks in three of eight subjects when ranitidine was administered into the stomach and in eight of eight subjects when the drug was delivered into the jejunum. No double peaks were seen in any of the subjects when the drug was delivered into the large intestine, although it may have been masked due to the low concentrations achieved. A typical concentration–time profile of a subject exhibiting dual plasma concentration peaks is illustrated in Fig. 3.

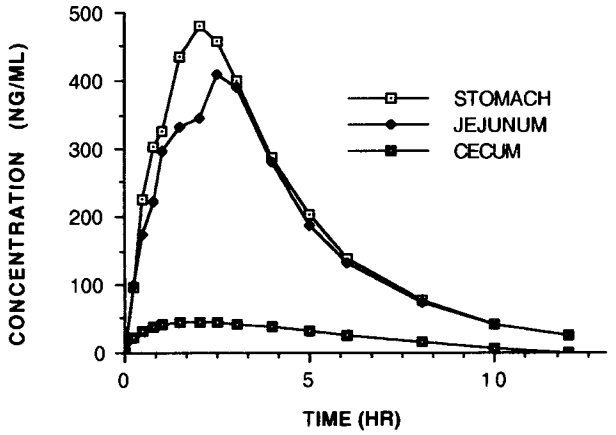

Fig. 1. Plasma ranitidine mean concentration–time profiles following bolus administration of ranitidine HCl, 150 mg, into the stomach, jejunum, and cecum. $N = 8$.

DISCUSSION

Pharmacokinetic analysis of the data demonstrates that absorption from the stomach and jejunum was essentially equal in extent and duration (no significant difference in AUC, C_{MAX}, MRT, and T_{MAX}). Absorption from the cecum, however, was much less extensive and occurred over a longer period of time. The relative bioavailability of ranitidine, after delivery into the cecum, was only approximately 15% of that observed when the drug was administered into the stomach or jejunum. The mean residence time (MRT) was 15 and 25% longer when the drug was administered into the cecum than into the jejunum or stomach, respectively. Since the MRT after oral administration equals the MRT after intravenous administration plus the mean absorption time (MAT), the results imply that the MAT is prolonged after cecal administration. Other evidence for prolonged absorption of ranitidine from the large intestine is provided by the Wagner–Nelson analysis, which demonstrated that absorption took place in the cecum throughout the 12-hr sam-

Table I. Mean (±SD) Ranitidine Concentration (ng/ml)

	Time (hr)							
	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50
Stomach	0.00 (0)	97.01 (45)	225.37 (81)	301.98 (102)	326.05 (72)	435.57 (163)	481.53 (131)*	458.76 (155)
Jejunum	0.00 (0)	100.19 (28)	174.95 (56)	223.57 (129)	298.06 (239)	331.26 (193)	343.67 (134)*	408.84 (143)
Cecum	0.00 (0)	21.77 (12)*	32.43 (13)*	38.95 (15)*	41.91 (19)*	44.57 (19)*	44.39 (17)*	43.83 (14)*
P value	NS	0.0003	0.0001	0.0002	0.0038	0.0003	<0.05	0.0001
	3.00	4.00	5.00	6.00	8.00	10.00	12.00	
Stomach	400.36 (86)	286.31 (64)	203.95 (42)	139.36 (27)	78.59 (16)	43.24 (13)	24.21 (7.5)	
Jejunum	390.81 (110)	281.71 (90)	187.38 (59)	131.66 (36)	75.21 (13)	40.80 (6.5)	25.50 (5.1)	
Cecum	43.16 (13)*	38.79 (12)*	32.73 (12)*	27.20 (14)*	15.92 (10)*	7.23 (7.3)*	0.00 (0)*	
P value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	

* Statistically significant difference from other sites of administration by two-way ANOVA and Duncan's analysis.

Table II. Mean (SD) Pharmacokinetic Parameters[a]

Parameter	K_{el}	AUCT	AUCI	MRT	Cl/F	C_{MAX}	T_{MAX}
Stomach	0.32 (0.03)	2196.40 (307)	2273.40 (315)	4.09 (0.55)	1119.10 (152.2)	580.60 (158)	2.69 (0.71)
Jejunum	0.31 (0.05)	1973.73 (608)	2060.78 (600)	4.49 (0.72)	1303.90 (339.4)	472.26 (190)	2.94 (0.73)
Cecum	0.23 (0.03)*	269.32 (114)*	330.97 (122)*	5.33 (0.61)*	9024.30 (4195)*	52.56 (18.2)*	2.69 (0.9)

[a] K_{el}, hr^{-1}; AUCT, ng · hr/ml; AUCI, ng · hr/ml; MRT, hr; Cl/F, ml/min; C_{MAX}, ng/ml; T_{MAX}, hr.
* Indicates a statistically significant difference from other sites of administration by Wilcoxon sign rank test with Bonferroni's correction: $P < 0.05$.

pling period and that the rate of absorption from the cecum was significantly less than from the stomach or jejunum. Additionally, the difference in oral clearance and elimination rate constant after cecum administration can probably be attributed to differences in the amount of drug absorbed from the cecum and to the prolonged absorption time, respectively.

