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Bioequivalence of Oral and Intravenous Ofloxacin after Multiple-Dose Administration to Healthy Male Volunteers

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The bioequivalence of oral and intravenous ofloxacin was investigated after the administration of multiple doses of 400 mg every 12 h to 20 healthy male volunteers in a randomized, crossover, open-label study. Ofloxacin concentrations in plasma were evaluated after 4 days of oral or intravenous (1-h infusion) dosing with a 3-day wash-out period between regimens. As expected, delivery to the systemic circulation took slightly longer after the oral dosing (time to maximum concentration of drug in serum of 1.7 h) relative to the 1-h intravenous infusion, but the systemic availabilities of ofloxacin by the two routes of administration were equivalent (area under the concentration-time curve from 0 to 12 h ratio of 95%). Since previous studies have not demonstrated any change in the bioavailability of ofloxacin in infectious disease patients, this study supports the interchangeability of these dosing regimens.

Ofloxacin is a synthetic carboxyquinolone antimicrobial agent with potent broad-spectrum bactericidal activity against gram-positive and gram-negative aerobic and facultatively anaerobic bacteria (8). Ofloxacin has been available in the United States as 200-, 300-, and 400-mg tablets since January 1991 and as a 200-, 300-, or 400-mg intravenous (i.v.) formulation since March 1992.

Previous studies have demonstrated that ofloxacin is rapidly absorbed from the gastrointestinal tract after oral (p.o.) administration and that it is nearly 100% bioavailable after a single dose (8), but no study had yet defined the absolute bioavailability of ofloxacin at steady-state levels. Thus, the present study was conducted to investigate the bioequivalence of the marketed p.o. and i.v. formulations when administered every 12 h (q12h).

MATERIALS AND METHODS

Subjects. Twenty healthy male subjects ranging in age from 18 to 41 years (mean, 26 years) and weighing from 134 (ca. 61 kg) to 221 (ca. 100 kg) lb (mean, 169 lb [ca. 77 kg]) were enrolled in the study. The subjects were judged healthy on the basis of the results of the prestudy values of vital signs (pulse, oral temperature, and sitting blood pressure), laboratory profiles (hematology profile, blood chemistry, and urinalysis), urine toxicology screen, and human immunodeficiency virus screen. None of the subjects had a previous history of allergy to quinolones or controlled-substance abuse. The protocol was reviewed and approved by the ethical committee of Pharmaco Dynamics Research Inc., Austin, Tex. Demographic characteristics of the subjects are given in Table 1.

Drug administration and blood sampling. Ofloxacin was administered p.o. as a 400-mg tablet (production batch from Ortho Pharmaceutical Corporation) with 8 fluid ounces (ca. 300 ml) of water and i.v. from a 10-ml single-dose vial containing 400 mg of ofloxacin (production batch from Schering, Puerto Rico). Prior to i.v. dosing, the contents of two vials were drawn into a syringe and added to 180 ml of D5W (dextrose). One hundred milliliters of this solution was infused over a 1-h period by using an IVAC infusion pump set to deliver 1.67 ml/min. The p.o. and i.v. dosing was carried out according to the following scheme. In a randomized, crossover, open-label fashion, subjects received either i.v. or p.o. ofloxacin (400 mg q12h) during days 1 to 4. On day 5, they received the morning p.o. or i.v. dose only. Washout was performed during days 6 to 8. On day 9, the crossover took place and subjects again received p.o. or i.v. ofloxacin (400 mg q12h) during days 9 to 12. On day 13, they received the last p.o. or i.v. morning dose. All subjects entered the study center at least 12 h prior to administration of the first dose and remained at the center until the last procedure was completed. Subjects were not allowed to eat within 2 h of a dose. For the morning doses, subjects fasted from at least midnight of the previous day. On days 5 and 13, food was not consumed after the prior evening meal until 2 h after the morning dose. Venous blood samples (5 ml) were drawn from each volunteer immediately prior to each dose on days 1, 3, 4, 9, 11, and 12. On days 5 and 13, blood samples were drawn immediately prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, and 24 h after dosing began.

