

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

LING-JAR LEE,^{1*} BARRY HAFKIN,² I-DER LEE,¹ J. HOH,¹ AND R. DIX¹

*Hoechst Marion Roussel, Inc., Bridgewater, New Jersey 08807-0800,¹
and Pharmaco LSR, Austin, Texas 78704-7792²*

Received 29 August 1996/Returned for modification 27 December 1996/Accepted 14 July 1997

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 (C_{\max}), the time to C_{\max} (T_{\max}), the area under the concentration-time curve (AUC), half-life ($t_{1/2}$), clearance (CL/F), renal clearance (CL_R), and cumulative amount of levofloxacin in urine (A_e) 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 C_{\max} was slightly reduced (T_{\max} , 1.0 and 2.0 h for fasting and fed conditions, respectively [$P = 0.002$]; C_{\max} , 5.9 ± 1.3 and 5.1 ± 0.9 $\mu\text{g/ml}$ [90% confidence interval = 0.79 to 0.94] for fasting and fed conditions, respectively). Sucralfate, which was administered 2 h after the administration of levofloxacin, appeared to have no effect on levofloxacin's disposition compared with that under the fasting condition. Mean values of C_{\max} and AUC from time zero to infinity were 6.7 ± 3.2 $\mu\text{g/ml}$ and 47.9 ± 8.4 $\mu\text{g} \cdot \text{h/ml}$, respectively, following the administration of sucralfate compared to values of 5.9 ± 1.3 $\mu\text{g/ml}$ and 50.5 ± 8.1 $\mu\text{g} \cdot \text{h/ml}$, respectively, under fasting conditions. The mean $t_{1/2}$, CL/F, CL_R, and A_e values were similar among all three treatment groups. In conclusion, the absorption of levofloxacin was slightly delayed by food, although the overall bioavailability of levofloxacin following a high-fat meal was not altered. Finally, sucralfate did not alter the disposition of levofloxacin when sucralfate was given 2 h after the administration of the antibacterial agent, thus preventing a potential drug-drug interaction.

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 that of 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 (C_{\max}) following the coadministration 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). 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.

(This study was presented, in part, at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., 18 to 20 September 1995.)

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 there was no evidence of significant major organ dysfunction, the electrocardiogram was normal, and there were no clinically significant abnormal values by hematologic, serum chemistry, or urinalysis studies. In addition, all participants were within 15% of their ideal body weights 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

* Corresponding author. Mailing address: Global Clinical Pharmacology, Hoechst Marion Roussel, Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800. Phone: (908) 231-4130. Fax: (908) 231-2007.

TABLE 1. Demographic characteristics of the subjects in each treatment sequence arm^a

Treatments ^b	Age (yr)	Wt (lb)	Ht (in.)
Fed-fasting-sucralfate	25.0	150	67.8
Fasting-fed-sucralfate	22.3	138	68.3
Fed-sucralfate-fasting	26.3	150	67.0
Fasting-sucralfate-fed	22.3	153	69.3
Sucralfate-fed-fasting	29.3	147	68.8
Sucralfate-fasting-fed	22.3	141	66.8

^a Mean values are reported.

^b Each group consisted of four subjects (two males and two females).

virus infection, previous history of allergy to a fluoroquinolone or a food substance that could interfere with a standard diet, alcohol or controlled substance abuse, or use of an investigational agent within 30 days of entry into the study. Potential subjects were also excluded if they had used any medication within 2 weeks prior to administration of the first study dose. All subjects signed an informed consent form approved by the institutional review board.

Study design and drug administration. A single-dose, open-label, randomized, three-treatment-period, crossover study was conducted. Each subject received a single dose of one 500-mg levofloxacin tablet (R. W. Johnson Pharmaceutical Research Institute) with 8 oz. of water under each of the following conditions: fasting, fed (immediately after a standardized high-fat breakfast without sucralfate), or fasting with sucralfate (1 g of sucralfate was given 2 h following the administration of levofloxacin). The three treatments were administered separately on days 1, 8, and 15. Subjects were confined for at least 12 h prior to and 48 h after the dosing. During confinement, food and fluids were standardized in order to obtain standard basal conditions for all subjects. Subjects who received the study drug under fed conditions were served a standard, high-fat breakfast (two eggs fried in butter, two strips of bacon, hash brown potatoes [~56 g], two slices of toast with butter, and 180 ml of whole milk) which was consumed over a 30-min period. Ingestion of substances containing alcohol, caffeine, or methylxanthine (i.e., chocolate) and antacids was not permitted during the confinement for the three treatment periods.

