

The Effects of Oral Doses of Lansoprazole and Omeprazole on Gastric pH

Keith G. Tolman, M.D., Steven W. Sanders, Pharm.D., Kenneth N. Buchi, M.D., Michael D. Karol, Ph.D., Dennis E. Jennings, Ph.D., and Gary L. Ringham, Ph.D.

We compared gastric pH values after therapeutic doses of lansoprazole and omeprazole in 17 healthy adult men. The pharmacokinetics of the two drugs were studied. A three-way crossover design compared the effects on gastric pH of 15 and 30 mg lansoprazole and 20 mg omeprazole—each given once daily for 5 days. Ambulatory 24-h intragastric pH levels were measured before dosing, after the first and fifth doses in each period, and 15 days after each dosing period. A positive relationship between the lansoprazole or omeprazole area under the curve (AUCs) and the 24-h mean pH values was found for each regimen. No differences in maximum concentration (C_{max}) and AUC were noted from day 1 to day 5 for the two lansoprazole doses. With omeprazole, both C_{max} and AUC levels were greater on day 5 than on day 1. All three regimens increased 24-h mean gastric pH, although 30 mg lansoprazole had the most significant effect. The percentage of time that gastric pH was >3 , >4 , and >5 was also significantly higher with 30 mg lansoprazole. All three regimens were associated with reversible elevations of serum gastrin, which more than doubled at some points. No clinically significant adverse events were documented.

Key Words: Proton pump inhibitors—Lansoprazole—Omeprazole—Pharmacokinetics—Pharmacodynamics—Gastric pH—Serum gastrin.

Despite changing concepts about the etiology of peptic ulcer disease, gastric acid remains the primary mediator of injury, and inhibition of its secretion leads to ulcer healing. The most effective agents in inhibiting acid secretion are the $H^+/K^+-ATPase$, or proton pump, inhibitors, such as omeprazole and lansoprazole. Both drugs have shown considerable efficacy in the treatment of duodenal and gastric ulcers as well as

gastro-esophageal reflux disease (GERD), and both are generally considered safe. Because of its effects on hepatic oxidative metabolism, however, omeprazole interacts with numerous other drugs and has the potential for toxicity based on these interactions. For example, omeprazole inhibits the hepatic metabolism of diazepam (1–3), carbamazepine (4), antipyrine and aminopyrine (5), and the R (but not the S) isomer of warfarin (6). Lansoprazole has shown no effect on the metabolism of diazepam (7), phenytoin (8), antipyrine (8), propranolol (9), the R or S isomers of warfarin (10–11), or low-dose oral contraceptives (12). Theophylline clearance is marginally increased with both drugs (13–14). Bioavailability of the two drugs after oral dosing also appears to differ: lansoprazole bioavailability after oral dosing (15) is ~85% compared with 30–40% for omeprazole (16–17). This study was designed to compare the pharmacodynamic effects of lansoprazole and omeprazole and to determine whether a correlation exists between plasma AUC values and 24-h gastric pH.

MATERIALS AND METHODS

Seventeen healthy adult men were enrolled in the study. Three left the study prematurely—one because of an abnormal laboratory test before drug administration and two for personal reasons after 5 days of dosing. The subjects were nonsmokers with a mean age of 27 years (range, 19–40 years), a mean height of 71 inches (range, 66–76 inches), and a mean weight of 173.4 lb (range, 141–224 lb). Physical examinations, ECGs, and laboratory evaluations were normal at the time of entry. None of the subjects had a history of drug or alcohol abuse, and none was taking medications that might interfere with evaluation of the study drugs. The study was approved by the Investigational Review Board of the University of Utah, and all subjects gave written informed consent before participation.

This was a randomized, double-blind, three-way crossover study comparing once-daily doses of 15 and 30 mg lansoprazole and 20 mg omeprazole. The selected doses were those ap-

Received September 22, 1995. Sent for revision November 7, 1995. Accepted November 7, 1996.

From the University of Utah School of Medicine (K.G.T., S.W.S., K.N.B.), Salt Lake City, Utah; and Abbott Laboratories (M.D.K., D.E.J., G.L.R.), Abbott Park, Illinois, U.S.A.

