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Safety and Pharmacokinetics of Multiple Doses of Intravenous Ofloxacin in Healthy Volunteers

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The safety and pharmacokinetics of ofloxacin in 48 healthy male volunteers were studied in a two-center, randomized, double-blind, placebo-controlled study. Ofloxacin (200 or 400 mg) or placebo was administered as 1-h infusions every 12 h for 7 days. Plasma ofloxacin concentrations were measured by high-performance liquid chromatography. Mean harmonic half-lives ranged from 4.28 to 4.98 h in the 200-mg dosing group and from 5.06 to 6.67 h in the 400-mg dosing group. Intragroup comparisons of trough plasma concentration-versus-time data from study days 2 through 7 revealed that steady state was achieved by day 2 of both multiple-dose regimens. Intergroup comparisons of mean harmonic half-lives, the areas under the concentration-time curve from 0 to 12 and 0 to 60 h, clearance, and apparent volume of distribution (area method) revealed that the pharmacokinetics of ofloxacin are dose independent. Both ofloxacin dosage regimens appeared to be reasonably well tolerated. The two dosage regimens of ofloxacin, 200 or 400 mg every 12 h, appear to be safe and provide serum drug concentrations in excess of the MICs for most susceptible pathogens over the entire dosing interval.

Ofloxacin is a synthetic carboxyquinolone antimicrobial agent which exhibits broad-spectrum *in vitro* bactericidal activities against gram-positive and gram-negative aerobes (5). The clinical efficacy of ofloxacin has been documented in patients with respiratory tract, upper and lower urinary tract, and skin and soft tissue infections and gonococcal and nongonococcal urethritis (5, 8). In December 1990, the oral tablet formulation of ofloxacin was approved by the U.S. Food and Drug Administration, and marketing commenced in February 1991.

In certain circumstances, such as in patients who are seriously ill, have ileus, or are nauseated and/or vomiting, the oral route of ofloxacin administration may not be appropriate. In these situations, an intravenous (i.v.) formulation may prove useful. This study was designed to evaluate the safety and pharmacokinetics of multiple-dose intravenous (i.v.) ofloxacin in healthy adult volunteers in two proposed therapeutic dosing regimens (200 and 400 mg every 12 h [q12h]).

MATERIALS AND METHODS

Volunteers. Healthy male volunteers, aged 18 to 40 years inclusive, participated in the study after granting written, informed consent as approved by the Human Subjects Review Committee of Hennepin County Medical Center and the Institutional Review Board of the Clinical Research Center, Tulane University School of Medicine. Subjects were judged to be healthy on the basis of normal findings on medical history, physical and neurological examinations, clinical laboratory tests, electroencephalography, and electrocardiography.

Design. This study was conducted as a two-center, double-blind, randomized placebo-controlled, parallel study, with

the protocols of 200 and 400 mg q12h conducted at the University of Minnesota and Tulane University, respectively. Subjects were randomized to receive either 200 or 400 mg of ofloxacin or identical placebo q12h as 1-h i.v. infusions for 7 days. Subjects were confined from 12 h prior to administration of the first dose until after all final plasma and urine samples had been collected. Ingestion of caffeine and alcohol was prohibited during the study period.

The safety tests that were performed included audiometry, ophthalmology (funduscopy, slit lamp, tonometry, color vision, acuity), clinical laboratory tests, electrocardiography (performed prestudy and on days 1, 4, and 8), and electroencephalography (performed prestudy and on days 2 and 5). In addition, urine was screened for crystalluria daily during treatment, and visual reaction times (assessed by using a brake reaction timer [American Automobile Association, Heathrow, Fla.]) were obtained prestudy and on days 1 and 4 of treatment.

Blood samples of 5 ml were obtained from the arm contralateral to the infusion site immediately prior to the morning doses on days 1 through 7. In addition, blood samples were obtained on days 1, 4, and 7 at 0.5 h after the start of the morning infusion; at the end of the infusion; and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 11 h after the end of the infusion. Blood samples were also obtained 24, 36, 48, and 60 h after the start of the final infusion. Blood samples were collected in heparinized tubes and centrifuged, and the plasma was separated and stored frozen at -20°C until it was assayed.

