Effect of Sodium Acid Pyrophosphate on Ranitidine Bioavailability and Gastrointestinal Transit Time

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During development of a ranitidine effervescent oral solution dosage form, a marked decrease was observed in the extent of ranitidine absorption relative to the conventional oral tablet. Two studies were conducted in healthy volunteers to confirm the involvement of an excipient, SAPP (sodium acid pyrophosphate), and the mechanism of interaction, altered gastrointestinal transit. The first study (n = 12) involved single-dose crossover comparisons of (A) 150 mg ranitidine with 1132 mg SAPP versus (B) 150 mg ranitidine and (C) 150 mg ranitidine with all the effervescent tablet excipients except SAPP versus (D) a 150-mg ranitidine effervescent tablet, all administered as oral solutions. Serum ranitidine AUC, C_{max}, and t_{max} were compared using two one-sided t test 90% confidence intervals (CI). Comparing treatments A to B and D to C, all 90% CI were below the 80–120% range, indicating significantly less extensive ranitidine absorption (54% based on AUC) from the oral solutions containing SAPP. The second study (n = 12) was a single-dose crossover comparing 50 μCi ^{111}InCl solutions with and without 1132 mg SAPP. Gastrointestinal transit times, determined by scintigraphic imaging, were compared between treatments. Gastric emptying time was unchanged, but small intestinal transit time was decreased to 56% in the presence of SAPP. More rapid small intestinal transit associated with an excipient of a solution dosage form apparently resulted in a decreased extent of ranitidine absorption. This observation contradicts the conventional wisdom that oral solutions are unlikely to fall short of bioequivalence relative to solid oral formulations.

KEY WORDS: ranitidine; effervescent tablet; absorption; bioavailability; bioequivalence; sodium acid pyrophosphate; gastrointestinal transit time.

INTRODUCTION

Ranitidine HCl (Zantac, Glaxo Inc.) is a histamine H_2-receptor antagonist used primarily in tablet and injectable dosage forms. An oral effervescent solution of ranitidine was developed as an alternative formulation. Such an effervescent formulation requires an acid excipient to react with sodium bicarbonate, producing effervescence in solution. Because ranitidine is unstable in the presence of most acids, including those commonly used in effervescent preparations, a series of potential acid excipients was evaluated.

Sodium acid pyrophosphate (SAPP) was identified as an acceptable acid excipient. SAPP is a commonly used food additive found most frequently in bakery products. The average daily intake of SAPP is 214 mg, or 2.8% of the maximum safe daily intake of phosphorus (1). SAPP was chemically compatible with ranitidine, provided rapid disintegration of the effervescent tablet, and produced a palatable, carbonated solution.

Because the effervescent formulation delivers ranitidine in solution, the rate, if not the extent, of absorption might be expected to equal or possibly exceed that from a conventional oral tablet. However, the first study in which this effervescent formulation was administered revealed that the extent of ranitidine absorption was nearly half that from the conventional tablet (data on file, Glaxo Inc. Research Institute).

Thus, we undertook a study to determine the effect of SAPP on ranitidine bioavailability. In addition, we conjectured that SAPP might exert an effect by altering intestinal motility. Therefore, a second study was carried out to determine the effect of SAPP on gastrointestinal transit.

MATERIALS AND METHODS

Subjects

Two studies were conducted in two different groups of 12 healthy adult males. Volunteers were accepted for study participation based on medical history, physical examination, and routine clinical laboratory tests. Both studies were reviewed and approved by institutional review boards. All participants gave written informed consent.

Study Design

Study One. The effect of SAPP on the relative bioavailability of ranitidine was determined in a balanced, open-label, single-dose, four-period, crossover study in which four treatments were given:

(A) 150 mg ranitidine with 1132 mg SAPP (powder),
(B) 150 mg ranitidine (powder),
(C) 150 mg ranitidine with all excipients of the effervescent tablet *except* SAPP (powder), and
(D) 150 mg ranitidine effervescent formulation containing 1132 mg SAPP (tablet).

Treatments A and B were randomly assigned within the first two periods, and treatments C and D in the second two periods. All treatments were separated by 3 days.

Immediately prior to dosing, each treatment formulation was dissolved for 5 min in 120 mL room temperature tap water. Another 120 mL of water was used to rinse the dosing glass and ensure complete ingestion. Volunteers were fasted from 8 hr before to 5 hr after dosing (absorptive phase). Water was available ad libitum after 4 hr postdosing.

Blood samples were taken prior to dosing and 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 16 hr after dosing. Serum was separated and stored at −20°C until assayed.

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Study Two. The effect of SAPP on gastrointestinal transit was evaluated in a single-dose, crossover study in which volunteers were randomly assigned each of two treatments.

Control: 200 mL sterile water (Baxter Travenol, Chicago, IL) containing 50 μCi of ^{111}InCl (Amersham, Arlington Heights, IL).

SAPP: 200 mL sterile water (Baxter Travenol, Chicago, IL) containing 50 μCi of ^{111}InCl (Amersham, Arlington Heights, IL) with 1132 mg SAPP.