Address correspondence and reprint requests to Dr. Keith G. Tolman, Division of Gastroenterology, University of Utah School of Medicine, 4R118 School of Medicine, 50 No. Medical Drive, Salt Lake City, UT, U.S.A.

proved by the U.S. Food and Drug Administration. Each treatment period lasted 5 days, with a 2-week washout period between treatments. Postdosing evaluations were conducted 14–16 days after the last dose of each treatment (hereafter referred to as 15 days post-treatment).

Subjects were confined to the Drug Research Center at the University of Utah during the dosing periods, from the time before dinner on day -3 to the morning of day 6, so that 24-h ambulatory pH recordings could be made under controlled conditions. Standardized meals were given at 9:00 a.m., 1:00 p.m., and 6:00 p.m. and a snack at 9:00 p.m.. Xanthine-containing foods and beverages were prohibited. Study medications were taken at ~8:00 a.m. (1 h before breakfast).

Safety evaluation included monitoring of adverse events, vital signs, clinical laboratory results (including gastrin levels), physical condition, and ECGs. On each day of confinement, subjects were questioned about symptoms or side effects possibly related to treatment. Vital signs were recorded daily during confinement and again at postdosing; laboratory evaluations were done on days 1 and 6, and postdosing, interim physical examinations were performed on days -2 and 5, and ECGs were recorded on day 5 and postdosing. Serum gastrin levels were measured from samples collected 1 h before and 1 h after meals on days -2, 1, and 5; 15 days post-treatment; and at the end of each 24-h gastric pH recording period (days -1, 2, and 6 and 15 days post-treatment). Gastrin was measured using a double antibody technique (Product KGAD-2, Gastrin Double Antibody; Diagnostic Products Corporation, Los Angeles, CA, U.S.A.).

Pharmacodynamic Evaluation

During each crossover period, ambulatory 24-h gastric pH was monitored on days -2, 1, and 5 and on day 15 post-treatment. A monocrystalline antimony electrode (Synectics Medical Inc., Irving, TX) was positioned in the stomach before the start of pH recording. Electrode placement in the stomach was confirmed by a drop in pH during introduction of the electrode. The electrodes were connected to a Digtrapper Mark II single-channel recorder (Synectics Medical Inc.), which was calibrated before each use with buffer solutions at pH 1 and 7. On days 1 and 5 of each crossover period, monitoring began immediately after drug administration and continued every 4 s for 24 h. Values were digitized and stored by the Digtrapper unit. The median of each 15-min period was calculated for analysis.

Pharmacokinetic Evaluation

On days 1 and 5 of each treatment period, blood samples were drawn at several time intervals: immediately before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after dosing. Venous plasma samples were analyzed for lansoprazole and omeprazole using validated high-performance liquid chromatography methods (18). The following model-independent pharmacokinetic parameters were evaluated: individual plasma concentrations, peak concentration (C_{max}), time to peak concentration (T_{max}), and area under the plasma concentration curve ($AUC_{0-\infty}$). Elimination half-life ($t_{1/2}$) was estimated based on linear regression of a log-transformed concentration of the terminal phase of the individual plasma concentrations. Comparisons were not made between lansoprazole and omeprazole because clinical rather than identical doses were given.

Statistical Analysis

Gastric pH

All statistical tests were two-tailed, with significance designated as $p \leq 0.05$. The preregimen value was the value obtained

before each treatment regimen (day -2); the postregimen value was that obtained 14–16 days after completion (day 15 post-treatment). The 15-min median pH values for each subject were used for comparison between treatment groups. Gastric pH variables analyzed were mean gastric pH values (calculated as the average of the 15-min medians) and the percentage of time that gastric pH was >2 , >3 , >4 , and >5 (based on the 15-min medians). All gastric pH analyses were performed over the total 24-h period as well as over four specified time intervals (0800–1300, 1300–1800, 1800–2300, and 2300–0800 h). The onset of action was examined similarly on an hourly basis, with time to effect described as the first hour in which significant differences from baseline were noted.