Sample collection. On days 1, 8, and 15, 7-ml blood samples were collected through an indwelling catheter and placed into heparinized tubes. The samples were collected before administration of the dose and at 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 30.0, 36.0, and 48.0 h after administration of the dose. When sucralfate was administered, the 2-h blood sample was taken immediately prior to administration of the sucralfate dose. Following centrifugation, the plasma was separated and was stored at -20°C until it was assayed.

Urine samples were collected on days 1, 8, and 15 at the following time intervals: -2 to 0 (before dosing) and 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h following levofloxacin administration. The volume and pH of each urine sample were recorded, and an 8- to 10-ml aliquot from each collection was frozen at -20°C until it was assayed.

Analytical procedures. The concentrations of total levofloxacin in plasma and urine were determined by a high-pressure liquid chromatography method (23). Briefly, the procedure used a single-step liquid-liquid extraction, followed by chromatography with UV detection at 330 nm. Stock standard solutions of levofloxacin and the internal standard (ciprofloxacin) were prepared in methanol. An aliquot of plasma or urine was added to the internal standard stock solution along with phosphate buffer and dichloromethane to perform the extraction. A reversed-phase Intersil ODS-2 column (5 µm, 4.6 by 150 mm [inner diameter]; Keystone Scientific) was used to separate levofloxacin and the internal standard. Elution was accomplished by using a mobile phase consisting of 0.005 copper sulfate pentahydrate, 0.01 M L-isoleucine, and 12.5% methanol at a flow rate of 1.0 ml/min. For plasma, the range of detection was linear from 0.08 to 5.12 µg/ml; the inter- and intra-assay precision values (as percent coefficient of variation) for levofloxacin were each <10. Plasma samples which contained concentrations above the detection range were reassayed by dilution. For urine, the range of detection was linear from 22.9 to 1464 µg/ml; the inter- and intra-assay precision values for levofloxacin were each <10%.

Pharmacokinetic analysis. Plasma and urine levofloxacin concentration data were analyzed by standard model-independent methods. The individual C_{max} of levofloxacin and the time to reach C_{max} (T_{max}) were obtained by visual inspection of the semilogarithmic plots of the concentration in plasma versus time. Following the administration of a single dose of levofloxacin, the following pharmacokinetic parameters were estimated by use of a software package (model 200 of PCNONLIN) by a noncompartmental approach: area under the concentration-time curve (AUC) from 0 h to infinity ($AUC_{0-\infty}$), AUC from 0 to 24 h (AUC_{0-24}), total oral clearance (CL/F), elimination phase, half-life ($t_{1/2}$), renal clearance (CL_R), and cumulative amount of levofloxacin in urine from 0 to 24 h (A_{e0-24}). AUC values were calculated by using the linear trapezoidal rule method. The terminal phase was identified from the log-linear portion of the concentration-versus-time curve.

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_{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 α level of 0.05.

Repeated-measure analysis of variance was used to compare ranked T_{max} , $t_{1/2}$, logarithmically transformed C_{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 was <0.05. For T_{max} , the difference in treatments was considered significant if the P value for the null hypothesis (equality of mean rank T_{max}) was <0.05. Schiurmann'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_{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_{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. The pharmacokinetic

