Effect of Food on Absorption of Lomefloxacin

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Twelve subjects participated in an open-label, single-dose, balanced three-way crossover study in which the absorptions of lomefloxacin were compared following (i) an overnight fast, (ii) a carbohydrate meal, and (iii) a high-fat meal. The time to peak concentration of lomefloxacin was delayed, but peak concentration in plasma and amount of drug absorbed were unchanged following both meals.

Lomefloxacin [1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid] is a fluoroquinolone antibacterial agent which is currently undergoing clinical development. Like other members of this class, lomefloxacin has a broad spectrum of bactericidal activity against gram-negative and gram-positive bacteria. This drug shares with other newer fluoroquinolones the additional advantage of a relatively long elimination half-life (7 to 8 h) (J. Woodworth and S. Fitzsimmons, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1268, 1989).

The influence of food on drug absorption is complex and often unpredictable. Different food components can have different effects, and food may have opposite effects on absorption of different drugs, even those which are chemically related (4). Therefore, the previous demonstration that food has only slight effects on the absorption rates of enoxacin (5) and ciprofloxacin (2) gives no guarantee of a similar outcome with lomefloxacin.

(This study was previously reported in part [W. D. Hooper, R. G. Dickinson, and M. J. Eadie, 29th ICAAC, abstr. no. 1274, 1989].)

Twelve fully informed volunteers (eight males and four females) participated in the study, which had the prior approval of the Human Experimentation Ethical Review Committee of The University of Queensland. The study protocol permitted enrollment of males and females randomly, and no allowance was made in the timing of the studies for the hormonal cycle of females. The volunteers' ages were 19 to 22 years (mean, 20 years), weights ranged from 54 to 79 kg (mean, 67 kg), and all were nonsmokers. The health of the subjects was assessed by physical examination and biochemical, hematological, and urine screening.

Each subject took a single 400-mg dose of lomefloxacin (two capsules containing 200 mg of lomefloxacin as the hydrochloride, taken with 200 ml of water) on three occasions with a 7-day interval between doses. The study followed an open-label, balanced three-way crossover design, with each subject receiving lomefloxacin (i) after a 12-h overnight fast, (ii) within 5 min after eating a standard carbohydrate breakfast, and (iii) within 5 min after eating a high-fat breakfast. The carbohydrate breakfast (fruit juice, cereal, toast, and coffee) contained 605 calories (70% carbohydrates, 22% fat, and 8% protein), and the high-fat breakfast (fruit juice, fried eggs and bacon, toast, and coffee) contained 612 calories (25% carbohydrates, 62% fat, and

13% protein). After the fasting dose, no food was allowed for 4 h. All subjects abstained from alcohol intake from 3 days prior to the first dose of lomefloxacin until after the completion of the study. Venous blood samples were collected just prior to the lomefloxacin dose and at the following times postdose: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 4, 6, 8, 10, 12, 24, 32, and 48 h. Samples to 12 h were collected via an indwelling forearm venous catheter, and samples thereafter were collected by separate venipuncture. Blood (10 ml) was collected into tubes containing lithium heparin (125 IU); the specimens were centrifuged, and the plasma was separated and frozen ($-20°C$) within 30 min. All urine was collected for 72 h postdose over the following intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 h. Urine pH and volume were recorded at the end of each collection interval, and a 20-ml sample was stored at $-20°C$ until analyzed. Appropriate precautions were taken to protect samples from exposure to light during collection, storage, and analysis.

Lomefloxacin in plasma was assayed by high-performance liquid chromatography using fluorescence detection. The method used was adopted without significant modification from an analytical report supplied by G. D. Searle. The internal standard was a structural analog, KK-123. In brief, plasma specimens (0.5 ml) were extracted at pH 7 with chloroform-isoamyl alcohol (95:5; 5.0 ml), the aqueous phase and precipitated proteins were removed by aspiration, and the organic phase was evaporated at 40°C under a nitrogen stream. The residue was reconstituted in high-performance liquid chromatography mobile phase (0.5 ml), and a sample (30 μl) was applied to the high-performance liquid chromatograph. The mobile phase was 22% acetonitrile and 1% ammonium acetate (1.0 M) in citric acid (0.05 M), at a flow rate of 1.3 ml/min. We used a Waters μBondapak C_{18} (10 μm) steel-jacketed column (30 cm by 3.9 mm [inner diameter]). Under these conditions, the retention time of lomefloxacin was approximately 6.5 min and that of KK-123 was approximately 12.5 min. The detector was a Hitachi F-1000 fluorescence spectrophotometer with an excitation wavelength of 280 nm and emission monitored at 455 nm. The signal was recorded with a Shimadzu CR3-A integrator with FDD-1A floppy disk drive and cathode-ray tube display. Peak areas were measured.