Specimen analysis. The concentration of ofloxacin in plasma was determined by a high-pressure liquid chromatography method. After extraction at pH 7 with dichloromethane, the extract was injected onto a C18 μ Bondapak 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

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TABLE 1. Subject demographic characteristics

Group ^a	Age (yr) ^b	Race (no. C/B/O) ^c	Ht (cm) ^b	Wt (kg) ^b
200 mg of ofloxacin	27.2 ± 6.2 (19–37)	9/2/1	181.6 ± 7.4 (170.2–195.6)	77.4 ± 10.2 (60.5–101.8)
200 mg of placebo	27.9 ± 4.5 (21–37)	7/5/0	182.4 ± 7.6 (172.7–193.0)	79.6 ± 12.5 (57.0–98.6)
400 mg of ofloxacin	30.5 ± 5.5 (22–40)	4/7/1	180.6 ± 7.6 (165.1–193.0)	75.4 ± 13.7 (49.1–95.9)
400 mg of placebo	33.3 ± 4.9 (23–38)	10/2/0	176.3 ± 5.8 (167.6–186.7)	75.1 ± 9.0 (60.5–85.0)

^a There were 12 subjects in each group.

^b Values are means ± standard deviations (ranges).

^c C/B/O, Caucasian/black/other.

of methanol and adjusted to pH 3 with phosphoric acid. An imidazolic analog of ofloxacin (Daiichi Seiyaku) was used as the internal standard. Detection at 313 nm was done with a UV detector. The limit of quantitation was 0.01 mg/liter, and the extraction efficiency was greater than 95%. 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 (2).

Pharmacokinetic analysis. Pharmacokinetic analysis was done as described previously (3). Areas under the plasma concentration-versus-time curve from time zero to 12 h (AUC_{0–12}) on days 1, 4, and 7 and from time zero to 60 h (AUC_{0–60}) on day 7 were determined by trapezoidal integration. The elimination rate constant (k_{el}) and terminal disposition half-life ($t_{1/2\beta}$) were determined from model fitting of the 0- to 12-h postdose plasma concentration-versus-time data to polyexponential equations by using CSTRIP (7) followed by nonlinear regression analysis using PC NONLIN (Statistical Consultants, Lexington, Ky.). Data fits were unweighted, and the appropriate exponential model was determined by examining the Akaike information criterion (1, 9), the sum of weighted residuals, and the observed versus fitted plasma concentration-versus-time data. Each subjects' day 1, 4, and 7 data fits were analyzed independently. Plasma clearance (CL) was calculated by dividing the dose by AUC_{0–12} on days 4 and 7. The apparent volume of distribution (V) was calculated by dividing CL by k_{el} .

Statistical analysis. Analysis of variance followed by the Tukey-Kramer test was performed to determine whether significant differences occurred between days for the AUC, k_{el} , CL, and V parameters. Bartlett's test was used to determine the homogeneity of variance between days for the AUC, morning trough concentrations (C_{min}), k_{el} , CL, and V parameters. Friedman's test with Page's statistic and Doksum's test with Hollander's statistic were performed to test for day-to-day differences and trends on the ranked C_{min} values. Comparisons between the ofloxacin and placebo groups regarding adverse experiences were determined by using a one-tailed Fisher's exact test. Adverse experience rates were calculated as the number of subjects with a given experience divided by the total number of subjects that were evaluable for safety. All statistical evaluations were performed by using the SAS statistical package (6). Significance was assessed at the 5% level. Data are presented as means ± standard deviations unless otherwise noted.

RESULTS

Patient demographics. Demographics of the groups receiving 200 mg of ofloxacin and placebo at the University of Minnesota and the groups receiving 400 mg of ofloxacin and placebo at Tulane University are given in Table 1. Within-

and between-site comparisons of the ofloxacin and placebo groups from both study sites did not reveal any statistically significant differences in demographic parameters.

Safety. At the University of Minnesota site, two ofloxacin recipients were switched to placebo in a blinded fashion because of adverse events. One of these subjects developed a fine macular erythematous rash on his back and front torso during the morning dose on study day 4; the rash resolved spontaneously after the switch to placebo. The other subject developed dizziness and tachycardia as well as erythema and pruritus at the i.v. infusion site during the initial infusion; these adverse events also resolved spontaneously after the switch to placebo. All recipients of 200 mg of placebo completed the study. Overall, 8 of 12 subjects who received 200 mg of ofloxacin and 8 of 12 subjects who received placebo experienced adverse events during the study. A total of 49 and 32 adverse events were reported in the ofloxacin and placebo recipients, respectively. These were the totals of all reactions independent of the degree of association to study therapy. Adverse events (number of subjects in parentheses) in the ofloxacin group included extremity pain ($n = 1$), dizziness ($n = 1$), headache ($n = 2$), paresthesia ($n = 1$), ocular dryness ($n = 1$), ocular redness ($n = 1$), edema ($n = 1$), tachycardia ($n = 1$), abnormal chest sounds ($n = 1$), diarrhea ($n = 5$), urinary incontinence ($n = 1$), skin erythema ($n = 2$), rash ($n = 1$), and i.v. infusion site skin reaction ($n = 30$). Adverse events in the placebo group included chills ($n = 1$), trunk pain ($n = 1$), extremity pain ($n = 2$), headache ($n = 1$), syncope ($n = 1$), edema ($n = 2$), gastrointestinal cramps ($n = 2$), gastrointestinal distress ($n = 1$), diarrhea ($n = 3$), skin lesions ($n = 1$), skin erythema ($n = 3$), and i.v. infusion site skin reaction ($n = 14$). There were no statistically significant differences between the ofloxacin and placebo groups in terms of vital signs at baseline or mean changes. No subjects in either group developed neurological abnormalities during the study. No clinically significant alterations in ophthalmologic, audiometric, electrocardiographic, electroencephalographic, or clinical laboratory tests were noted in either group over the course of the study. In addition, there were no statistically significant within-group or between-group differences in visual reaction times (data not shown).