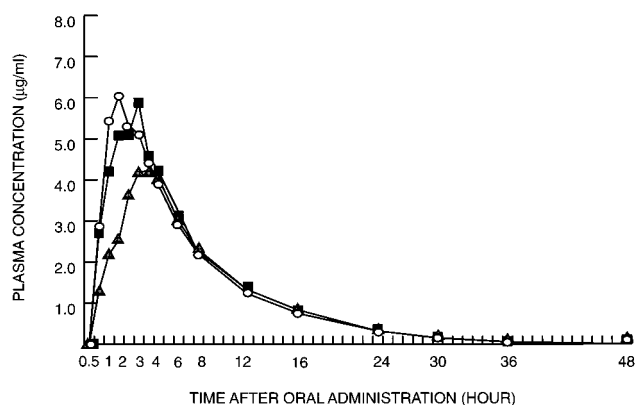


FIG. 1. Mean observed plasma levofloxacin concentration-versus-time profiles following administration of a single 500-mg oral dose under fasting (■), fed (▲) and fasting plus sucralfate (○) conditions for 24 healthy volunteers.

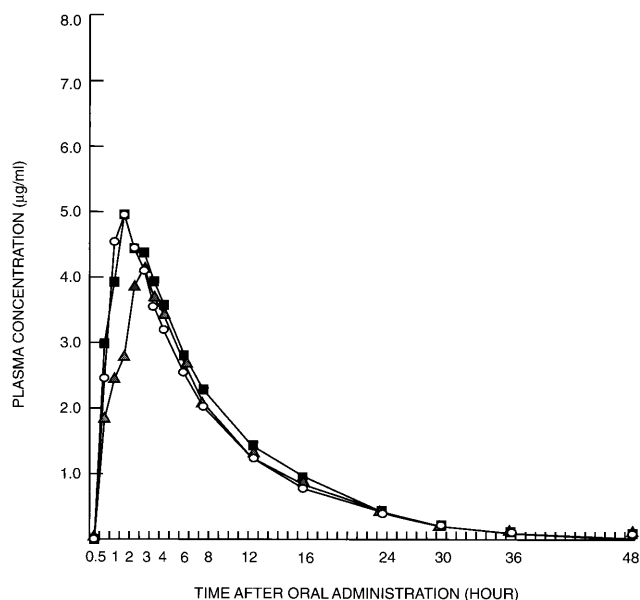


FIG. 2. Mean observed plasma levofloxacin concentration-versus-time profiles following administration of a single 500-mg oral dose during fasting (■), fed (▲), and fasting plus sucralfate (○) conditions for 12 healthy male volunteers.

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_{max} [mean, 2.0 h; $P = 0.0023$]) and a 14% reduction in the mean C_{max} (5.1 $\mu\text{g/ml}$; 90% CI = 0.79 to 0.94) compared with that under the fasting condition (1.0 h and 5.9 $\mu\text{g/ml}$, respectively). Mean $t_{1/2}$ and oral CL/F values, however, were similar for subjects under the fasting and fed conditions.

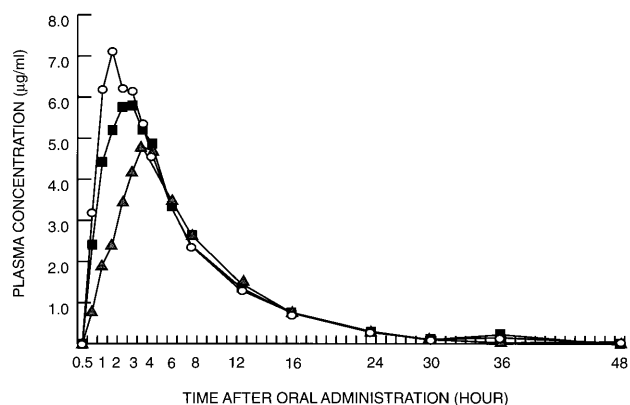


FIG. 3. Mean observed plasma levofloxacin concentration-versus-time profiles following administration of a single 500-mg oral dose during fasting (■), fed (▲), and fasting plus sucralfate (○) conditions for 12 healthy female volunteers.

