The Effect of Raising Gastric pH with Ranitidine on the Absorption and Elimination of Theophylline from a Sustained-Release Theophylline Tablet

Charles J. Betlach,[1] Arthur B. Straughn,[2,4] Marvin C. Meyer,[2] Meir Bialer,[3] V. I. Vashi,[2] Philip Lieberman,[2] and Mario A. González[1]

Received December 14, 1990; accepted June 7, 1991

Prior to evaluating the effect of ranitidine on theophylline absorption from a sustained-release theophylline tablet, the effect of ranitidine on the time course of gastric pH in 12 healthy subjects was evaluated with an encapsulated radio-telemetry device (Heidelberg capsule). Gastric pH was measured hourly from 7 AM to 1 PM prior to beginning ranitidine treatment at 2 PM (150 mg every 4 hr for eight doses). The next day, pH was again measured hourly from 7 AM to 7 PM. Subjects fasted overnight and remained fasted until lunch at 11 AM. Prior to ranitidine treatment, the mean morning gastric pH remained between 1.5 and 2.2. After lunch, the pH increased to 2.2–2.3. During ranitidine treatment the mean morning gastric pH measurements were 5.5 to 5.8, decreasing after lunch to 3.1 by 4 PM and increasing to 3.9 at 7 PM. One week later the subjects participated in a three-way crossover theophylline bioavailability study receiving at weekly intervals, single doses at 7 AM of (a) 5 × 100-mg immediate-release tablets, (b) 2 × 300-mg sustained-release theophylline tablets, and (c) 2 × 300-mg sustained-release theophylline tablets after ranitidine pretreatment of 150 mg every 4 hr beginning at 2 PM the previous day. The increase in gastric pH with ranitidine had no effect ($P > 0.05$) on the rate and extent of absorption or on the elimination rate of theophylline.

KEY WORDS: theophylline; ranitidine; Heidelberg capsule; gastric pH; pharmacokinetics; absorption; drug interaction.

INTRODUCTION

It has been recognized that changes in physiologic function can influence the gastrointestinal absorption of certain drugs (1,2). An example of such a disorder is achlorhydria (3,4), which is characterized by a lack of gastric acid production. Elevation in gastric pH can also be due to the intake of antacids or H_2 antagonists such as cimetidine and ranitidine (5). While the effects of H_2 antagonists on theophylline metabolism have been extensively investigated (6–13), the influence of ranitidine on theophylline's absorption has not been studied.

The objectives of the current study were as follows: (a) to investigate the interaction between ranitidine and theophylline, with a special emphasis on theophylline absorption, and (b) to monitor with the Heidelberg capsule the time course of changes in gastric pH after ranitidine treatment. The present report deals with the effect of multiple doses of ranitidine tablets on gastric pH in healthy male subjects. The same subjects then participated in a three-way crossover study, to determine the effect of multiple doses of ranitidine on the absorption and/or elimination of theophylline from a sustained-release tablet (Theo-Dur tablets).

MATERIALS AND METHODS

Subjects

Twelve healthy male volunteers, aged 22 to 29 years and weighing 64 to 90 kg, participated in this study. Selection for the study involved providing a complete medical history, a physical examination, an acceptable clinical laboratory examination to include SMA 18/90, CBC with differential and urinalysis, and an electrocardiogram. The subjects were free of any medication for 7 days prior to the study and of any theophylline-containing medication for 30 days prior to the study. Xanthine-containing food and beverages were excluded from the diet during each 49-hr study period as well as the 48 hr prior to each treatment. Each subject signed a written informed consent.

Gastric pH Study

On the first day the subjects reported after an overnight fast and each swallowed a Heidelberg capsule along with 60 ml of water. The capsule was tethered with unwaxed dental floss to an anterior mandibular tooth. The floss was adjusted so that the Heidelberg capsule remained in the fundus of the stomach. The floss length was individualized for each subject by measuring from the tip of the subject's nose (with his head tilted back) to his xiphoid process. The Heidelberg capsule is an encapsulated radiotelemetric device (14) that measures the pH and transmits the reading to a receiver that is located within 1 m of the subject. Gastric pH was measured every hour beginning at 7 AM and ending at 1 PM. After the last reading the capsule was recovered by withdrawing the floss; the calibration was checked and the capsule was discarded.

