Effect of Pancreatico-Biliary Secretions and GI Transit Time on the Absorption and Pharmacokinetic Profile of Ranitidine in Humans

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Purpose. Ranitidine plasma concentration vs. time profiles and the extent of ranitidine absorption were examined in the presence and absence of pancreatico-biliary secretions in order to elucidate factors which may contribute to secondary peaks after oral ranitidine administration.

Methods. Ranitidine solution (300 mg) was administered to 4 fasting healthy subjects via an indwelling small-bore oroenteric tube located ~16 cm distal to the pylorus. On 3 consecutive days, subjects randomly received ranitidine alone (control), ranitidine 10 min after 0.04 μg/kg IV cholecystokinin (CCK) sufficient to cause gall bladder emptying into the duodenum, and ranitidine 30 min after inflation of an occlusive duodenal balloon located ~10 cm distal to the pylorus to prevent pancreatico-biliary secretions from reaching the dosing port or beyond. Small bowel transit time (SBTT; min) was measured by breath H_2. Serial blood samples, obtained over 12 hours in each treatment, were analyzed by HPLC to determine ranitidine $AUC_{0\text{-}12}$ (ng*h/mL), as well as C_{max} (ng/mL) and T_{max} (min) of the first and subsequent peaks, if subsequent peaks were observed.

Results. Ranitidine $AUC_{0\text{-}12}$ and C_{max1} were not altered significantly by treatments; treatment effects on SBTT varied. Secondary peaks were observed in subjects #1 and #3 during the control treatment and subjects #2 and #4 during the CCK treatment. No secondary peaks were observed in any subject during the balloon treatment, and T_{max1} was delayed.

Conclusions. Results support the hypothesis that pancreatico-biliary secretions (present in the intestinal lumen during control or CCK treatment) and gastrointestinal transit time may influence the occurrence of secondary peaks in ranitidine concentration vs. time profiles.

KEY WORDS: ranitidine; absorption; secondary peak; bile; CCK; GI transit time.

INTRODUCTION

Ranitidine is a H_2 receptor antagonist used in the management of peptic ulcer disease and hypersecretory states. The pharmacokinetics of ranitidine have been examined in animal and in human clinical studies after oral administration. In normal fasting patients, ranitidine absorption is rapid with a negligible lag time. Bioavailability varies greatly between patients, but generally is in the 50–80% range (1).

Two peaks frequently are evident in the serum ranitidine concentration vs. time profiles after oral administration to fasting patients; the first peak usually occurs 1–2 hr after dosing, while the second peak usually is evident 3–5 hr after dosing (2,3). When ranitidine is administered with food, the secondary peak is either blunted or does not appear (1,4). Several other compounds, including the H_2 receptor antagonists cimetidine (5), famotidine (6), and etinidine (7), also display a secondary peak after oral administration.

Several mechanisms have been postulated to explain the secondary peaks observed after ranitidine administration. It is unlikely that enterohepatic recirculation contributes significantly to the occurrence of secondary peaks because 0.3–1.0% of an oral ranitidine dose was recovered in human bile (8) and less than 3% of the dose was excreted in rat bile (9). Cimetidine sulfoxide metabolite conversion to the parent drug in the gastrointestinal tract, with subsequent reabsorption, has resulted in bioavailabilities greater than 100% in healthy volunteers (10). However, this also is an unlikely explanation for secondary peaks with ranitidine because the extent of appearance of luminal sulfoxide in rat jejunum was significantly less for ranitidine than for cimetidine (11). A third possibility is that ranitidine is stored and subsequently released from a postabsorptive depot site; food may be the stimulus for release. Contradicting this theory are studies demonstrating that the time of the second peak did not change when food was administered 2 or 4 hr after ranitidine administration (2,12).