The occurrence of the double peak after administration of the drug into the jejunum refutes the hypothesis of Oberle and Amidon (8) that this phenomenon is due to variable gastric emptying. This hypothesis suggests that gastric retention of a portion of the drug for some period of time is necessary for two peaks to occur. Although double peaks did occur in three of eight patients after gastric delivery, the occurrence of the phenomenon in all eight patients after direct jejunal delivery disproves the proposed model.

The data presented here may also be inconsistent with the "absorption window" theory. This theory proposes that ranitidine may be absorbed largely from a specific area within the proximal gastrointestinal tract (an absorption window), resulting in the initial peak plasma concentration. A second absorption window more distal in the gastrointestinal tract (i.e., ileum or colon) may absorb some of the remaining drug and produce a smaller, second absorption peak 2 or 3 hr later. The specific site(s) of ranitidine absorption throughout the gastrointestinal tract is (are) not known, although one previous study has shown that ranitidine is absorbed when administered in the rectal vault (12). Our data demonstrate that ranitidine appears to be equally well absorbed from the stomach and jejunum, but poorly absorbed from the large intestine, giving no support to the absorption window theory.

Little evidence exists to support the hypothesis of enterohepatic recycling as an explanation for the double-peak phenomenon. This hypothesis is refuted by the evidence from rat studies which found low (2–17%) but variable recovery of a histamine H2-receptor antagonist dose in the bile (13,14) and human studies which reported the recovery of only 1–2% of a cimetidine dose in the bile (15,16). These studies, however, measured only unchanged drug in the bile, and did not account for metabolites. Recovery of the drug in the bile would need to exceed 10% of the original administered dose to account for this double-peak phenomenon (17). Additionally, under this hypothesis one would expect double peaks to occur following both oral and intravenous dosing. However, double peaks have not been observed following intravenous administration of cimetidine. The possible accumulation of drug in some other physiologic site, with subsequent bolus release into the systemic circulation, cannot be ruled out. Additionally, the presence of metabolites in the bile that could be converted back to ranitidine by enteric flora needs to be explored. The data presented in this study do not support or refute this hypothesis.

CONCLUSIONS

This study demonstrates that the extent and duration of ranitidine absorption after gastric administration are equivalent to absorption after administration into the jejunum.

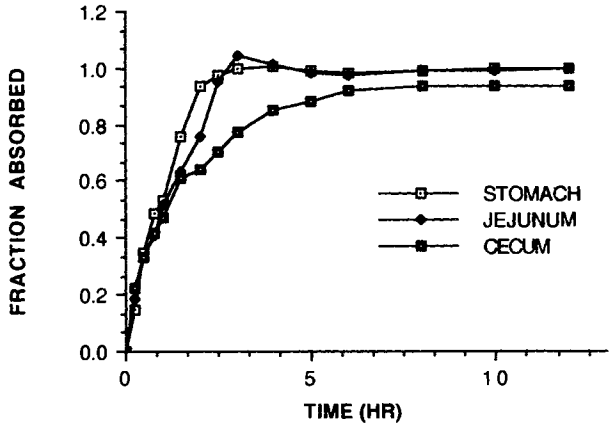

Fig. 2. Wagner–Nelson plot of cumulative fraction (mean) of absorbed ranitidine dose (150 mg) after administration into the stomach, jejunum, and cecum. $N = 8$.

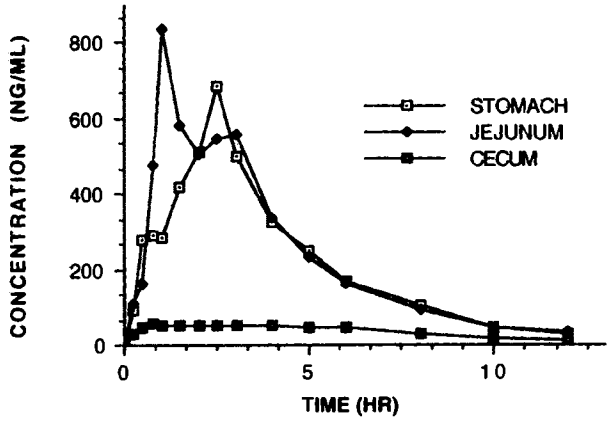

Fig. 3. Typical subject's plasma ranitidine concentration–time profiles following bolus administration of ranitidine HCl, 150 mg, into the stomach, jejunum, and cecum. Note the double concentration peaks after jejunal administration.

The extent of absorption after cecal administration, however, is significantly less than from the upper gastrointestinal sites, and the duration of absorption is prolonged. The occurrence of double peaks in the concentration vs time data after gastric and jejunal delivery are similar to those reported after oral administration of ranitidine.

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