Analytical procedures. Plasma samples were analyzed for ofloxacin by a sensitive and specific high-pressure liquid chromatographic method previously described (3). After extraction at pH 7 with dichloromethane, the extract was injected onto a C_{18} μBondapak column (25 cm by 4.6 mm [inner diameter]; Waters Associates Inc., Milford, Mass.). The mobile phase consisted of 1.74 g of potassium dihydrogen phosphate and 20 mg of 1-hexanesulfonic sodium salt (Eastman Kodak Co., Rochester, N.Y.) dissolved in 650 ml of distilled water, combined with 350 ml of methanol, and adjusted to pH 3 with phosphoric acid. The imidazolic derivative of ofloxacin (Daiichi Seiyaku) was used as the internal standard. Detection was done with a UV detector at 313 nm. The limit of quantitation was 0.01 mg/liter, and the extraction efficiency was more than 75%. The assay was linear over the concentration range of 0.025 to 9 mg/liter. The intra- and interday coefficients of variation ranged from 3 to 6% over the standard curve concentration range of 0.025 to 9 mg/liter.

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TABLE 1. Demographic characteristics of subjects

Group[a]	Mean (yr) ± SD (range)	Race (no. C/B/O)[b]	Mean wt (lb)[c] ± SD (range)
I	27.0 ± 6.9 (21–41)	5/2/4	166.1 ± 21.0 (134–202)
II	25.3 ± 5.7 (18–36)	13/0/0	172.1 ± 28.0 (144–221)

[a] Group 1 (11 subjects) was given 400 mg i.v. (period 1) and 400 mg p.o. (period 2), whereas group 2 (13 subjects) was given 400 mg p.o. (period 1) and 400 mg i.v. (period 2).
[b] C/B/O, Caucasian/black/other.
[c] One pound equals 0.373242 kg.

Pharmacokinetic and statistical analyses. Day 5 and 13 plasma ofloxacin concentration-time profiles were prepared, and the following pharmacokinetic parameters were evaluated: peak ofloxacin concentration in plasma (C_{max}), the time to reach C_{max} (T_{max}), the predose concentration at 0 h (C_{min}), and the area under the concentration-time curve over the 12-h dosing interval (AUC_{0-12}). The C_{max} and T_{max} values were determined by visual inspection of the plasma ofloxacin concentration-time profiles. AUC_{0-12} was calculated by the trapezoidal summation method. The terminal elimination rate constant, λ, was estimated from the slope of the terminal exponential phase of the plasma ofloxacin concentration-time curve (by means of the linear regression method) which was compiled of no less than three datum pairs and a correlation coefficient, r, of no less than 0.95. The terminal elimination half-life, $t_{1/2}$, was then calculated as $0.693/\lambda$.

At steady-state levels, the apparent systemic clearance (CL/F) and apparent volume of distribution (V_{ss}/F) were calculated as dose/AUC_{0-12} and dose/AUC_{0-12} × ($AUMC_{ss}$/AUC_{0-12} − $T/2$), respectively, where F is the bioavailability of the corresponding ofloxacin formulation, T is the i.v. infusion time or T_{max} after p.o. dosing with the assumption of apparent zero-order absorption rate, and $AUMC_{ss}$ is the steady-state area under the first moment of the concentration-time curve calculated by the method of Smith and Schentag (12).

Statistical analyses were performed with the SAS computer program package (9). Steady-state attainment by the fifth day of continuous dosing for each treatment was confirmed by comparing the fourth and fifth day morning predose ofloxacin concentrations. A P value of <0.05 was used to determine the level of significant difference.

Analysis of variance (ANOVA) and 90% nonsymmetrical confidence interval tests were used to compare the bioavailability parameters (C_{max}, C_{min}, T_{max}, and AUC_{0-12}) from the p.o. and i.v. formulations. ANOVA was performed by the SAS general linear model procedure (9). The model used in the ANOVA tested for the effects of treatment sequence, subject within sequence, study period, and treatment. If there were no significant period effects, the ANOVA was repeated without a period term in the model. The degrees of freedom, P values, and standard deviation (SD) estimates (from residual mean square error term) were obtained from the ANOVA with period effects. Differences in treatment means were deemed statistically significant at P values of <0.05.

Two one-sided t analyses (shortest confidence intervals) (10) were calculated with 90% confidence limits. Confidence intervals within ±20% implied bioequivalence between treatment means.

Safety evaluation. Safety evaluations were based on the incidence, severity, and type of adverse experiences which occurred during each phase, changes in physical findings from prestudy to poststudy, and comparisons of hematology, serum chemistry, and urinalysis results prior to and after each treatment phase. Hematology tests included hemoglobin, leukocytes, and platelet count. Serum chemistry tests included glucose, creatinine, blood urea nitrogen, total bilirubin, uric acid, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and lactate dehydrogenase. Urinalysis included specific gravity, pH, presence of glucose or protein, and microscopic examination of sediment (erythrocytes, leukocytes, and casts).