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

Condition	C_{max} ($\mu\text{g/ml}$)	T_{max} (h)	$AUC_{0-\infty}$ ($\mu\text{g} \cdot \text{h/ml}$)	$t_{1/2}$ (h)	CL/F (liters/h)	CL _R (liters/h)
Fasting	5.9 \pm 1.3	1.0	50.5 \pm 8.1	6.2 \pm 1.6	10.1 \pm 1.6	7.3 \pm 1.4
Fed ^a	5.1 \pm 0.9	2.0 ^b	45.6 \pm 6.1	6.5 \pm 1.9	11.1 \pm 1.4	7.6 \pm 1.9
Fasting plus 1 g of sucralfate	6.7 \pm 3.2	1.0 ^c	47.9 \pm 8.4	6.1 \pm 1.4	10.7 \pm 1.8	7.5 \pm 1.3

^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).

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 CL_R 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_{max} , T_{max} , and $t_{1/2}$. The mean values of C_{max} were higher and the values of T_{max} were lengthened for the female subjects. The mean $t_{1/2}$ was shorter for the female (~6 h) subjects than for the male (~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

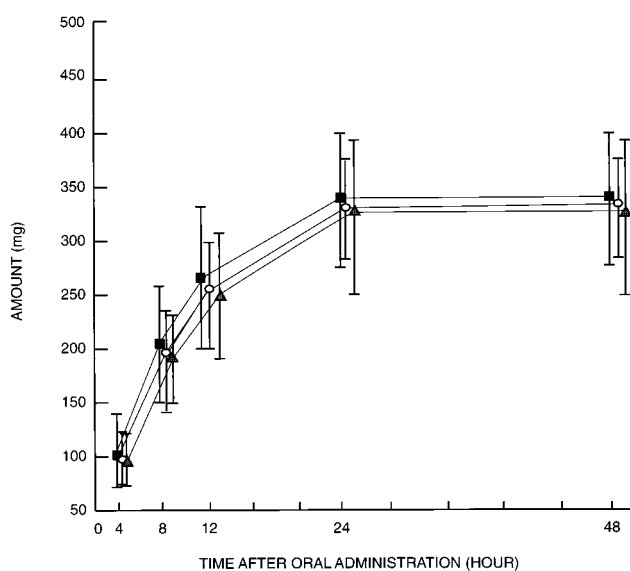


FIG. 4. Cumulative amount (mean \pm standard deviation) of levofloxacin in urine following oral administration of 500 mg of levofloxacin under fasting (■), fed (▲), and fasting plus sucralfate (○) conditions.

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_{max} and T_{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_{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_{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 $t_{1/2}$ s than their male counterparts; however, CL_R values were similar between the genders. The similarities of the CL_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_{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

