Effects of Food and Sucralfate on a Single Oral Dose of 500 Milligrams of Levofloxacin in Healthy Subjects

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The effects of food and sucralfate on the pharmacokinetics of levofloxacin following the administration of a single 500-mg oral dose were investigated in a randomized, three-way crossover study with young healthy subjects (12 males and 12 females). Levofloxacin was administered under three conditions: fasting, fed (immediately after a standardized high-fat breakfast), and fasting with sucralfate given 2 h following the administration of levofloxacin. The concentrations of levofloxacin in plasma and urine were determined by high-pressure liquid chromatography. By noncompartmental methods, the maximum concentration of drug in serum (Cmax), the time to Cmax (Tmax), the area under the concentration-time curve (AUC), half-life (t1/2), clearance (CL/F), renal clearance (CLr), and cumulative amount of levofloxacin in urine (A) were estimated. The individual profiles of the drug concentration in plasma showed little difference among the three treatments. The only consistent effect of the coadministration of levofloxacin with a high-fat meal for most subjects was that levofloxacin absorption was delayed and Cmax was slightly reduced after administration of sucralfate (11). The interaction between ofloxacin and sucralfate is well known (6, 19). Chelation probably results in the gastrointestinal tract (7, 11, 12, 15). Chelation probably occurs between the aluminum cations and the 4-keto and 3-carboxyl groups of the fluoroquinolones.

The bioavailability of ofloxacin has been reduced by approximately 60% when it is administered simultaneously with 1 g of sucralfate (11). The interaction between ofloxacin and sucralfate was negligible, however, when ofloxacin was given 2 h before administration of the sucralfate dose (11). As such, sucralfate would also be expected to reduce the absorption of levofloxacin if the two drugs were administered simultaneously. The interaction, however, should be minimal if the interval separating the intake of both agents is lengthened.

The purpose of this study was to determine the effects of food (immediately before levofloxacin dosing) and sucralfate (given 2 h after levofloxacin dosing) on the pharmacokinetics of a single, oral, 500-mg dose of levofloxacin.

(Materials and Methods

Volunteers. Healthy male and nonpregnant female subjects between 18 and 40 years of age were eligible for entry into the study. Subjects qualified for the study if they had normal findings following a prestudy medical history and a physical examination performed within 2 weeks before entry into the study. Subjects were eligible for entry into the study if they were in good health and were nonsmokers (>6 months prior to entry into the study). Key exclusion criteria included clinically significant illness within 3 months of enrollment in the study, seropositivity for hepatitis B surface antigen or human immunodeficiency

Levofloxacin, the l isomer of racemic ofloxacin, is an investigational antibacterial agent undergoing extensive clinical studies in the United States. Levofloxacin is the more active of the two isomers, with twofold greater antibacterial activity compared to the racemic mixture. It has broad-spectrum in vitro activity, including activity against many clinically encountered gram-positive and gram-negative organisms (5, 6, 21). The pharmacokinetic profile of levofloxacin in humans is similar to that of the racemic mixture, in which the pharmacokinetics of single and multiple oral doses of 500 mg of levofloxacin administered once daily appear to mimic that of ofloxacin (2).

Food has been shown to alter the pharmacokinetics of many drugs by binding to or chelating drugs, changing gastrointestinal motility, or altering gastric pH and enzyme activity (22). Food, milk, and sucralfate have affected the absorption of fluoroquinolones to various degrees (4, 7, 8, 10–12, 15, 16, 18). Ledergerber and coworkers (10) reported a delay in the time to reach the maximum concentration of drug in serum (Cmax) following the administration of ciprofloxacin with a standard breakfast, although the overall extent of absorption was unchanged. Similar findings have been described with other fluoroquinolones with healthy volunteers (4, 8, 19). Sucralfate is known to diminish the absorption of the fluoroquinolone antibiotics via the formation of nonabsorbable chelate complexes in the gastrointestinal tract (7, 11, 12, 15).