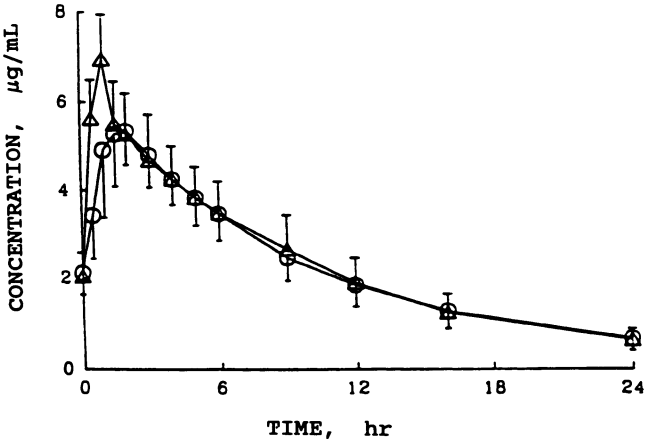

FIG. 1. Mean plasma ofloxacin concentration-versus-time profiles following 5 days of 400-mg i.v. infusion (△) or p.o. (○) administration. The bars indicate SDs.

RESULTS

Clinical data. The physical characteristics of the subjects entered in the study are summarized in Table 1. In the group given ofloxacin i.v. and then p.o. (group I), one subject withdrew during i.v. dosing because of intermittent episodes of dizziness, nausea, and headache and was replaced. Thus, 11 subjects were entered in this study group. Of these subjects, five were Caucasian, two were black, three were Hispanic, and one was a Native American. The mean age of group I subjects was 27 years (range, 21 to 41 years), with seven subjects in 18-to-25-year range, two in the 26-to-35-year range, and two in the 36 to 45 years range. In the group given ofloxacin p.o. and then i.v. (group II), three subjects dropped out; one had abnormal predosing laboratory values and was withdrawn from the study after the first dose (the information had not been available prior to dosing [period I]), one withdrew after his first p.o. dose because of mild urticaria, and the third withdrew because of mild urticaria at the injection site following his first i.v. dose. Each of these subjects was replaced. All subjects in group II were Caucasian. The mean age of group II subjects was 25.2 years (range, 18 to 36 years), with eight subjects in the 18-to-25-year range, four in the 26-to-35-year range, and one in the 36-to-45-year range. With the exception of the three subjects who withdrew because of adverse experiences, the volunteers tolerated ofloxacin well. Of the 23 subjects who received p.o. treatment, 6 (26%) reported seven adverse experiences during the p.o. phase of their trial. Of the 22

TABLE 2. Pharmacokinetic parameters of ofloxacin after administration of multiple 400-mg doses q12h i.v. or p.o. to healthy volunteers[a]

Drug route	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-12} (μg · h/ml)	CL/F (liter/h)[b]	V_{ss}/F (liter)[c]	$t_{1/2}$ (h)
i.v.	7.17 ± 0.87 (5.27–8.52)	1.1 ± 0.5 (0.5–3.0)	43.52 ± 7.81 (33.93–63.59)	9.43 ± 1.46 (6.29–11.79)	93.14 ± 15.89 (75.28–133.20)	7.6 ± 0.98 (5.73–9.58)
p.o.	5.79 ± 1.07 (4.38–7.69)	1.7 ± 0.5 (1.0–3.0)	41.20 ± 6.98 (33.29–59.91)	9.95 ± 1.51 (6.68–12.02)	101.72 ± 15.17 (79.06–128.01)	7.88 ± 1.17 (5.87–9.99)

[a] Values are means ± standard deviations (ranges).
[b] CL/F, apparent systemic clearance/bioavailability.
[c] V_{ss}/F, apparent volume of distribution/bioavailability.

subjects who received i.v. treatment, 9 (41%) reported 18 adverse experiences during the i.v. phase of their trial. All the adverse experiences observed in this study are commonly known to occur after administration of ofloxacin and other quinolones. There were no clinically significant changes in laboratory values from baseline levels after either route of administration.