For each evaluation day, the effects of the three regimens on gastric pH variables were compared with a crossover model that included regimen, period, sequence, and subjects within sequence as factors. Within each regimen, gastric pH variables were compared across days using a repeated-measures model that included day, sequence, and subject as factors. Within the framework of this model, pairwise comparisons were made of day 1 versus preregimen, day 5 versus preregimen, day 5 versus day 1, and day 15 post-treatment versus preregimen.

Pharmacokinetics

Analyses of variance were performed for lansoprazole and omeprazole pharmacokinetic parameters. For lansoprazole, the following effects were included in the model: period, subject, dose, day, period-by-day interaction, and dose-by-day interaction. For omeprazole, the effects included were period, subject nested within period, and day. The C_{max} and AUC values from the 30-mg lansoprazole regimen were normalized to a 15-mg dose to judge dose proportionality.

Relationship of AUC to Gastric pH

Analysis of covariance was employed to explore the relationship between 24-h average gastric pH and plasma AUC for lansoprazole and omeprazole. The dependent variable was average pH; the covariate was the natural logarithm of AUC. For lansoprazole, an analysis was performed for data on days 1 and 5 jointly, with effects for period, day, subject, day-by-subject interaction, and separate slopes (interaction between day and AUC) in the initial model. The relationship between the 24-h average gastric pH and the plasma drug concentration AUC was also examined using a sigmoidal E_{max} model (19–21).

Serum Gastrin

Gastrin values were measured 1 h before and after each meal on day -2 (preregimen), days 1 and 5, and day 15 (post-treatment) for each of the three regimens. An additional measurement was obtained 14 h after dinner. Gastrin variables analyzed included values at each of these time points as well as integrated gastrin, defined as the area under the gastrin curve from 1 h before breakfast to 1 h after dinner (0800–1900), as calculated by the trapezoidal method. Changes from preregimen serum gastrin values were analyzed between and within regimens using the crossover and repeated-measures model, respectively.

Safety

The incidence of adverse events during each regimen, or within 3 days of the last dose of any regimen, were tabulated and grouped by the COSTART term and body system. Changes from preregimen clinical laboratory variables and vital signs were compared using the crossover model described for gastric pH; changes in ECG and results of physical examination were reviewed and tabulated.

RESULTS

Gastric pH

Gastric pH, as shown in Fig. 1, increased significantly on all three regimens, but was highest on the 30-mg lansoprazole regimen. The difference between the 30-mg dose of lansoprazole and either 20 mg omeprazole or 15 mg lansoprazole was statistically significant after the first and fifth doses ($p \leq 0.002$). At almost all time points, gastric pH was significantly higher with the 30-mg dose of lansoprazole than with the other two regimens ($p < 0.05$). No statistically significant differences were evident between 15 mg lansoprazole and 20 mg omeprazole.

Figure 2 shows the mean gastric pH over 24 h for all three regimens, including a combined preregimen profile (an average of the three preregimen values). Gastric pH was consistently higher with 30 mg lansoprazole than with the other two regimens. Gastric pH remained above 3, 4, and 5 longest in the 30-mg lansoprazole regimen after both the first and fifth dose. A statistically significant difference ($p < 0.01$) in the mean percentage of time pH was >3 , >4 , and >5 on day 5 was observed between 30 mg lansoprazole and the other two regimens (Fig. 3). Gastric pH rose more rapidly after 30 mg lansoprazole than after the other two regimens.