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The terminal phase was identified from the log-linear portion of the concentration-time curve.

Pharmacokinetic analysis. Plasma levofloxacin concentrations for the three treatments for all subjects, for males, and for females are presented in Fig. 1 to 3, respectively. The pharmacokinetic

<table>
<thead>
<tr>
<th>TABLE 1. Demographic characteristics of the subjects in each treatment sequence arm*</th>
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<tr>
<td>Treatments</td>
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<tr>
<td>Fed-fasting-sucralfate</td>
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<tr>
<td>Fasting-fed-sucralfate</td>
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<tr>
<td>Fed-sucralfate-fasting</td>
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<tr>
<td>Fasting-sucralfate-fed</td>
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<tr>
<td>Sucralfate-fed-fasting</td>
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<tr>
<td>Sucralfate-fasting</td>
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* Mean values are reported.
† Each group consisted of four subjects (two males and two females).

Safety analysis. Subjects were monitored for adverse events throughout the study. The intensity of each adverse event was assessed by one of the investigators as to severity (mild, moderate, or marked) and its relationship to the study drug (definite, probable, possible, remote, or none). A physical examination, including vital signs and electrocardiogram, was performed at the baseline and on day 17. Additionally, clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed at the time of entry into the study while the subjects were in the fasting state and were repeated on the mornings of study days 1 and 17.

Statistical analysis. To provide sufficient power for the significance test for levofloxacin $C_{\text{max}}$ and AUC variables, a $25\%$ coefficient of variance was used for the sample size estimation. On the basis of the two-mean one-sided test procedure, if the true ratio of either the fed condition or sucralfate condition over the fasting condition was about 1, a sample size of 24 should provide adequate power (power = 0.84) at an $\alpha$ level of 0.05.

Repeated-measure analysis of variance was used to compare ranked $T_{\text{max}}$ and $1/2$, logistically transformed $C_{\text{max}}$, and AUC data. The between-subject factors were sequence and gender; period and treatment were within-subject factors. The gender-treatment interaction effect was included in the model to determine the appropriateness of pooling the data for males and females. An effect was considered to be significant when $P < 0.05$. For $T_{\text{max}}$, the difference in treatments was considered significant if the $P$ value for the null hypothesis (equality of mean rank $T_{\text{max}}$) was $< 0.05$. Schürmann’s (18) two-mean one-sided test procedure was used to construct 90% confidence intervals (90% CI) for the ratio between two treatments for the mean $t_{1/2}$ and log ratios for $C_{\text{max}}$ and AUC.

The decision on the lack of pharmacokinetic interaction was based on bioequivalence criteria (9, 13, 20). It indicated that the difference between two treatments was within an accepted range of 80 to 125% for $C_{\text{max}}$ and AUC values and 80 to 120% for $t_{1/2}$.

Clinical safety data (adverse events, clinical laboratory tests, vital signs) were analyzed by using the SAS statistical software package (17). The overall incidence of adverse events by treatment was summarized by body system and in primary and secondary terms. All statistical inferences regarding safety analyses were based on a type I error rate of 0.05.

RESULTS

Population demographics. Twenty-four subjects (12 males and 12 females) were enrolled in the study and completed all three treatment phases of the study. Sixteen subjects were Caucasian, one was African-American, two were Asian, and five were Hispanic. Four subjects were included in each of the six treatment sequences. Mean demographic characteristics indicated that there were no differences in the subjects receiving the different treatment sequences (Table 1). Data for all 24 subjects were included in the pharmacokinetic and safety analysis. Only one subject (fasting-sucralfate-fed group) deviated from the dosing schedule: he received the third levofloxacin dose on day 22 instead of day 15 due to a false-positive drug test result.

Pharmacokinetics. Plasma levofloxacin concentrations for the three treatments for all subjects, for males, and for females are presented in Fig. 1 to 3, respectively.
parameters of levofloxacin for the three treatment conditions are given in Table 2. There were no significant sequence or period effects in the analysis of any of the pharmacokinetic variables between the fasting and fed conditions or the fasting and fasting with sucralfate conditions. Data for both genders were pooled for comparison since there was no significant treatment interaction by gender.