Treatments were separated by 3 days. A standard meal was provided 8 hr prior to dosing, following which, volunteers fasted until completion of the study. Water was available ad libitum after 4.5 hr postdosing.

Anterior gamma-scintigraphic imaging in sequential 1-min increments was performed with each volunteer in the supine position, beginning immediately after dosing and continuing until radioactivity reached the cecum. Volunteers whose radioactivity had not reached the cecum after 4.5 hr of continuous imaging were allowed to ambulate freely for 0.5 hr before resuming imaging.

Assessments

Ranitidine Concentrations. Serum ranitidine concentrations were determined by HPLC with UV absorbance detection (2). The method was linear ($r \geq 0.99$) over the 10 to 250 ng/mL range. Precision was within 7%, and accuracy was within 3% of nominal. The limit of quantitation was 10 ng/mL.

Pharmacokinetic Parameters. Model-independent pharmacokinetic analysis was performed using Biopak 1.25 software (SCI, Lexington, KY). Observed peak serum concentration (C_{max}) and time (t_{max}) were determined. Area under the serum concentration-versus-time curve (AUC) was calculated by linear trapezoidal interpolation with logarithmic trapezoidal extrapolation to infinity. Elimination half-life ($t_{1/2}$) was calculated by log-linear regression.

Gamma-Scintigraphic Methods. Dosing solutions contained 50 μCi ^{111}InCl with gamma emissions at 172 and 247 keV and a half-life of 2.8 days. A gamma-scintillation camera (Siemens BasiCamera, Chicago, IL) was used to record images, which were converted for electronic analysis using applicable software (ACE; Springfield, WI).

Gastrointestinal Transit Times. Gastric emptying time (GET) was the time required for 50% of the radioactive label to pass the pylorus. Small intestinal transit time (SITT) was the difference between the GET and the time required for 50% of the radioactive label to pass the cecum.

Statistical Methods. AUC, C_{max}, and t_{max} were compared as ratios of values for treatments with SAPP relative to treatments without SAPP (i.e., treatments A/B and D/C). Relative bioavailability of ranitidine was assessed using 90% CI derived from two one-sided t tests to determine whether AUC, C_{max}, and t_{max} for treatments with SAPP were within 80–120% of the same parameters for treatments without SAPP. Treatment, period, and subject effects were tested with analyses of variance (ANOVA) using SAS 6.03 software (SAS, Cary, NC). Gastrointestinal transit times were compared using two-sided, paired t tests.

RESULTS

Pharmacokinetic Parameters

Mean serum ranitidine concentrations for treatments A, B, C, and D are plotted in Fig. 1. Mean serum ranitidine pharmacokinetic parameters are listed in Table I.

The ratios of C_{max}, t_{max}, and AUC for treatments A to B and D to C indicate that less ranitidine was absorbed from

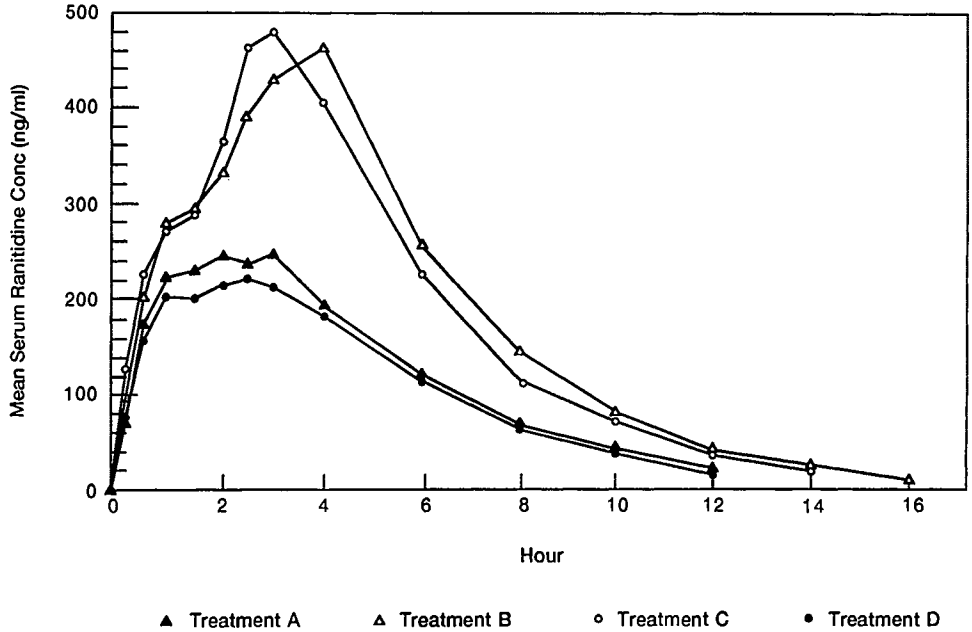

Fig. 1. Mean serum ranitidine concentrations following 150-mg oral solution doses of ranitidine: with 1132 mg SAPP (Treatment A), alone (Treatment B), with all the excipients of the effervescent tablet except SAPP (Treatment C), and as the effervescent tablet containing 1132 mg SAPP (Treatment D).