Pharmacokinetics. Because of a technical malfunction, one data set was lost during sample analysis, hence the pharmacokinetic and statistical analyses were based on a total of 19 subjects. Mean steady-state plasma ofloxacin concentrations obtained after p.o. or i.v. administration are plotted in Fig. 1. As shown in Fig. 1, slight concentration differences were observed between the two routes at 0.5 and 1 h postdose. After 1 h postdose, however, the plasma ofloxacin concentration-time profiles generated from the two routes were essentially superimposable. Steady-state pharmacokinetic parameters after p.o. or i.v. administration are summarized in Table 2. Trough plasma ofloxacin concentrations are plotted in Fig. 2.

Following multiple 400-mg i.v. infusions given q12h, the mean (± SD) C_{max} of 7.17 ± 0.87 μg/ml occurred at 1.1 ± 0.5 h after the start of the final infusion (T_{max}). p.o. administration of ofloxacin at the same dosing regimen resulted in a mean (± SD) C_{max} of 5.79 ± 1.0 μg/ml, which occurred at 1.7 ± 0.5 h postadministration (T_{max}). The mean percent differences in C_{max} and T_{max} from i.v. infusion to p.o. dosing were 23.9 and 35.3%, respectively. Mean (± SD) C_{min} values on day 5 of i.v. and p.o. ofloxacin administration were 2.04 ± 0.53 and 2.12 ± 0.49 μg/ml, respectively. The mean percent difference in C_{min} from i.v. infusion to p.o. dosing was 3.78%. The mean (± SD) AUC_{0-12} values on day 5 of ofloxacin i.v. infusion and p.o. administration were 43.5 ± 7.81 and 41.2 ± 6.98 μg · h/ml, respectively. The mean percent difference in AUC_{0-12} from i.v. infusion to p.o. dosing was 5.65%; alternatively, the ratio of AUC_{0-12} (p.o. relative to i.v. administration) was 95.0 ± 6.45%. These values suggested the systemic availability from multiple-dose administration of the two formulations was essentially identical. The mean (± SD) values of $t_{1/2}$ following i.v. and p.o. ofloxacin administration were 7.61 ± 0.98 and 7.88 ± 1.17 h, respectively. The mean percent difference in $t_{1/2}$ from i.v. infusion to p.o. dosing was 3.43%.

Steady-state attainment by the fifth day of 400-mg q12h dosing was achieved, since no significant differences were observed between the fourth and fifth day morning predose plasma ofloxacin concentrations following either p.o. or i.v. administration (P = 0.913 and 0.818, respectively).

Least-square mean parameter values from the two (i.v. and p.o.) treatments were compared by ANOVA and 90% nonsymmetrical confidence interval tests. No significant treatment sequence and period effects were observed. Results of the statistical comparisons are given in Table 3. Both the C_{max} and T_{max} values were significantly different following multiple i.v. and p.o. treatments, as indicated by the ANOVA P values and the 90% confidence intervals. The C_{min} values between the two treatments, however, were not different. The differences in AUC_{0-12} values between treatments were small but statistically significant by the ANOVA test. However, the AUC_{0-12} values were well within the 90% nonsymmetrical confidence intervals, indicating equivalence in systemic availability from the two formulations after multiple doses.