At the Tulane University site, all 24 enrolled subjects (12 who received ofloxacin, 12 who received placebo) completed participation in the study. Overall, 5 of 12 subjects who received 400 mg of ofloxacin and 3 of 12 subjects who received placebo experienced adverse events during the study. A total of 16 and 8 events were reported in the ofloxacin and placebo recipients, respectively. As stated above, these totals were independent of the degree of association to study therapy. Adverse events in the ofloxacin group included dizziness ($n = 1$), headache ($n = 1$), otalgia ($n = 1$), vasodilation ($n = 2$), pharyngitis ($n = 1$), constipation

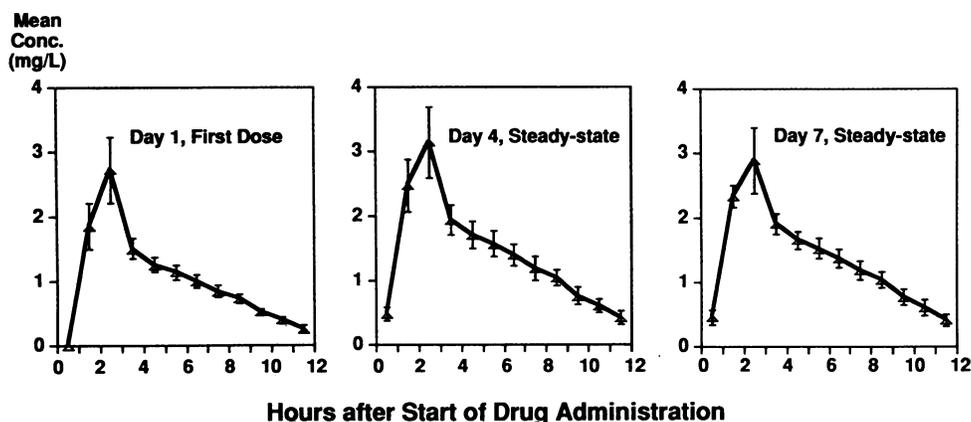


FIG. 1. Mean \pm standard deviation plasma ofloxacin concentration-versus-time profiles following single and multiple 200-mg q12h i.v. dose administration in normal volunteers.

($n = 1$), keratoderma ($n = 1$), rash ($n = 1$), i.v. infusion site skin reaction ($n = 5$), diaphoresis ($n = 1$), and muscle stiffness ($n = 1$). Adverse events in the placebo group included dizziness ($n = 1$), tremor ($n = 1$), dream abnormality ($n = 1$), dyspnea ($n = 1$), pharyngitis ($n = 1$), rash ($n = 2$), and arthralgia ($n = 1$). As in the University of Minnesota subjects, there were no statistically or clinically significant alterations in ophthalmologic, audiometric, electrocardiographic, electroencephalographic, clinical laboratory, or visual reaction time tests in either study group.

The discrepancies in i.v. infusion site skin reaction rates between the two study sites may have been due to the racial imbalance in study populations between the study sites. At the University of Minnesota site, the major i.v. infusion site skin reaction in both study groups was erythema (15 of 30 reactions in ofloxacin recipients, 11 of 14 reactions in placebo recipients), which occurred in a predominantly Caucasian study population. Perhaps the predominance of blacks at the Tulane University site made assessment of erythema as a reaction more difficult, leading to the much lower i.v. infusion site reaction incidence noted at that site.