When comparing the treatments under the fed versus fasting conditions, the mean AUC$_{0-\infty}$ values were approximately 10% less when levofloxacin was taken with food. This reduction was within the equivalence acceptance range (90% CI = 0.87 to 0.94). The effects of food in most of the subjects were a slightly delayed absorption phase (lengthened $T_{\text{max}}$ [mean, 2.0 h; $P = 0.0023$] and a 14% reduction in the mean $C_{\text{max}}$ (5.1 µg/ml; 90% CI = 0.79 to 0.94) compared with that under the fasting condition (1.0 h and 5.9 µg/ml, respectively). Mean $t_{1/2}$ and oral CL/F values, however, were similar for subjects under the fasting and fed conditions.

The extents of absorption of levofloxacin were similar for subjects under the fasting and fasting with sucralfate conditions. Plasma levofloxacin concentration profiles were unchanged when sucralfate was taken 2 h postdosing with levofloxacin compared with the profiles under the fasting condition. No apparent differences in pharmacokinetic parameter values were observed during this phase of the study (Table 2).

The cumulative amounts of levofloxacin in urine over 24 h were similar among the subjects receiving the three treatments (Fig. 4). Approximately 64 to 68% of the dose was recovered in the urine in the first 24 h postdosing. Similar CLR values were also obtained for the subjects receiving the different treatments (mean 7.5 liters/h).

Irrespective of treatment, there were significant ($P < 0.05$) gender differences in $C_{\text{max}}$, $T_{\text{max}}$, and $t_{1/2}$. The mean values of $C_{\text{max}}$ were higher and the values of $T_{\text{max}}$ were lengthened for the female subjects. The mean $t_{1/2}$ was shorter for the female ($\sim$6 h) subjects than for the male ($\sim$7 h) subjects. Nevertheless, the AUC$_{0-\infty}$ values were not statistically significantly different between genders, and the cumulative amounts of levofloxacin in urine over 24 h were similar between genders.

**Safety evaluation.** Six levofloxacin-treated subjects reported adverse events. Five of the subjects reported one adverse event

### Table 2. Mean pharmacokinetic parameters of levofloxacin in 24 healthy male and female volunteers under fasting, fed, and fasting plus sucralfate (1 g) conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>AUC$_{0-\infty}$ (µg·h/ml)</th>
<th>$t_{1/2}$ (h)</th>
<th>CL/F (liters/h)</th>
<th>CLR (liters/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>5.9 ± 1.3</td>
<td>1.0</td>
<td>50.5 ± 8.1</td>
<td>10.1 ± 1.6</td>
<td>7.3 ± 1.4</td>
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<tr>
<td>Fed$^a$</td>
<td>5.1 ± 0.9</td>
<td>2.0$^b$</td>
<td>45.6 ± 6.1</td>
<td>11.1 ± 1.4</td>
<td>7.6 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>Fasting plus 1 g of sucralfate</td>
<td>6.7 ± 3.2</td>
<td>1.0$^c$</td>
<td>47.9 ± 8.4</td>
<td>10.7 ± 1.8</td>
<td>7.5 ± 1.3</td>
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</tr>
</tbody>
</table>

$^a$ Standard high-fat breakfast.

$^b$ Median value; $P = 0.0023$ for the comparison between rank means (fasting versus fed states).

$^c$ Median value; $P = 0.054$ for the comparison between rank means (fasting versus fasting plus sucralfate states).
during the study, including dizziness, subcutaneous hematoma, menstrual disorder, asthenia, and pain in the extremity. All of these events were resolved within 1 to 3 days of their onset. One subject experienced nausea (twice), dizziness (twice), and headache; these adverse events were reported in different treatment periods and were resolved on the day of onset. All but one of the adverse events were mild in severity; one episode of dizziness was rated as moderate. None of the adverse events resulted in premature discontinuation of the study.