Several viable hypotheses to explain the secondary peaks observed following oral administration of ranitidine remain to be examined. Separation of the dose into two or more discrete boluses in the GI tract may contribute to the secondary peaks observed following oral administration of ranitidine. Although the mechanism(s) responsible for segmentation of the dose have not been defined, the observations that two ranitidine plasma concentration peaks were evident in 3 of 8 subjects after gastric administration and in 8 of 8 subjects after jejunal administration (13) support the hypothesis that alterations in GI transit, in addition to variable or delayed gastric emptying, contribute to the observed secondary peaks. Another plausible explanation is that the first ranitidine concentration peak may be due to duodenal absorption and the second peak may be due to ileal absorption, with decreased or no absorption in the mid small bowel. This hypothesis is supported by studies indicating that ranitidine absorption rates in humans are highest in two regions: the duodeno-jejunal junction and the distal jejunal-ileal junction (14). A final explanation put forth for the appearance of secondary peaks is the influence of bile. In a recent study, fasted male Sprague-Dawley rats with chronic indwelling bile duct cannulae received ranitidine by oral gavage with bile flow intact or interrupted in a cross-over fashion. Secondary peaks or prolonged plateaus were evident in all ranitidine serum concentration vs. time profiles when bile flow was intact, but were not evident in 3 of 4 rats when bile flow was interrupted (9). Bile also significantly enhanced the rate of ranitidine absorption from the rat ileum *in situ* (15).

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The mechanism of bile-associated alterations in ranitidine absorption and the relationship between bile flow and the incidence of secondary peaks in ranitidine plasma concentration vs. time profiles merit investigation. Therefore, the purpose of this study was to examine ranitidine plasma concentration vs. time profiles and the extent of ranitidine absorption in humans in the presence and absence of pancreatico-biliary secretions in order to elucidate factors which may contribute to secondary peaks after oral ranitidine administration.

MATERIALS AND METHODS

This study was conducted in the General Clinical Research Center (GCRC) at the University of North Carolina Hospitals and was approved by the Committee for the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine. All subjects gave written informed consent prior to participation in the study.

A total of 4 healthy male volunteers with a mean (range) age of 29 years (22–37), weight of 68.4 kg (59.4–81), height of 177. 9 cm (162.6–186) and within 26% of their ideal body weight participated in the study. Each subject underwent a physical examination, laboratory tests, and a thorough medical history to determine that all inclusion criteria were met.

This was a single dose, randomized, three-way crossover study. On three consecutive days subjects randomly received ranitidine alone (control), ranitidine 10 min after 0.04 μg/kg IV cholecystokinin (CCK) sufficient to cause gall bladder emptying into the duodenum, and ranitidine 30 min after inflation of an occlusive balloon located approximately 10 cm distal to the pylorus to prevent pancreatico-biliary secretions from reaching the dosing port or beyond.

Ranitidine was administered via an oroenteric multilumen tube assembly. One tube of the three-tube assembly was a 10 Fr sump tube opening into the second part of the duodenum, allowing aspiration of bile above the lumen-occluding balloon. The second tube (2 mm outside diameter) was a dual lumen. One lumen was used to inflate the occluding balloon in the distal second or proximal third part of the duodenum. The other lumen opened distal to the balloon and was used for drug administration. A stiffening wire was placed in this lumen prior to passing the tube assembly and was removed when the assembly was properly placed. The third tube (3 mm outside diameter) contained 2 pH probes, one located 2 cm from the tip of the assembly, and the other located 16 cm from the tip (10 cm proximal to the balloon).

Subjects were admitted to the GCRC on the evening prior to ranitidine administration. The multilumen tube assembly (6 mm diameter) was passed orally into the stomach, and the tip manipulated into the duodenum. Location and positioning of the tube assembly were monitored with the pH probes. A plain abdominal radiograph verified that the tip of the tube was located approximately 16 cm distal to the pylorus.

At the beginning of each treatment day, the position of the tube assembly was verified utilizing pH probes and radiographs. At 0730, 100 ml of water was administered via the drug delivery port. Fifteen min later, lactulose (5 gm) was administered via the drug administration port followed by 3 ml of water to flush the system. End expiratory breath was collected while the subjects exhaled into Quintron® breath bags at baseline and at 10 min intervals after lactulose administration until a significant rise in breath hydrogen was detected. This was defined as an increase in breath hydrogen concentration (ppm) for three consecutive samples, where at least a 10 ppm incremental increase existed between the third sample and the baseline hydrogen concentration. The midpoint time for these 3 samples was defined as the small bowel transit time (SBTT; 16–18). Free H_2 concentrations in breath were measured by an H_2 gas analyzer (Microlyzer Model 12, Quintron, Division of The Brewer Company).