The precision and accuracy of the method in the assay of study plasma samples were determined by analysis of seeded controls processed with each sample batch. This showed precisions (relative standard deviations) of 7.3% at 0.2 μg/ml, 8.3% at 1.0 μg/ml, and 5.9% at 5.0 μg/ml. Accuracies were 5.4% at 0.2 μg/ml, 6.5% at 1.0 μg/ml, and 5.7% at 5.0
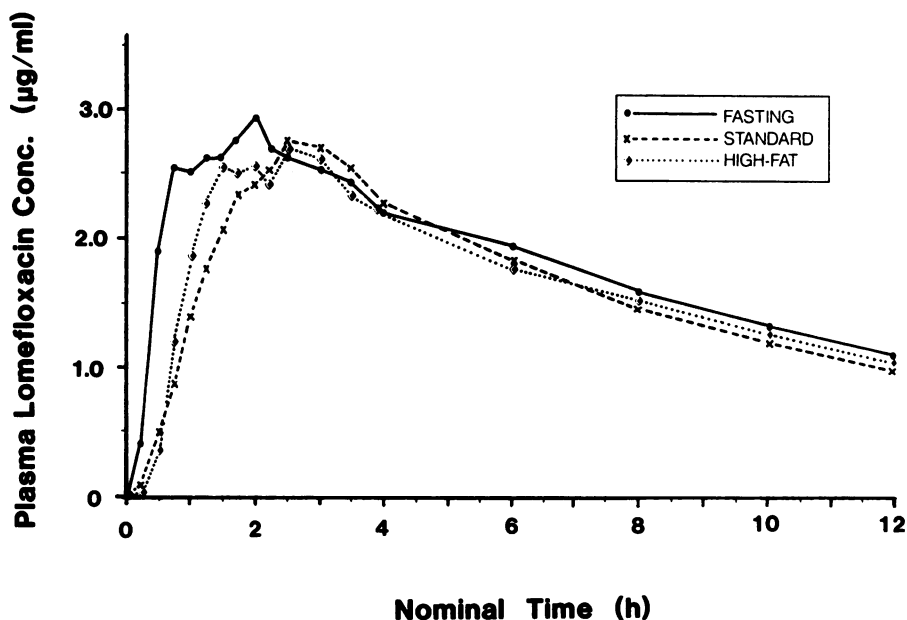
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FIG. 1. Mean plasma lomefloxacin concentration-time profiles in 12 subjects after a 400-mg oral dose fasting and after a carbohydrate or high-fat meal. (Data are shown only to 12 h for clarity, but concentrations were measurable at 48 h in every instance.)

μg/ml. The minimum quantifiable concentration was 20 ng/ml in plasma.

Lomefloxacin in urine was assayed by high-performance liquid chromatography using an identical procedure. Assays were done directly on urine to determine the concentration of lomefloxacin eliminated unchanged (i.e., free lomefloxacin) and on urine following base hydrolysis to determine the concentration of free lomefloxacin plus lomefloxacin liberated from conjugates. The extent of lomefloxacin conjugation was obtained by the difference. Data supplied by G. D. Searle indicated that the conjugate was predominantly the acyl glucuronide.

Linearity was demonstrated on three occasions over the concentration range of 3 to 1,000 μg/ml, and the minimum quantifiable concentration was determined as 3 μg/ml. The precision and accuracy of the method in the assay of study urine samples were determined by analysis of seeded controls processed with each sample batch. This showed precisions (relative standard deviations) of 8.0% at 3 μg/ml, 9.3% at 30 μg/ml, and 5.3% at 300 μg/ml. Accuracies were 13.5% at 3 μg/ml, 8.2% at 30 μg/ml, and 5.0% at 300 μg/ml. In the calculation of lomefloxacin conjugates, difference values of <2 μg/ml were disregarded.

Pharmacokinetic parameters were calculated by model-independent methods as follows. Maximum concentration in plasma and the time to reach the maximum concentration in plasma were determined by inspection of the raw data. In all instances, the graphs of log plasma concentration versus time were reasonably linear from 8 to 48 h. The terminal elimination rate constant (k_{el}) was calculated as the slope of this line, using linear least-squares regression with reciprocal weighting; coefficients of determination exceeded 0.98 in all but a few cases (which all exceeded 0.90). Elimination half-life was calculated as $0.693/k_{el}$. The area under the plasma concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) was the sum of the AUC from 0 to 48 h (AUC_{0-48}) (determined by trapezoidal rule) and $AUC_{48-\infty}$ (determined as plasma concentration at 48 h/k_{el}). The apparent oral clearance was obtained from the quotient oral

dose/$AUC_{0-\infty}$. The urinary recoveries of lomefloxacin and lomefloxacin conjugates were expressed as percentages of dose. Analysis of variance and Dunnett's test were used to test statistical significance of differences in the various parameters in relation to treatment.