Ranitidine (Zantac, 150-mg tablets, Glaxo, Inc., NC) was dosed as 150 mg every 4 hr with 8 oz water. Dosing began 1 hr after the Heidelberg capsule was recovered for a total of eight doses at 2 PM, 6 PM, 10 PM, 2 AM, 6 AM, 10 AM, 2 PM, and 6 PM. On the second day the subjects reported to the study site to receive the 6 AM ranitidine dose. Another Heidelberg capsule was swallowed with 60 ml of water by all the subjects and gastric pH measurements were made hourly from 7 AM until 7 PM. The Heidelberg capsule was recovered and the calibration checked. On both study days the subjects remained in the fasted state until 11 AM, at which time a standard lunch was served (1062 kcal, 44% fat). A standard supper was administered at 5 PM on the second day and contained 840 kcal, of which 46% was fat. Water was per-

[1] Department of Biopharmaceutics and Pharmacokinetics, Schering-Plough Research, Miami, Florida.
[2] Department of Pharmaceutics, College of Pharmacy, University of Tennessee, Memphis, Tennessee 38163.
[3] Visiting Professor from Hebrew University of Jerusalem, School of Pharmacy, Jerusalem, Israel.
[4] To whom correspondence should be addressed at Department of Pharmaceutics, College of Pharmacy, University of Tennessee, 874 Union Avenue, Room 5, Memphis, Tennessee 38163.

0724-8741/91/1200-1516$06.50/0

mitted ad lib. except for 1 hr after each dose and 0.5 hr before each gastric pH measurement.

Theophylline Absorption Study

A week after the gastric pH study all 12 subjects received the following treatments in a randomized crossover at 1-week intervals: 500 mg of immediate-release theophylline tablets (5 × 100 mg, Slo-Phyllin, W. H. Rorer, Inc.), 600 mg of sustained-release theophylline (SRT) tablets (2 × 300 mg, Theo-Dur tablet, Schering-Plough Corporation), and 600 mg of the SRT tablets with concomitant treatment of ranitidine. For the ranitidine treatment phase, subjects began taking 150-mg doses at 2 PM on the day prior to receiving theophylline and continued taking the ranitidine every 4 hr for eight consecutive doses. On each of the 3 theophylline dosing days, the subjects reported to the study site after an overnight fast and received their dose of theophylline between 6:50 AM and 7:00 AM with 180 ml of water. No food was allowed until a standard lunch was served 4 hr after dosing, and a standard supper served 10 hr after dosing. The consumption of water was the same for both theophylline treatments. Gastric pH readings were not taken during this phase, to avoid any potential effect of the Heidelberg capsule on the absorption of theophylline from the dosage form.

Blood Sampling Scheme

Eight-milliliter blood samples were obtained before dosing and then at 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 25, 30, 34, and 49 hr after theophylline dosing. Samples were collected either by venipuncture or through an indwelling venous catheter using a 10-ml plastic syringe (Becton-Dickinson, Rutherford, NJ). The samples that were obtained from the catheter were cleared of residual heparin before obtaining the 8-ml blood sample. The blood was transferred to a 10-ml red-topped vacutainer tube, and the blood allowed to clot at room temperature. After centrifugation, the serum fraction was transferred to glass vials for storage at −20°C until assayed.

Theophylline Assay

Theophylline concentrations in serum were determined by high-performance liquid chromatography and employed a reversed-phase μBondapak C18 column with detection at 274 nm based on the method of Farrish and Wargin (15). The assay was fully validated and the detection limit was 0.1 μg/ml.

Pharmacokinetic and Statistical Analysis

The area under the serum concentration–time curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to time infinity. The extrapolation was accomplished by dividing the last experimental data point in the concentration–time curve by the first-order terminal rate constant (K). This value was then added to the AUC determined to the last experimental data point used for the calculation of K (16). The first-order (terminal) elimination rate constant was determined by least-squares fit of the natural log-transformed terminal serum concentration-versus-time curve in each data set. The data points utilized for this fit were those which visually appeared to be linear. The half-life of theophylline was calculated from the quotient of ln 2 (natural log of 2) and K. The extent of absorption (F) of the SRT tablet was calculated from the ratio of the SRT's AUC to the AUC of the dose normalized immediate release reference. Previous reports showed that the immediate-release theophylline reference was completely absorbed (17). Peak serum concentration (C_{max}) and time to reach C_{max} (t_{max}) were obtained by inspection of the individual serum concentration-time profiles. The percentage of drug absorbed at each time point was calculated using the Wagner–Nelson method utilizing the terminal K as determined above (18). The time to 50% (T-50) and 80% (T-80) absorption was calculated from the Wagner–Nelson absorption data. Each parameter was statistically evaluated using analysis of variance (ANOVA). The power analysis was utilized to detect the presence of type 2 errors.