During each treatment, a predose blood sample was collected at 0755. Ranitidine (300 mg; 12 ml of 25 mg/ml ranitidine for injection) was administered via the drug delivery port at 0800 followed by a 10 ml water flush. Twenty-two blood samples were collected from 0800 to 2000 at 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360 min and 7, 8, 10, 12 hr after dosing. No other procedures were performed during the control treatment. During the CCK treatment, an IV dose of CCK (0.04 μg/kg over 3 min) was administered at 0750, 10 min prior to the ranitidine administration. During the balloon treatment, 30 min prior to the ranitidine dose, the duodenal balloon was inflated with air (~20 ml) until the subject experienced mild discomfort to occlude the bowel and prevent the flow of bile into the third part of the duodenum. Bile was aspirated via a sump tube by continuous moderate suction. To insure that bile was not leaking below the balloon, 1.0 mCi technetium sulfacolloid (10 mL) was administered at 1200 into the proximal duodenum via the sump tube. Suction on the sump tube was interrupted for 15 min. Gamma camera images of the abdomen were obtained at 1215 and if necessary, at 1230. The balloon was deflated at 1230. For all treatment groups, meals were provided at 1300 and 1800 followed by a snack at 2200. The tube assembly was removed on the third day, five hours after dosing.

Ranitidine concentrations in serum were determined by HPLC (19). The area under the ranitidine serum concentration vs. time profile from 0–12 hr (AUC_{0-12}) was calculated by the linear trapezoidal method. The first and second (if present) ranitidine serum concentration maxima (C_{max1} and C_{max2}, respectively) and the time of each maximum (T_{max1} and T_{max2}, respectively) were determined by visual inspection of the profiles. When a second peak was observed, the reported C_{max} was the greater of either C_{max1} or C_{max2}. Distinct multiple peaks were defined as at least 2 consecutive concentrations between maxima that were <90% of both maxima, or 1 concentration at a 1-hr interval between either maximum that was <90% of both maxima (9).

RESULTS

All subjects tolerated ranitidine administration and the balloon procedures. No significant adverse events or physical or laboratory changes occurred during the three treatment periods. No leakage of sulfacolloid beyond the balloon occurred when the balloon was inflated. Ranitidine concentration vs. time data are graphically displayed in Figure 1 for all 4 subjects. The pharmacokinetic parameters and SBTT for each treatment are listed in Table 1.

The extent of ranitidine absorption measured by AUC_{0-12} and peak concentration (C_{max}) overlapped for the three treatments. These parameters were also similar for those profiles which did or did not exhibit a second peak. The mean AUC_{0-12}