- Chien, S. C., A. T. Chow, J. Natarajan, R. R. Williams, F. A. Wong, M. C. Rogge, and R. K. Nayak. 1997. Absence of age and gender effects on the pharmacokinetics of a single 500-milligram oral dose of levofloxacin in healthy subjects. *Antimicrob. Agents Chemother.* **41**:1562-1565.
- Chien, S.-C., M. C. Rogge, L. G. Gisclon, C. Curtin, F. Wong, J. Natarajan, R. R. Williams, C. Fowler, and A. Chow. 1997. Pharmacokinetic profile of levofloxacin following once-daily 500-milligram oral or intravenous doses. *Antimicrob. Agents Chemother.* **41**:2256-2260.
- Dudley, M. N., C. R. Marchbanks, S. C. Flor, and B. Beals. 1991. The effect of food or milk on the absorption kinetics of ofloxacin. *Eur. J. Clin. Pharmacol.* **41**:569-571.
- Frost, R. W., J. D. Carlson, A. J. Dietz, Jr., A. Heyd, and J. T. Lettieri. 1989. Ciprofloxacin pharmacokinetics after a standard or high-fat/high-calcium breakfast. *J. Clin. Pharmacol.* **29**:953-955.
- Fu, K. P., S. C. Lafredo, B. Folen, D. M. Isaacson, J. F. Barrett, A. J. Tobia, and M. E. Rosenthale. 1992. In vitro and in vivo antibacterial activities of levofloxacin (*l*-ofloxacin), an optically active ofloxacin. *Antimicrob. Agents Chemother.* **36**:860-866.
- Fujimoto, T., and S. Mitsuhashi. 1990. In vitro antibacterial activity of DR-3355, the S-(−) isomer of ofloxacin. *Chemotherapy* **36**:268-276.
- Garrelts, J. C., P. J. Godley, J. D. Peterie, E. H. Gerlach, and C. C. Yakshe. 1990. Sucralfate significantly reduces ciprofloxacin concentrations in serum. *Antimicrob. Agents Chemother.* **34**:931-933.
- Hoffken, G., H. Lode, R. Wiley, et al. 1988. Pharmacokinetics and bioavailability of ciprofloxacin and ofloxacin: effect of food and antacid intake. *Rev. Infect. Dis.* **10**(Suppl. 1):S138-S139.
- Lagniere, S., F. D. Richard, G. Carignan, et al. 1996. Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin. Pharmacol. Ther.* **60**:255-264.
- Ledgergerber, B., J.-D. Bettex, B. Joos, M. Flepp, and R. Luthy. 1985. Effect of standard breakfast on drug absorption and multiple-dose pharmacokinetics of ciprofloxacin. *Antimicrob. Agents Chemother.* **27**:350-352.
- Lehto, P., and K. T. Kivisto. 1994. Effect of sucralfate on absorption of norfloxacin and ofloxacin. *Antimicrob. Agents Chemother.* **38**:248-251.
- Lubowski, T. J., C. H. Nightingale, K. Sweeney, and R. Quintiliani. 1992. Effect of sucralfate on pharmacokinetics of feroxacin in healthy volunteers. *Antimicrob. Agents Chemother.* **36**:2758-2760.
- Moore, K. H. P., G. J. Yuen, R. H. Rassach, J. J. Eron, D. Martin, P. K. Mydow, and E. K. Hussey. 1996. Pharmacokinetics of lamivudine administered alone and with trimethoprim-sulfamethoxazole. *Clin. Pharmacol. Ther.* **59**:550-558.
- Neuvonen, P. J., and K. T. Kivisto. 1992. Milk and yogurt do not impair the absorption of ofloxacin. *Br. J. Clin. Pharmacol.* **33**:346-348.
- Parpia, S. H., D. E. Nix, L. G. Hejmanowski, H. R. Goldstein, J. H. Wilton, and J. J. Schentag. 1989. Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob. Agents Chemother.* **33**:99-102.
- Polk, R. E. 1989. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. *Am. J. Med.* **87**(Suppl 5A):76S-81S.
- SAS Company. 1990. SAS/STAT user's guide 1990, vol. 2, version 6, 4th ed. SAS Company, Cary, N.C.
- Schuirman, D. J. 1989. Confidence intervals for the ratio of two means from a crossover study, p. 121-126. *In Proceedings of the Biopharmaceutical*

- Section of the American Statistical Association. American Statistical Association, Washington, D.C.
19. **Somogyi, A. A., F. Bochner, J. A. Keal, P. E. Rolan, and M. Smith.** 1987. Effect of food on enoxacin absorption. *Antimicrob. Agents Chemother.* **31**: 638–639.
 20. **Steirijans, V. W., M. Hartmann, and H. W. Radtke.** 1991. Lack of pharmacokinetic interaction as an equivalence problem. *Int. J. Clin Pharmacol. Ther. Toxicol.* **29**:323–328.
 21. **Une, T., T. Fujimoto, K. Sato, and Y. Osada.** 1988. In vitro activity of DR-3355, an optically active ofloxacin. *Antimicrob. Agents Chemother.* **32**:1336–1340.
 22. **Welling, P. G., and F. L. S. Tse.** 1982. The influence of food on the absorption of antimicrobial agents. *J. Antimicrob. Chemother.* **9**:7–27.
 23. **Wong, F.-A., S. J. Juzwin, and S. C. Flor.** 1997. Rapid stereospecific high-performance liquid chromatographic determination of levofloxacin in human plasma and urine. *J. Pharmacol. Biomed. Anal.* **15**:765–771.