RESULTS

All 12 subjects successfully completed the study. Several subjects complained of a headache, abdominal cramps, and/or nervousness. In general, the subjects felt somewhat uncomfortable with the tethered Heidelberg capsule and reported soreness in their throat. Several subjects did evoke a gag reflex when swallowing and/or recovering the capsule but none of the subjects vomited.

The mean (±standard error) gastric pH before and after ranitidine is illustrated in Fig. 1. The mean gastric pH before the ranitidine and before lunch ranged from 1.5 to 2.2; after lunch the mean pH increased slightly to 2.2 to 2.3. After ranitidine treatment and prior to lunch, the mean pH was steady with a range of 5.5 to 5.8. After lunch, the pH declined over the next 5 hr to a mean pH of 3.1. After supper the mean pH increased slightly to 3.5 and remained approximately at this pH for the next 2 hr. All Heidelberg capsules were recovered and recalibrated at the end of the study and were fully active and operational. It was assumed that these pH levels were indicative of the pH changes occurring during the theophylline absorption study since all subjects were treated identically during the pH assessment and theophylline dosing phase.

The ranitidine treatment had no effect on the absorption or elimination of theophylline as can be seen in Fig. 2a and Table 1. The extent of absorption of theophylline from the SRT tablets was the same with (90%) and without ranitidine (89%). The C_{max}, t_{max}, and elimination $t_{1/2}$ were unchanged with ranitidine treatment. The rate of theophylline absorption was also examined with the Wagner–Nelson method.

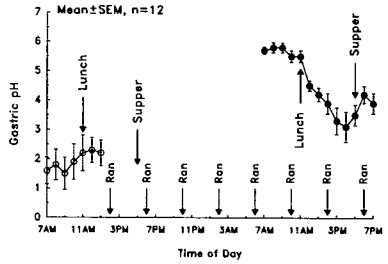

Fig. 1. The mean ±SE gastric pH prior to ranitidine administration and after multiple treatments with 150 mg of ranitidine dosed every 4 hr. The time of the ranitidine dose is indicated by "Ran."

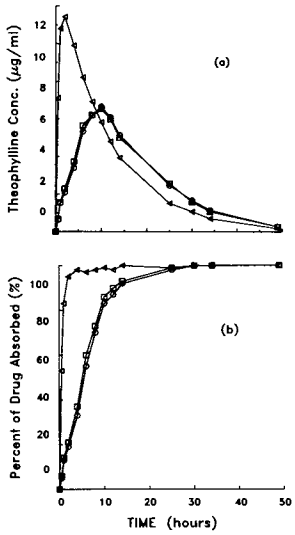

Fig. 2. (a) Mean serum theophylline levels and (b) Wagner–Nelson absorption profiles for Slo-Phyllin tablets (◁), Theo-Dur tablets (○), and Theo-Dur tablets with concomitant treatment with ranitidine (□).

These results, presented in Fig. 2b and Table 1, illustrate that ranitidine has no significant effect on the rate of theophylline absorption from the SRT tablets. The time to 50 and 80% absorption was the same for both sustained-release treatments. Power to detect a 20% difference for all parameters except t_{max} was >0.9. The power for t_{max} was 0.1. This low power reflects the inherient large variation in t_{max} that is often observed with oral products.

DISCUSSION

This study shows that an increase in gastric pH caused by ranitidine did not affect the extent and rate of theophylline absorption after oral administration of the SRT. These results are supported by the pH independent *in vitro* dissolution studies (19) and the lack of food effects on the absorption of theophylline from this SRT (19–21).