Pharmacokinetics

Details of the pharmacokinetic parameters for all three regimens are shown in Table 1. There were no statistically significant differences between day 1 and day 5 in C_{max} , T_{max} , $t_{1/2}$, or AUC (Fig. 4A) for the two lansoprazole doses, nor was there a statistically significant difference in dose-normalized C_{max} and AUC for

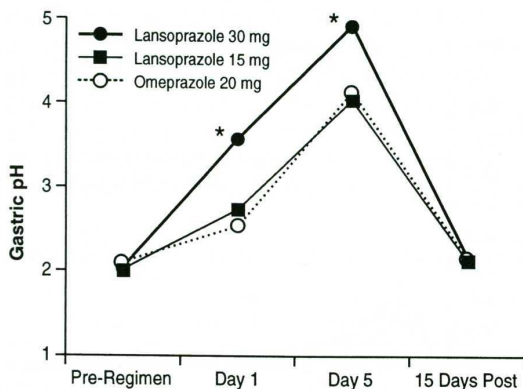


FIG. 1. Mean 24-h gastric pH levels. The asterisks mark statistically significant differences ($p \leq 0.002$) between 30 mg lansoprazole and 20 mg omeprazole or 15 mg lansoprazole.

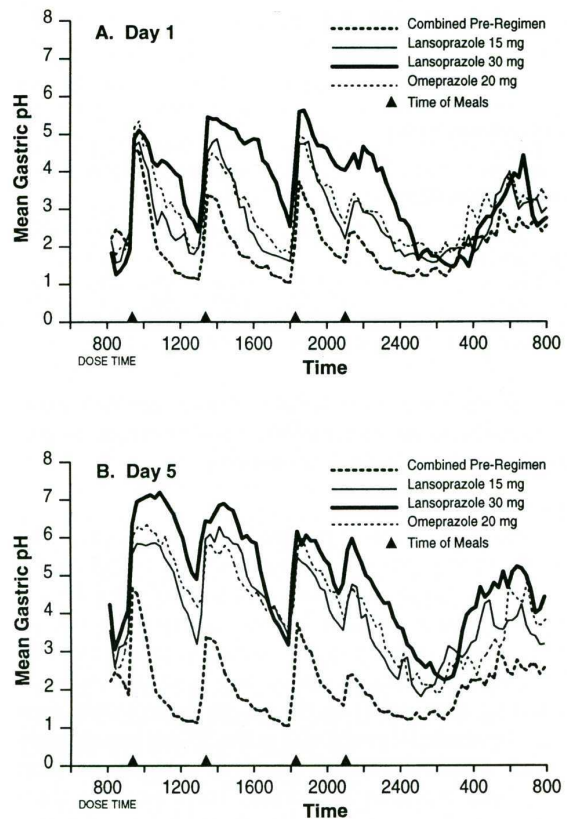


FIG. 2. Mean gastric pH for the two lansoprazole and the omeprazole regimens on day 1 (A) and day 5 (B).

the two regimens. For omeprazole, no statistically significant differences in T_{max} or $t_{1/2}$ between day 1 and day 5 were observed. Differences did exist between day 1 and day 5 results of other pharmacokinetic parameters, including C_{max} , AUC (Fig. 4B), dose-normalized C_{max} , and dose-normalized AUC, all of which were higher on day 5 than on day 1 ($p < 0.05$). For both lansoprazole and omeprazole, a significant positive relationship was found between 24-h pH and AUC values, that is, increased gastric pH correlated with increased AUC values. Figure 5 shows a comparison of the mean day 5 24-h pH plotted against AUC and includes the regression curves obtained from the sigmoid E_{max} model.

Serum Gastrin

Increases in serum gastrin levels from preregimen to day 5 were significant with all three regimens ($p < 0.05$). In most instances, day 5 values were significantly higher than the corresponding day 1 values and were similar for all regimens (Table 2). Two weeks after dosing, serum gastrin tended to return to preregimen

TABLE 1. Pharmacokinetic parameters for lansoprazole and omeprazole (mean \pm SD)