**DISCUSSION**

The current study demonstrated three important clinical findings regarding the pharmacokinetics of a single oral dose of levofloxacin. (i) The absorption of levofloxacin was slightly delayed by a high-fat meal, but the overall bioavailability was not affected; (ii) sucralfate did not alter levofloxacin’s disposition when sucralfate was given 2 h after administration of the antibacterial agent, thus minimizing a potential drug-drug interaction; and (iii) there were no clinically significant differences in the bioavailability of levofloxacin in males and females.

Previous studies have indicated that food and milk have clinically insignificant effects on the absorption of several fluoroquinolones (3, 4, 8, 10, 14, 19), although statistically significant differences in $C_{\text{max}}$ and $T_{\text{max}}$ have been observed for subjects receiving the drug under fasting and fed conditions following ofloxacin administration (3). Our findings regarding the effect of food on levofloxacin’s bioavailability are consistent with the aforementioned observations with ofloxacin and other marketed fluoroquinolones. The absorption of levofloxacin was delayed by food, with the median $T_{\text{max}}$ of 1.0 h during the fasting state prolonged to 2.0 h following ingestion of a high-fat breakfast. There was also a clinically insignificant reduction in the mean $C_{\text{max}}$ (14% decrease) when levofloxacin was coadministered with food. The decrease in peak levofloxacin concentrations in plasma may be explained by the interaction between the fluoroquinolone and calcium ions in milk; 180 ml of whole milk was included in the high-fat breakfast.

Although determination of differences in pharmacokinetics between genders was not a major objective of this study, no clinically meaningful differences were observed following administration of a single 500-mg levofloxacin tablet. Female subjects were found to have higher peak concentrations in plasma than male subjects, which is probably explained by the smaller volume of distribution in women as a result of a smaller mean body weight (133 lb for females versus 160 lb for males). Female subjects also had somewhat shorter elimination $t_{1/2}$ than their male counterparts; however, $CL_{\text{R}}$ values were similar between the genders. The similarities of the $CL_{\text{R}}$ values support the comparable $AUC_{0-\infty}$ values between the genders. These findings are consistent with those presented in a previous report demonstrating the lack of clinically significant differences in the pharmacokinetics of levofloxacin in males and females (1).

Coadministration of sucralfate and ofloxacin has been reported to reduce the bioavailability of the quinolone significantly (11). Following the simultaneous administration of sucralfate and ofloxacin, the mean $C_{\text{max}}$ and $AUC_{0-24}$ of ofloxacin were reduced by 70 and 61%, respectively. In addition, the mean amount of unchanged ofloxacin excreted in the urine over the first 24 h was decreased by 54% in the presence of sucralfate. However, when sucralfate was given 2 h following the administration of ofloxacin, no significant effect on the bioavailability of the quinolone was observed (11). In this study we also demonstrated that the administration of sucralfate 2 h after the administration of a single oral dose of levofloxacin produced a negligible effect on the rate and extent of levofloxacin’s absorption. Because sucralfate is usually administered four times daily, it is difficult to completely escape a pharmacokinetic interaction with a fluoroquinolone that must be given multiple times per day. However, since levofloxacin is administered once daily, this drug interaction is easier to manage.

In summary, the concurrent administration of a high-fat meal with levofloxacin did not clinically alter the disposition of this fluoroquinolone in male or female subjects. As such, it is reasonable to assume that levofloxacin can be given without regard to type of meal or mealtimes. However, the presence of disease in different populations of patients may lead to results more variable than those reported here. Of additional importance, when sucralfate was given 2 h after the administration of a levofloxacin dose, sucralfate failed to significantly affect levofloxacin’s bioavailability. Thus, in order to prevent a drug-drug interaction, sucralfate doses should be administered at least 2 h following the administration of the single daily dose of levofloxacin.

**REFERENCES**