The decrease in acid secretion and subsequent increase in the gastric pH (Fig. 1) have the potential of directly affecting the dissolution and absorption of a drug from a sustained-release formulation and indirectly affecting these processes by changing gastric motility and emptying rate. It is well accepted that gastric emptying is promoted by a high pH (22). It has been demonstrated, in a number of articles, that ranitidine accelerates gastric emptying (23–26). There have been others, however, who have reported a decrease (27–29) or no effect on gastric emptying (30).

As observed here and by others (26), ranitidine treatment caused an increase in the gastric pH over baseline. An interesting observation is that, despite ranitidine treatment, the gastric pH was lowered after lunch in the volunteers. This decrease in pH after lunch may be due to gastrin stimulation by the food, which overrides ranitidine's ability to block acid secretion.

Table I. The Mean (Coefficient of Variation) Pharmacokinetic Parameters[a]

Parameter	1	2	3
AUC (μg · hr/ml)	154 (24)	139 (27)	138 (28)
F (%)	—	89 (11)	90 (9)
C_{max} (μg/ml)	12.1 (18)*	6.8 (25)	6.6 (20)
t_{max} (hr)	1.8 (50)*	10.5 (21)	9.0 (24)
T-50 (hr)	0.5 (40)*	6.0 (27)	5.4 (20)
T-80 (hr)	1.1 (54)*	9.8 (36)	9.7 (28)
Elim $t_{1/2}$	7.2 (35)	7.6 (16)	7.6 (13)

[a] (1) Slo-Phyllin tablets, 5 × 100 mg; (2) Theo-Dur tablets, 2 × 300 mg; (3) Theo-Dur tablets, 2 × 300 mg with concomitant ranitidine dosing.

* $P \leq 0.05$ in comparison to Treatments 2 and 3.

ACKNOWLEDGMENTS

We wish to thank Ms. Jonalynn Birnbaum for her assistance in the preparation of this manuscript. The loan of a Heidelberg capsule system by Heidelberg International, Division of Electro-Medical Device, Inc., Norcross, GA 30092, is gratefully acknowledged.

This paper was presented at the Second National Meeting of the American Association of Pharmaceutical Scientists, Boston, Massachusetts, 1987.

REFERENCES

1. P. G. Welling. Interactions affecting drug absorption. *Clin. Pharmacokin.* 9:404–434 (1984).
2. A. Rubinstein, V. Hon Kin Li, P. Gruber, and J. R. Robinson. Gastrointestinal-physiological variables affecting the performance of oral sustained release dosage forms. In A. Yacobi and E. Halperin-Walega (eds.), *Oral Sustained Release Formulations: Design and Evaluation*, Pergamon Press, New York, 1988, pp. 125–156.
3. A. Pottage, J. Nimmo, and L. F. Prescott. The absorption of aspirin and paracetamol in patients with achlorhydria. *J. Pharm. Pharmacol.* 26:144–145 (1974).
4. W. O. Frank, K. E. Peace, M. Watson, J. J. Seaman, P. L. Szego, A. Braverman, B. Mico, and B. Dickson. The effect of single intravenous doses of cimetidine or ranitidine on gastric secretion. *Clin. Pharmacol. Ther.* 40:665–672 (1986).
5. R. L. Lalonde, R. A. Koob, W. M. McLean, and A. J. Balsys. The effects of cimetidine on theophylline pharmacokinetics at steady state. *Chest* 83:221–224 (1983).
6. J. R. Powell, J. F. Rogers, W. A. Wargin, R. E. Cross, and F. N. Eshelman. Inhibition of theophylline clearance by cimetidine but not ranitidine. *Arch. Int. Med.* 144:484–486 (1989).
7. D. P. Reitbery, H. Bernhard, and J. Schentag. Alteration of theophylline clearance and half-life by cimetidine in normal volunteers. *Arch. Int. Med.* 95:182–184 (1981).
8. R. Dal Negro, C. Pomari, O. Zoccatelli, and F. Trevisan, C. Carloni. Pharmacokinetics of theophylline and H_2 antagonist drugs cimetidine and ranitidine. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 22:221–226 (1984).
9. R. C. Vestal, K. E. Thummell, and B. Musser. Cimetidine inhibits theophylline clearance in patients with chronic obstructive pulmonary disease; A study using stable isotope methodology during multiple oral dose administration. *Br. J. Clin. Pharmacol.* 15:411–418 (1983).
10. H. W. Kelly, J. R. Powell, and J. F. Donohue. Ranitidine at very large doses does not inhibit theophylline elimination. *Clin. Pharmacol. Ther.* 39:577–581 (1986).
11. M. E. Gardner and G. W. Sikorski. Ranitidine and theophylline. *Ann. Intern. Med.* 102:559 (1985).
12. S. Rolf Smith and M. J. Kendall. Ranitidine and cimetidine; A comparison of their potential to cause clinically important interactions. *Clin. Pharmacokinet.* 15:44–56 (1988).