	T_{max} (h)	$t_{1/2}$ (h)	C_{max} (ng/ml)	AUC (ng·h/ml)	C_{max} dose, normalized ([ng/ml]/mg)	AUC dose, normalized ([ng·h/ml]/mg)
Lansoprazole, 15 mg						
Day 1	1.6 \pm 0.7	1.06 \pm 0.43	335 \pm 199	623 \pm 287	22.33 \pm 13.27	41.53 \pm 19.13
Day 5	1.5 \pm 0.5	1.09 \pm 0.56	351 \pm 1.31	723 \pm 323	23.40 \pm 8.73	48.20 \pm 21.53
Lansoprazole, 30 mg						
Day 1	1.5 \pm 0.3	0.97 \pm 0.33	729 \pm 385	1,371 \pm 755	24.30 \pm 12.83	45.70 \pm 25.17
Day 5	1.7 \pm 1.3	0.62 \pm 0.32	217 \pm 140	298 \pm 186	10.85 \pm 7.00	14.90 \pm 9.30
Omeprazole, 20 mg						
Day 1	1.7 \pm 1.3	0.62 \pm 0.32	217 \pm 140	298 \pm 186	10.85 \pm 7.00	14.90 \pm 9.30
Day 5	1.6 \pm 0.7	0.87 \pm 0.50	315 \pm 149 ^a	595 \pm 377 ^a	15.75 \pm 7.45 ^a	29.75 \pm 18.85 ^a

^aStatistically significantly higher than day 1 ($p < 0.05$).

men levels; there were no statistically significant differences between the preregimen and postregimen gastrin levels in any treatment regimen.

Adverse Events

Adverse events were reported by five subjects (31%) on the 15-mg lansoprazole regimen, six (43%) on the 30-mg lansoprazole regimen, and six (40%) on the 20-mg omeprazole regimen. Events that were reported by two or more subjects in any treatment group included asthenia, headache, dizziness, and acne (two subjects reporting each event) on the 15-mg lansoprazole regimen; headache (six subjects) in the 30-mg lansoprazole regimen; and nausea and acne (two subjects each) on the 20-mg omeprazole regimen. There were no clinically significant changes in physical examinations, ECGs, vital signs, or laboratory tests of hematology, chemistry, or urinalysis in any treatment regimen. One subject with a normal screening alanine aminotransferase (ALT) level (27 IU/L) had elevated values (81 IU/L) just before dosing with 15 mg lansoprazole; on day 4 of the first crossover period, his ALT had increased to 224 IU/L, and he was discontinued from the

study after testing positive for hepatitis C. Another subject had elevated AST/ALT values attributed to study drugs at the end of each crossover period. His pretreatment AST and ALT levels were 30 and 36 IU/L, respectively. After the fifth dose of 30 mg lansoprazole, values were 57 and 108 IU/L, respectively; by the post-treatment examination, AST/ALT values had decreased to 30 and 45 IU/L, respectively.

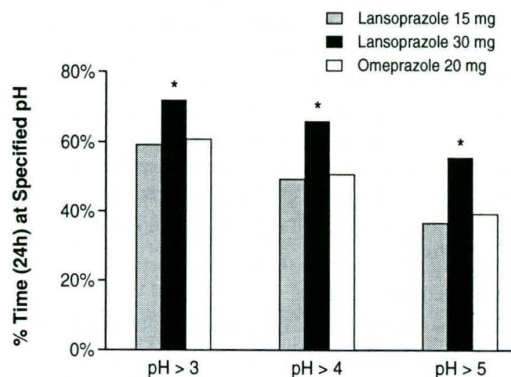


FIG. 3. Mean percentage of time gastric pH was >3 , >4 , and >5 on day 5. The asterisks mark statistically significant differences ($p \leq 0.01$) between 30 mg lansoprazole and the other two regimens.