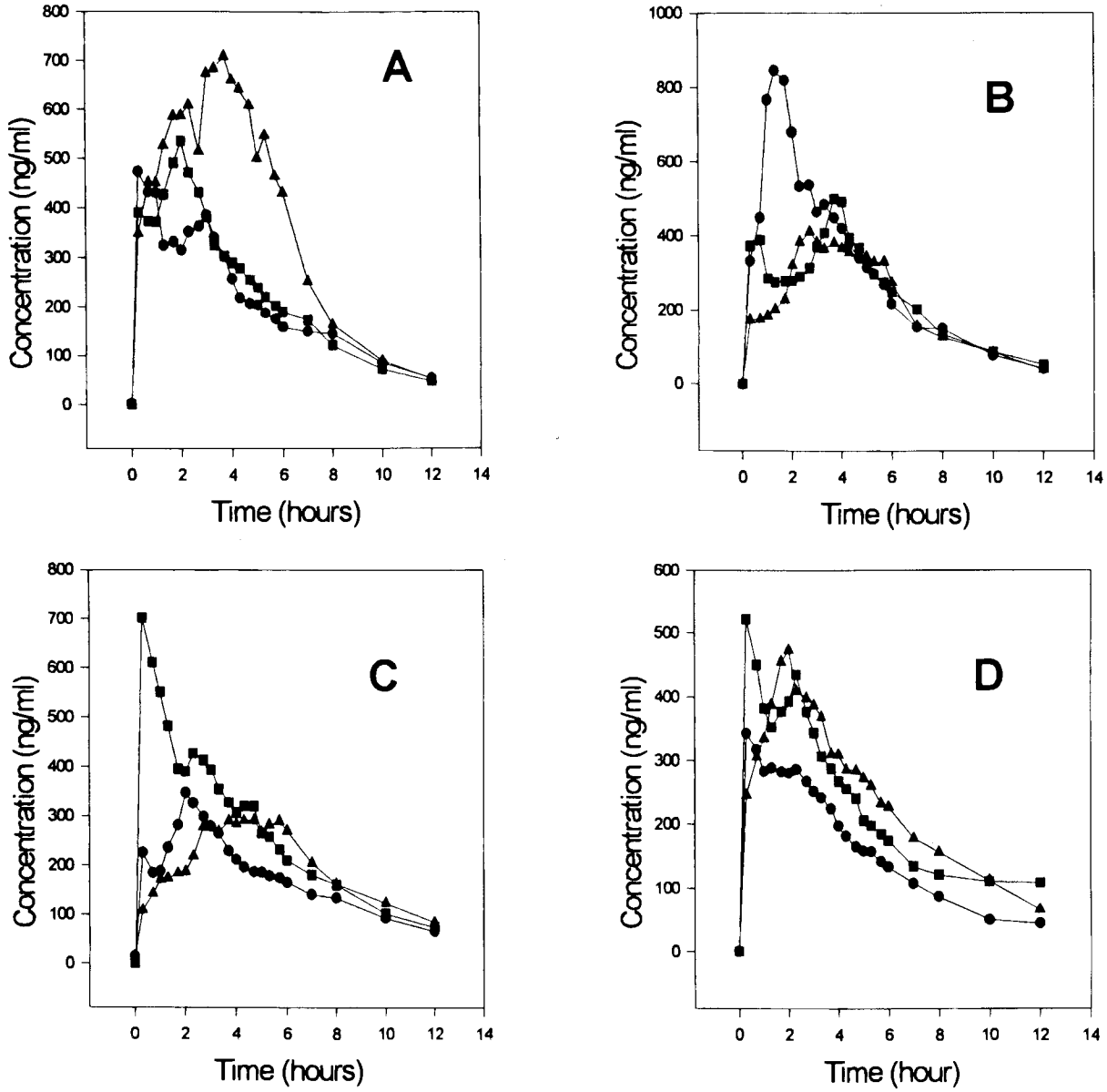

Fig. 1. Ranitidine concentration in plasma versus time profiles for subject 1 (A), subject 2 (B), subject 3 (C), subject 4 (D) for the three treatments; control (●), CCK (■), and balloon (▲).

± S. D. for profiles exhibiting a second peak was 2466 ± 314 ng*hr/ml and 2853 ± 738 ng*hr/ml for profiles not exhibiting a second peak. The C_{max} ± S.D. achieved in the profiles with and without a second peak was 460 ± 78 ng/ml and 538 ± 196 ng/ml, respectively. The ranges for both the reported C_{max} and AUC_{0-12} were large in this study, both within and across treatments. The extensive pharmacokinetic variability observed in this study is consistent with results from previous ranitidine studies that reported large interpatient as well as intrapatient variability (2).

Double peaks were observed during either the control or CCK treatments for all subjects. Profiles for subjects #1 and #3 exhibited a double peak during the control treatment while profiles for subjects #2 and #4 demonstrated double peaks during the CCK treatment. In the profiles with secondary peaks, the time of the first peak ranged from 20–40 min and the time of the second peak ranged from 120–220 min. Similar times for the occurrence of the first and second peaks were reported by Woodings et al. (30–90 min and 180–240 min, respectively; 3) and Shim *et al.* (30–150 min and 180–360 min, respectively; 2).