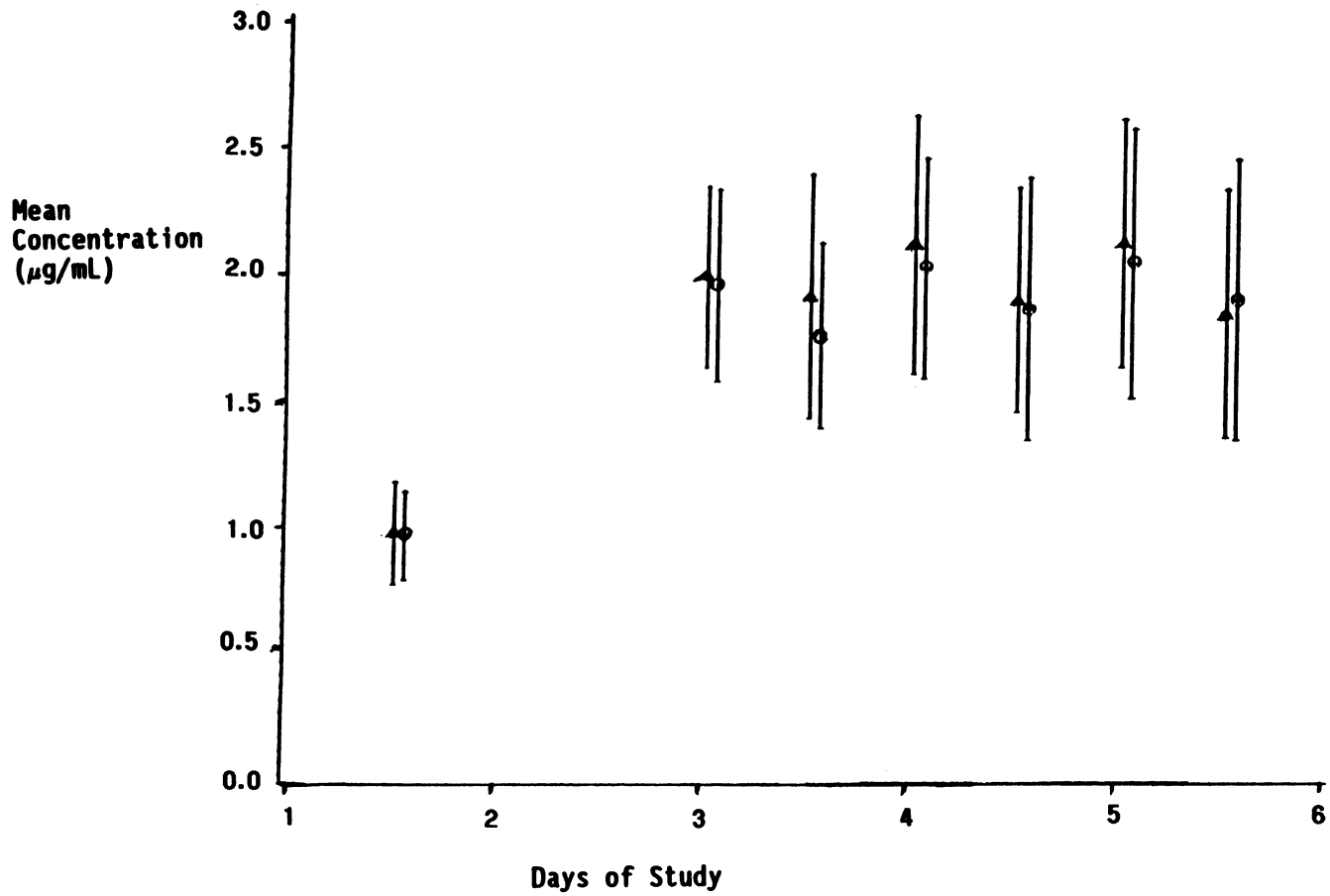

FIG. 2. Mean morning and evening trough ofloxacin concentrations in plasma over time following multiple 400-mg i.v. (△) or p.o. (○) doses given q12h to healthy volunteers. The bars indicate SDs.

DISCUSSION

This study investigated the interchangeability of the p.o. and i.v. formulations of ofloxacin under the most commonly used clinical regimen of 400 mg q12h.

The pharmacokinetic results and concentrations in plasma were comparable to those previously observed after administration of similar dosing regimens, i.v. or p.o., to volunteers or patients with normal renal function (1, 5). Previous studies have not shown any change in the bioavailability of ofloxacin in infectious disease patients versus normal volunteers (1, 2, 6, 7, 11, 13, 14). The bioavailability of ofloxacin has been previously investigated after administration of single doses (5, 15), but to our knowledge this is the first study that has investigated it under steady-state conditions.

TABLE 3. Results of the ANOVA and 95% confidence interval tests in comparing the steady-state bioavailability parameters of ofloxacin administered as 400-mg i.v. or p.o. doses q12h to healthy volunteers

Parameter	*P* value by ANOVA test	90% confidence interval	
		Lower	Upper
C_{max}	0.0001	116.5	131.2
C_{min}	0.4146	88.17	104.2
T_{max}	0.0082	48.42	86.33
AUC_{0-12}	0.0042	102.7	108.6

As has been previously shown after single doses, the 400-mg tablet showed complete p.o. bioavailability. Since the absorption of ofloxacin from the tablet formulation required more time than the 1-h i.v. infusion period, modest but statistically significant differences in T_{max} and C_{max} values were observed between these forms of administration. This phenomenon was also observed in the single-dose studies (5, 15). As expected, these slight differences in absorption rate and duration (i.v. versus p.o.) resulted in higher C_{max} values after i.v. infusion (on average, 1.4 μg/ml higher than after p.o. administration), in spite of both formulations having equivalent extents of absorption. Given the wide safety margin of this drug, this slight difference in C_{max} is unlikely to have any clinical significance.