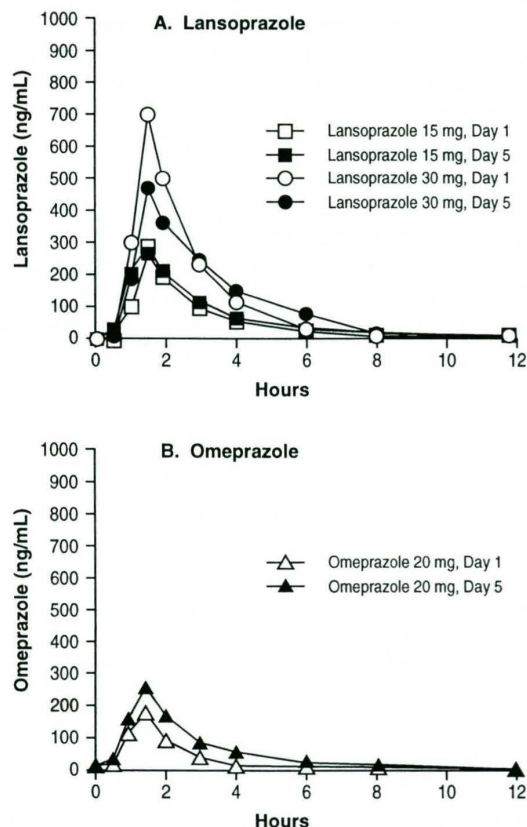


FIG. 4. Mean plasma concentrations of lansoprazole (A) and omeprazole (B) on days 1 (A) and 5 (B).

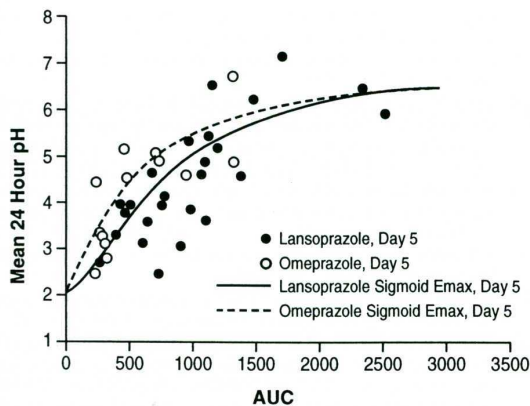


FIG. 5. Day 5 mean 24-h pH versus AUC sigmoid E_{max} model.

DISCUSSION

Pharmacokinetic parameters in our study are similar to data obtained from other studies for both lansoprazole and omeprazole (22–24). Dose-normalized C_{max} and AUC values were not different for the two doses of lansoprazole. With omeprazole, C_{max} and AUC levels were significantly higher on day 5 than on day 1, an effect also described by Clissold and Campoli-Richards (24), suggesting that omeprazole's bioavailability increases with repeated administration. Because the study was designed as a pharmacodynamic study, and because we did not use equal doses of omeprazole and lansoprazole, we did not make a direct statistical comparison of the pharmacokinetic profiles of these two drugs; rather, our aim was to compare their effects on gastric pH and to determine whether a relationship exists between plasma AUC and mean 24-h gastric pH.

A positive relationship was found between AUC and mean 24-h gastric pH for both lansoprazole and omeprazole—an observation in keeping with those of earlier studies (25,26). Both drugs produced significant increases in gastric pH, although 30 mg lansoprazole was more potent than either 15 mg lansoprazole or 20 mg omeprazole, which were comparable to each other. Since both drugs produce irreversible inhibition

of the $H^+/K^+-ATPase$, it is likely that the higher gastric pH produced by repeated dosing represents an accumulation of blocked enzyme and fewer functional proton pumps (27,28).

Meta-analyses of several clinical studies found a significant correlation between the degree of acid suppression and the rate of healing in both ulcer disease and reflux esophagitis (29–30). For duodenal ulcer, a significant correlation existed for healing and degree and duration of gastric acid suppression. The healing rate increased as gastric pH and duration of acid suppression increased. The model demonstrated the importance of raising gastric pH to 3 and indicated that further elevation had a negligible effect. Both the duration of time (hours per day) that gastric pH was ≥ 3 and the duration of therapy (weeks) were more important than further elevation of pH. In gastric ulcer, a correlation also existed between suppression of 24-h gastric acidity and healing rates after 2, 4, and 8 weeks of treatment, although the correlation was less marked than for duodenal ulcer. In reflux esophagitis, Bell et al. (31) reported that maintaining pH levels above 4 was the most important factor in predicting healing rate. In this study, the mean time pH levels were above 3 and 4 was significantly greater with 30 mg lansoprazole than 20 mg omeprazole or 15 mg lansoprazole. It is uncertain whether this translates to more complete healing, although it may translate to more rapid healing.