The mean values for plasma lomefloxacin concentrations following each treatment are shown in Fig. 1; a slight delay in absorption of lomefloxacin after eating is apparent. All calculations were performed using exact sampling times, which often deviated slightly from the nominal sampling times shown in the figure.

(The mean [± standard error] values for concentrations in plasma [micrograms per milliliter] not shown in Fig. 1 were as follows: fasting—24 h, 0.37 ± 0.04; 32 h, 0.21 ± 0.03; and 48 h, 0.06 ± 0.01; standard—24 h, 0.36 ± 0.04; 32 h, 0.20 ± 0.02; and 48 h, 0.05 ± 0.01; and high fat—24 h, 0.37 ± 0.04; 32 h, 0.18 ± 0.02; and 48 h, 0.06 ± 0.01.)

The derived pharmacokinetic parameters are given in Table 1, which shows that the delay in lomefloxacin absorption resulted in a statistically significant ($P < 0.001$) increase in time to maximum concentration in plasma following both types of meal. The effects of the two meals did not differ. There were no statistically significant differences ($P > 0.05$) in any of the other parameters tabulated. The extents of recovery of lomefloxacin in urine were essentially the same after each treatment. There was no adverse effect attributable to the drug in any subject, and the only change in biochemical, hematological, or urinary parameters was a slight lowering in hematocrit and hemoglobin as a result of blood sampling. There were no unidentifiable or drug-related crystals in any urine samples following dosing with lomefloxacin.

In summary, the time to peak plasma lomefloxacin concentration following a carbohydrate meal or a high-fat meal was prolonged by a mean of approximately 1 h, compared to that seen in the fasting condition. The extent of absorption was not significantly reduced by either type of meal, and other aspects of the disposition of the drug were not affected by food. These results are generally similar to those obtained

TABLE 1. Pharmacokinetic parameters for lomefloxacin administered without or with food[a]

Treatment	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL_{ORAL} (ml/min)	$f_{u(LF)}$ (% of dose)	$f_{u(LFC)}$ (% of dose)
Fasting	3.76 (0.91)	1.45 (0.65)	8.54 (1.44)	36.58 (8.37)	193.3 (54.6)	67.6 (6.4)	8.2 (3.2)
Carbohydrate	3.12 (0.69)	2.45 (0.77)	8.15 (1.13)	33.30 (7.75)	211.4 (54.3)	63.6 (7.0)	6.7 (3.0)
High fat	3.28 (0.94)	2.50 (0.88)	8.46 (1.24)	34.35 (5.39)	199.1 (35.1)	66.5 (5.2)[b]	6.8 (3.6)[b]
Statistical significance (P)	>0.05	<0.001	>0.05	>0.05	>0.05	>0.05	>0.05

[a] Values are means for 12 subjects, with standard deviation in parentheses. C_{max}, Maximum concentration in plasma; T_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; $AUC_{0-\infty}$, area under the plasma concentration-time curve from 0 h to infinity; CL_{ORAL}, apparent oral clearance; $f_{u(LF)}$ and $f_{u(LFC)}$, urinary recoveries of lomefloxacin and lomefloxacin conjugates, respectively.

[b] Mean for 11 subjects (incomplete urine collection from 1 subject).

previously with enoxacin (5), ciprofloxacin (2), ofloxacin (1), and pefloxacin (3), for all of which absorption was slightly delayed by administration with at least some types of meals.

In conclusion, lomefloxacin may be taken with or without food, and the slight absorption delay caused by food is unlikely to have clinically significant consequences, since the extent of absorption is not reduced.

LITERATURE CITED

1. Kalager, T., A. Digranes, T. Bergan, and T. Rebstad. 1986. Ofloxacin: serum and skin blister fluid pharmacokinetics in the fasting and non-fasting state. J. Antimicrob. Chemother. 17:795–800.

2. Ledergerber, B., J.-D. Bettex, B. Joos, M. Flepp, and R. Lüthy. 1985. Effect of standard breakfast on drug absorption and multiple-dose pharmacokinetics of ciprofloxacin. Antimicrob. Agents Chemother. 27:350–352.

3. Mahr, G., U. Stephan, H. U. Koch, and H. G. Wiesemann. 1988. Effect of normal and fat-rich food on the absorption of pefloxacin in humans. Rev. Infect. Dis. 10:S137–S138.

4. Melander, A. 1978. Influence of food on the bioavailability of drugs. Clin. Pharmacokinet. 3:337–351.

5. 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.