13. M. C. Meyer, A. B. Straughn, E. J. Jarvi, G. C. Wood, V. I. Vashi, P. Hepp, and J. Hunt. Gastric pH and the absorption of CR-release theophylline products in man. *Pharm. Res.* 6:S179 (1989).
14. J. B. Dressman and G. L. Amidon. Radiotelemetric method for evaluating enteric coatings in vivo. *J. Pharm. Sci.* 73:935–938 (1984).
15. H. N. Farrish and W. A. Wargin. Separation and quantitation of theophylline paraxanthine by reversed-phase liquid chromatography. *Clin. Chem.* 26:524–525 (1980).
16. M. Gibaldi and D. Perrier. *Pharmacokinetics,* 2nd ed, Marcel Dekker, New York, 1982, p. 445.
17. L. Hendeles. Theophylline. In W. E. Evans, J. J. Schentag, and W. J. Jusko (eds.), *Applied Pharmacokinetics,* Applied Therapeutics, Spokane, WA, 1988, pp. 1105–1188.
18. J. G. Wagner and E. Nelson. Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single doses of drug. *J. Pharm. Sci.* 53:1392–1403 (1964).
19. J. P. Skelly. Bioavailability of sustained release dosage forms—Relationship with in-vitro dissolution. In A. Yacobi and E. Halperin-Walega (eds.), *Oral Sustained Release Formulations: Design and Evaluation,* Pergamon Press, New York, 1988, pp. 57–82.
20. A. P. Sips, P. M. Edelbrock, S. Kulstad, F. A. deWolff, and J. H. Dijkman. Food does not affect the bioavailability of theophylline from Theolin Retard. *Eur. J. Clin. Pharmacol.* 26:405–407 (1984).
21. J. H. G. Jonkman. Food interactions with sustained-release theophylline preparations: A review. *Clin. Pharmacokinet.* 16:162–179 (1989).
22. R. R. Levine. Factors affecting gastrointestinal absorption of drugs. *Am. J. Dig. Dis.* 15:171–188 (1976).
23. J. Myren, M. Osnes, S. Larsen, and T. E. Hansen. Gastric motility following peroral administration of ranitidine. A double-blind comparison with placebo. *Scand. J. Gastroenterol.* 19:21–21 (1984).
24. J. Bertrand, E. E. Dorval, and E. H. Metman. Action of ranitidine on the speed of gastric emptying. *Gastroenterol. Clin. Biol.* 7:932–933 (1983).
25. C. Huscher, D. Falchetti, F. Besozzi, *et al.* Ranitidine and total gastric emptying of liquids and solids. *Curr. Ther. Res.* 36:916–920 (1984).
26. P. Mojaverian, P. Vlasses, S. Parker, and C. Warner. Influence of single and multiple doses of oral ranitidine on the gastric transit of an indigestible capsule in humans. *Clin. Pharmacol. Ther.* 47:382–388 (1990).
27. S. Harasawa. Effect of ranitidine on gastric emptying of the meal and serum gastrin level. *J. Adult Dis.* 15:803–806 (1985).
28. C. Scarpignato, G. Bertaccini, G. Zimbaro, and F. Vitulo. Ranitidine delays gastric emptying of solids in man. *Br. J. Clin. Pharmacol.* 13:252–253 (1982).
29. K. Jonderko. Influence of oral cimetidine and ranitidine on gastric emptying in active duodenal ulcer. *J. Clin. Gastroenterol.* 10:143–149 (1988).
30. G. Dobrilla, G. dePretis, M. Comberlato, and S. Amplatz. H_2-antagonists and motility of the upper gastrointestinal tract in man. *Hepatogastroenterology* 35:30–33 (1988).