The healing rate for duodenal ulcer is already close to 100%, but the healing rates for gastric ulcer and GERD could be improved. Healing rates for GERD, particularly resistant esophagitis, are improved with proton pump inhibitors, as suggested by studies indicating a relationship between healing and degree of acid suppression (31,32). Healing of esophageal ulceration correlates with an increase in gastric pH rather than with prevention of reflux per se. In this regard, both omeprazole and lansoprazole have shown efficacy in the treatment of GERD (32–34). The dose-related suppression of gastric acid observed in our study parallels the dose-related healing of GERD (31).

As expected, both lansoprazole and omeprazole caused reversible increases in serum gastrin levels. Serum gastrin increased more with the 30-mg dose of lansoprazole, in agreement with the well-known relationship between the extent of acid inhibition and the extent of increase in fasting gastrin concentrations (25). However, no subject in the study experienced an increase in gastrin values more than double the upper limit of normal, and all values returned to the normal range within 15 days of discontinuing medication. The magnitude of changes and their return to preregimen levels are similar to findings of other published stud-

TABLE 2. Mean fasting serum gastrin levels (pg/ml)^a

Time point	15 mg Lansoprazole	30 mg Lansoprazole	20 mg Lansoprazole
Preregimen	33.7	41.2 ^b	33.1
Day 1	40.3	45.3	42.7
Day 5	52.9	59.3	59.2
15 Days after regimen	37.7	32.1	34.6

^a1 h before bedtime.

^bSignificantly higher than 15 mg lansoprazole and 20 mg omeprazole ($p \leq 0.05$).

ies using lansoprazole (34–37). In light of the correlation between increased gastric pH and healing of acid peptic ulcer disease and GERD, the results of our study show that, like omeprazole, lansoprazole is a potent inhibitor of acid secretion. It also is an effective treatment for duodenal ulcer, gastric ulcer, and GERD.

Acknowledgment: This study was supported by a grant from TAP Pharmaceuticals, Deerfield, Illinois.