Table I. Mean ± SD Ranitidine Pharmacokinetic Parameters[a]

	AUC (ng · hr/mL)	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)[b]
Treatment A	1586 ± 502	271 ± 81	2.0 ± 0.7	1.14
Treatment B	2891 ± 673	539 ± 175	3.5 ± 1.0	1.21
90% CI[c]	44–65%	34–66%	39–75%	
Ratio A/B[d]	0.534	0.503	0.572	
Treatment C	2757 ± 855	523 ± 214	2.8 ± 0.9	1.15
Treatment D	1449 ± 333	245 ± 62	2.0 ± 1.0	1.13
90% CI[c]	42–63%	30–64%	49–94%	
Ratio D/C[d]	0.540	0.501	0.671	

[a]Treatment A—ranitidine, 150 mg, with 1132 mg SAPP; B—ranitidine, 150 mg; C—ranitidine, 150 mg, with all effervescent tablet excipients except SAPP; D—ranitidine, 150-mg effervescent tablet containing 1132 mg SAPP.
[b]Harmonic mean.
[c]Confidence interval.
[d]Geometric mean of ratios relative to treatment without SAPP.

the solutions with SAPP than from those without SAPP (Table I). In comparing treatments with SAPP to those without SAPP, the 90% CI for serum ranitidine AUC, C_{max}, and t_{max} were all well below the 80–120% range, indicating less extensive and possibly more rapid absorption of ranitidine. The geometric mean ratio of AUC for treatments A to B and D to C were both approximately 0.54, indicating that the extent of ranitidine absorption was approximately halved from treatment solutions with SAPP compared to those without.

Gastrointestinal Transit Times

No significant difference was observed in mean GET after administration of ^{111}InCl solutions with SAPP compared to those without SAPP (Table II). However, mean SITT values were significantly ($P = 0.0002$) shortened after administration of solutions containing SAPP, resulting in values 56% of those from solutions without SAPP (Table II).

DISCUSSION

The extent of ranitidine absorption was decreased when administered orally in solutions containing SAPP. This effect was similar without regard for the presence of all the excipients of the effervescent tablet other than SAPP. Thus, the differences between treatments associated with the presence of SAPP indicate that the decrease in ranitidine absorption was brought about by this excipient of the effervescent solution dosage form.

Table II. Mean ± SD Gastrointestinal Transit Times[a]

Treatment	GET (min)	SITT (min)
Control treatment	21 ± 14	325 ± 66
SAPP treatment	17 ± 7	185 ± 52
Ratio (SAPP/control)[b]	0.90	0.56
P value	0.45	0.0002

[a]Control, 200 mL water containing 50 μCi ^{111}InCl; SAPP, 200 mL water containing 50 μCi ^{111}InCl with 1132 mg sodium acid pyrophosphate.
[b]Geometric mean.

Gastrointestinal transit was assessed after an oral dose of 1132 mg SAPP to determine whether this might be the mechanism by which ranitidine absorption was diminished. Gastric emptying was unaffected by inclusion of SAPP. However, small intestinal transit time was nearly halved after administration of solutions with SAPP compared to those without SAPP. Ranitidine is primarily absorbed proximal to the cecum (3), with an absolute bioavailability of 50% (4). Therefore, faster transit through the small intestine could explain the observed reduction in the extent of ranitidine absorption to 54% of control in the presence of 1132 mg SAPP. The shortened t_{max} is also consistent with more rapid transit of ranitidine through that portion of the gut where it is absorbed. The similarity in the extents to which ranitidine absorption and SITT were reduced was striking.

The effect of SAPP on intestinal transit is consistent with the pharmacological action of sodium phosphate salts (5). In this regard, SAPP may be considered a saline cathartic, osmotically retaining water within the gut lumen to indirectly stimulate increased peristalsis. Although the 1132-mg dose of SAPP used in these studies was below the lowest therapeutic dose as a cathartic (4 g), it was not without effect.

Previous experience indicated that the extent of ranitidine absorption was reduced from this effervescent tablet formulation administered as an oral solution. This finding was unexpected because the rate, if not the extent, of absorption from a solution was expected to equal or possibly exceed that from a solid dosage form (presuming dissolution to be rate-limiting). The present studies demonstrate that ranitidine absorption was decreased by SAPP, an excipient in the effervescent solution formulation.

SAPP has since been replaced by another acid excipient, in order to progress development of the effervescent ranitidine tablet. However, the results of these studies serve to demonstrate the danger in presuming that an oral solution formulation of ranitidine, and perhaps other drugs, will not be less bioavailable than a standard solid oral dosage form.

CONCLUSION

Ranitidine absorption was decreased by nearly 50% from solutions containing SAPP compared to those without SAPP. This decrease occurred regardless of the presence of all the other excipients of the effervescent tablet formulation and may be explained by the fact that SAPP caused a commensurate decrease in small intestinal transit time. These studies contradict the conventional wisdom that bioequivalence to standard solid oral formulations will be either met or exceeded by oral solution formulations.

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