In contrast to the control and CCK treatments, double peaks were not observed for any subjects during the balloon treatment. The time range (120–280 min) of the single peak observed in the balloon treatment profiles was similar to the time range (120–220 min) of the secondary peak in those profiles described above that exhibited a double peak.

The SBTT measured by breath H_2 was not different for profiles with and without a double peak. Mean SBTT ± S.D. for profiles with a double peak was 70 ± 29 min and for profiles without a double peak was 88 ± 87 min. However, during the treatments in which bile presumably was present

Table 1. Summary Data

Treatment	Subject	SBTT (min)	AUC (ng*h/mL)	T_{max1} (min)	C_{max1} (ng/mL)	T_{max2} (min)	C_{max2} (ng/mL)
Control	**1**	**80**	**2448**	**20**	**472**	**180**	**384**
	2	50	3500	80	844	—	—
	3	**70**	**2035**	**20**	**225**	**120**	**347**
	4	40	1823	20	343	—	—
CCK	1	30	2658	120	535	—	—
	2	**30**	**2763**	**40**	**389**	**220**	**497**
	3	50	3086	20	702	—	—
	4	**100**	**2618**	**20**	**522**	**140**	**435**
Balloon	1	70	4195	220	708	—	—
	2	90	2500	160	411	—	—
	3	314	2295	280	291	—	—
	4	60	2765	120	473	—	—

Note: —No secondary peak observed. Numbers in bold indicate those treatment periods with a secondary peak.

(control or CCK) and SBTT was longer (70, 80 and 100 min), a double peak was observed in 3 of the 4 subjects. In contrast, a double peak was not observed for the same 3 subjects during the control or CCK treatments when SBTT was shorter (30, 40, and 50 min). SBTT was longer (60, 70, 90 and 314 min) during the balloon occluded treatment but no secondary peaks were observed, presumably because pancreatico-biliary secretions were not present.

DISCUSSION

In the balloon occluded treatment, none of the 4 subjects exhibited a double peak. Due to the occlusion, these subjects had no pancreatico-biliary secretions entering into the small bowel. In contrast, varying amounts of pancreatico-biliary secretions undoubtedly entered the GI tract during the other two treatments. CCK-stimulated contraction of the gallbladder should release bile into the intestine. However, if the subject's gallbladder contracted prior to CCK administration, the volume of bile entering the GI tract may have been less than expected during this treatment. During the control treatment, bile may or may not have been present during the dosing period depending on whether and when the subject's gallbladder contracted in relation to the oral ranitidine dose. To circumvent this ambiguity, a sonagram of the gallbladder could have been utilized to determine gallbladder emptying during the control and CCK treatments. Sonograms were used in a recently published study that examined the effect of bile on the pharmacokinetic profile of a sustained-release theophylline formulation; 94.6% gallbladder evacuation was observed 36 min after CCK administration (20).

The appearance of double peaks in both the control and CCK treatments, but not during the balloon occluded treatment, indicates that the presence of pancreatico-biliary secretions may influence the occurrence of secondary peaks in ranitidine concentration vs. time profiles. Bile acids may affect drug absorption by increasing the solubility of the drug due to formation of mixed micelles of bile acids (21). The GI absorption of drugs such as heparin (22) and gentamycin (23) is enhanced by the production of micelles *in situ* resulting in increased permeability of the intestinal wall. However, the absorption of other drugs such as quinine and imipramine is decreased *in situ* (24) due to formation of a stable, poorly absorbed drug-bile micelle rather than altered permeability of the intestinal wall.

Ranitidine concentration vs. time profiles differed in appearance among treatments due to the occurrence of a second peak in some profiles during the control and CCK treatments, but not during the balloon occluded treatment. However, the extent of absorption, as measured by AUC_{0-12} and C_{max}, was similar across all three treatments. These results suggest that the presence of pancreatico-biliary secretions may be necessary for the occurrence of a second peak. However other factors such as longer SBTT may also influence the incidence of secondary peaks in the presence of bile. Further investigations are needed to fully elucidate the mechanism(s) responsible for the occurrence of secondary peaks in ranitidine plasma concentration vs. time profiles.

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