REFERENCES

- Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism. *Gastroenterology* 1985;89:1235–41.
- Prichard PJ, Walt RP, Kitchingman GK, et al. Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987;24:543–5.
- Andersson T, Cederberg C, Edvardsson G, Heggeland A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin Pharmacol Ther* 1990;47:79–85.
- Naidu MUR, Shobba JC, Dixit VK, et al. Effect of multi-dose omeprazole on the pharmacokinetics of carbamazepine. *Drug Invest* 1994;7:8–12.
- Henry DA, Somerville KW, Kitchingman G, Langman MJ. Omeprazole: effects on oxidative drug metabolism. *Br J Pharmacol* 1984;18:195–200.
- Suttin T, Balmer K, Bostrom H, Eriksson S, Hoglund P, Paulsen O. Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther Drug Monit* 1989;11:176–84.
- Lefebvre RA, Flouvat B, Karolac-Tamisier S, Moerman E, Van Ganse E. Influence of lansoprazole treatment on diazepam plasma concentrations. *Clin Pharmacol Ther* 1992;52:458–63.
- Karol MD, Mukherjee D, Cavanaugh JH. Lack of effect of concomitant multi-dose lansoprazole on single-dose phenytoin pharmacokinetics in normal subjects [Abstract]. *Gastroenterology* 1994;106:A103.
- Cavanaugh JH, Schneek DW, Mukherjee D, Karol MD. Lack of effect of concomitant lansoprazole on single-dose propranolol pharmacokinetics and pharmacodynamics [Abstract]. *Gastroenterology* 1994;106:A4.
- Braeckman RA, Winters EP, Cohen A, Locke CS, Cavanaugh JP. Lack of effect of lansoprazole on warfarin pharmacokinetics and anticoagulation effect in healthy subjects [Abstract]. *Pharm Res* 1991;8(suppl):S-295.
- Cavanaugh JH, Winters EP, Cohen A, Locke CS, Braeckman R. Lack of effect of lansoprazole on steady state warfarin metabolism [Abstract]. *Gastroenterology* 1991;100:A40.
- Fuchs W, Sennwald R, Klotz U. Lansoprazole does not affect the bioavailability of oral contraceptives. *Br J Clin Pharmacol* 1994;38:376–80.
- Gugler R, Jensen JC. Drugs other than H₂-receptor antagonists as clinically important inhibitors of drug metabolism in vivo. *Pharmacol Ther* 1987;33:133–7.
- Branneman G, Winters EP, Locke CS, et al. Lack of effect of concomitant lansoprazole on steady-state theophylline pharmacokinetics [Abstract]. *Gastroenterology* 1991;100:A75.
- Hussein Z, Granneman GR, Mukherjee D, et al. Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. *Br J Clin Pharmacol* 1993;36:391–8.
- Regardh CG. Pharmacokinetics and metabolism of omeprazole in man. *Scand J Gastroenterol* 1991;21(suppl 118):99–104.
- Physicians' desk reference, 47th ed. Montvale, N.J.: Medical Economics Data, 1993:1582–5.
- Karol MD, Granneman GR, Alexander K. Determination of lansoprazole and five metabolites in plasma by high performance liquid chromatography. *J Chromatogr B: Biomed Appl* 1995;668:182–6.
- Smith RB, Kroboth PD, Juhl RP, eds. *Pharmacokinetics and pharmacodynamics research design and analysis*. Cincinnati, OH: Harvey Whitney Books, 1986.
- SCI Software. PCNONLIN User Guide, Ver. 3.0. Lexington, KY: Statistical Consultants, Inc., 1989.
- Hartley HO. Modified G-N method for fitting of nonlinear regression functions by least squares. *Technometrics* 1969;3:269–80.
- Barradell LB, Faulds, D, McTavish D. Lansoprazole: a review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. *Drugs* 1992;44:225–50.
- Delhotal-Landes B, Petite JP, Flouvat B. Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet* 1995;28:458–70.
- Clissold SP, Campoli-Richards M. Omeprazole: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. *Drugs* 1986;32:15–47.
- Lind T, Cederberg C, Ekenved G, et al. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut* 1983;24:270–6.
- Sanders SW, Tolman KG, Greski PA, Jennings DE, Hoyos PA, Page JG. The effects of lansoprazole, a new H⁺/K⁺-ATPase inhibitor, on gastric pH and serum gastrin. *Aliment Pharmacol Ther* 1992;6:359–72.
- Olbe L, Cederberg T, Lind T, et al. Effect of omeprazole on gastric acid secretion and plasma gastrin in man. *Scand J Gastroenterol* 1989;24(suppl 166):27–32.
- Maton PN. Omeprazole. *N Engl J Med* 1991;324:965–75.
- Jones DB, Howden CW, Burget DW, et al. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. *Gut* 1987;28:1120–7.
- Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing of duodenal ulcers? *Gastroenterology* 1990;99:345–51.
- Bell NJV, Burget DL, Howden CW, et al. Appropriate acid suppression for the management of gastro-esophageal reflux disease. *Digestion* 1992;51(suppl 1):59–67.
- Hetzel DJ, Dent J, Laurence BH, et al. Omeprazole heals reflux oesophagitis: a placebo controlled trial. *Gut* 1986;27:A609.
- Dammann HG, Blum AL, Lux G, et al. Unterschiedliche Heilungstendenz der Refluxophagitis nach Omeprazole und Ranitidin. *Deutsch Med Wochenschr* 1986;111:123–8.
- Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996;124:859–67.
- Sontag S, Kogul DG, Fleischmann R, Campbell DR, Richter J, Haber M. Lansoprazole prevents recurrence of erosive reflux esophagitis previously resistant to H₂-RA therapy. *Am J Gastroenterol* 1996;91:1758–65.
- Muller P, Dammann HG, Leucht U, Dimon B. Human gastric acid secretion following repeated doses of AG-1749. *Aliment Pharmacol Ther* 1989;3:193–8.
- Avner DL, Porsch ER, Jennings DH, Greski-Rose PA. A comparison of three doses of lansoprazole (15, 30 and 60 mg) and placebo in the treatment of duodenal ulcer. *Aliment Pharmacol Ther* 1995;9:521–8.