Steady-state conditions were achieved by day 5 for both treatments. In addition, the predose concentrations (C_{min}) were not different between the two formulations, indicating that ofloxacin accumulated in plasma to the same extent after multiple p.o. or i.v. doses. Since no alterations in steady-state drug concentrations would be expected in interchanging i.v. and p.o. formulations of the same dose, hospitalized patients could be initiated on the i.v. formulation and, when appropriate, be converted to the p.o. formulation on a milligram-to-milligram basis.

This study has demonstrated the bioequivalence of the p.o. and i.v. formulations of ofloxacin. The study specifically investigated the most commonly used clinical regimen of 400

mg q12h, but the excellent dose proportionality previously exhibited by ofloxacin (3, 4) suggests that the current findings can be extrapolated to the 200- and 300-mg once-a-day or q12h regimens.

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REFERENCES

1. **Auten, G. M., L. C. Preheim, M. Sookpranee, M. J. Bittner, T. Sookpranee, and A. Vibhagool.** 1991. High-pressure liquid chromatography and microbiological assay of serum ofloxacin levels in adults receiving intravenous and oral therapy for skin infections. Antimicrob. Agents Chemother. **35:**2558–2561.
2. **Bitar, N., R. Claes, and P. Van der Auwera.** 1989. Concentrations of ofloxacin in serum and cerebrospinal fluid of patients without meningitis receiving the drug intravenously and orally. Antimicrob. Agents Chemother. **33:**1686–1690.
3. **Flor, S.** 1989. Pharmacokinetics of ofloxacin. Am. J. Med. **87**(Suppl. 6C)**:**245–305.
4. **Guay, D. R. P., J. A. Opsahl, F. G. McMahon, R. Vargas, G. R. Matzke, and S. Flor.** 1992. Safety and pharmacokinetics of multiple doses of intravenous ofloxacin in healthy volunteers. Antimicrob. Agents Chemother. **36:**308–312.
5. **Lode, H., G. Hoffken, P. Olschewski, B. Sievercs, A. Kirch, K. Borner, and P. Koeppe.** 1987. Pharmacokinetics of ofloxacin after parenteral and oral administration. Antimicrob. Agents Chemother. **31:**1338–1342.
6. **Naber, K. G., D. Adam, and F. Kees.** 1987. *In vitro* activity and concentrations in serum, urine, prostatic secretion and adenoma tissue of ofloxacin in urological patients. Drugs **34**(Suppl. 1)**:**44–50.
7. **Pedersen, S. S., T. Jensen, and E. F. Hvidberg.** 1987. Comparative pharmacokinetics of ciprofloxacin and ofloxacin in cystic fibrosis patients. J. Antimicrob. Chemother. **20:**575–583.
8. **Sanders, W. E., Jr.** 1992: Oral ofloxacin: a critical review of the new drug application. Clin. Infect. Dis. **14:**539–554.
9. **SAS Company.** 1990. SAS/STAT user's guide 1990, vol. 2, version 6, 4th ed. SAS Company, Cary, N.C.
10. **Schuirmann, D. J.** 1987. A comparison of the two one-sided test procedure and the power approach for assessing the equivalence of average bioavailability. J. Pharmacokinet. Biopharm. **15:**657–680.
11. **Silvain, C., S. Bouquet, J. P. Breux, B. Becq-Giraudon, and M. Beauchant.** 1989. Oral pharmacokinetic and ascitic fluid penetration of ofloxacin in cirrhosis. Eur. J. Clin. Pharmacol. **37:** 261–265.
12. **Smith, I. L., and J. J. Schentag.** 1984. Noncompartmental determination of the steady-state volume of distribution during multiple dosing. J. Pharm. Sci. **73:**281–282.
13. **Tartaglione, T. A., C. R. Johnson, P. Brust, K. Opheim, T. M. Hooton, and W. E. Stamm.** 1988. Pharmacodynamic evaluation of ofloxacin and trimethoprim-sulfamethoxazole in vaginal fluid of women treated for acute cystitis. Antimicrob. Agents Chemother. **32:**1640–1643.
14. **Yew, W. W., J. Lee, C. Y. Chan, S. W. Cheung, P. C. Wong, and S. Y. L. Kwan.** 1991. Ofloxacin penetration into tuberculous pleural effusion. Antimicrob. Agents Chemother. **35:**2159–2160.
15. **Yuk, J. H., C. H. Nightingale, R. Quintillani, and K. R. Sweeney.** 1991. Bioavailability and pharmacokinetics of ofloxacin in healthy volunteers. Antimicrob. Agents Chemother. **35:**384–386.