Pharmacokinetics. The mean plasma concentration-versus-time curves for the 200- and 400-mg q12h multiple-dose groups are illustrated in Fig. 1 and 2, respectively. The pharmacokinetic parameters for both dosing groups are

given in Table 2. Ofloxacin plasma concentration-versus-time data were best fit by a two-compartment open model in all subjects. The harmonic mean $t_{1/2\beta}$ for days 1, 4, and 7 for the 200-mg group (4.28, 4.91, and 4.98 h, respectively) and 400-mg group (5.06, 6.00, and 6.67 h, respectively) were comparable intradose and interdose (P was not significant for all comparisons). Comparable results were obtained when examining intradose and interdose CL and V data. Steady state was achieved by day 2 in both dosing groups, as evidenced by the nonsignificant differences in C_{\min} from study days 2 to 7 (Fig. 3). Intradose comparisons of AUC_{0-12} data in both the 200-mg (AUC_{0-12} day 4 = 12.96 ± 1.62 mg \cdot h/liter versus AUC_{0-12} day 7 = 12.71 ± 1.34 mg \cdot h/liter; P was not significant) and 400-mg (AUC_{0-12} day 4 = 30.17 ± 6.26 mg \cdot h/liter versus AUC_{0-12} day 7 = 28.99 ± 6.98 mg \cdot h/liter; P was not significant) groups corroborated the results of the C_{\min} data analysis. Interdose comparisons of the AUC_{0-12} on days 1, 4, and 7 and the AUC_{0-60} on day 7 revealed that the values for the recipients of 400 mg were not statistically significantly different from double the respective values for the recipients of 200 mg. Statistical analysis revealed no significant race-related differences in AUC, $t_{1/2\beta}$, CL, or V , even when logistic regression was used to examine the dose-race interaction.

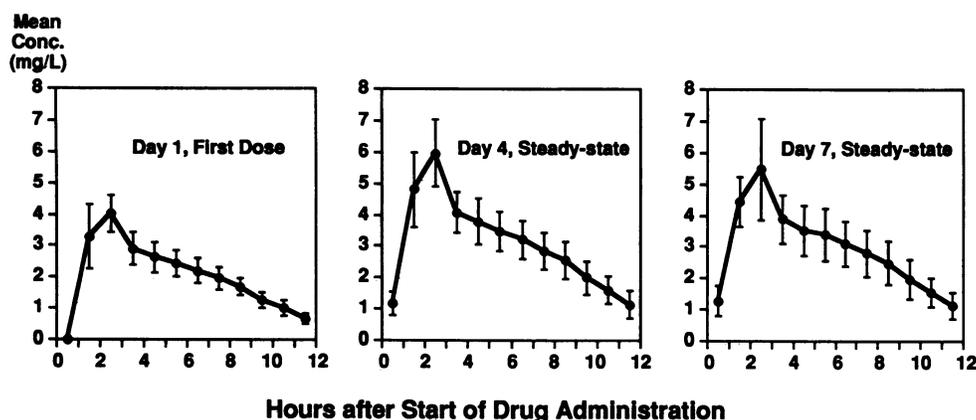


FIG. 2. Mean \pm standard deviation plasma ofloxacin concentration-versus-time profiles following single and multiple 400-mg q12h i.v. dose administration in normal volunteers.

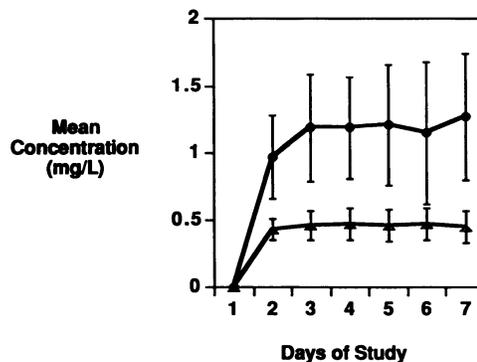


FIG. 3. Mean \pm standard deviation plasma morning trough ofloxacin concentrations over time following multiple 200-mg (Δ) and 400-mg (\bullet) q12h i.v. dose administration in normal volunteers.

DISCUSSION

The single-dose i.v. pharmacokinetic parameters obtained in this study were comparable to those reported previously in normal subjects (4, 10). In the study of Lode and coworkers (4), $t_{1/2\beta}$ ranged from 3.9 \pm 0.6 to 4.5 \pm 0.6 h, $AUC_{0-\infty}$ (comparable to AUC_{0-12} for days 4 and 7 in the present study) ranged from 1.5 \pm 0.2 to 14.4 \pm 1.8 mg \cdot h/liter, CL ranged from 14.0 \pm 1.7 to 17.2 \pm 2.0 liters/h, and V ranged from 86 \pm 10 to 103 \pm 32 liters for single i.v. doses ranging from 25 to 200 mg. Yuk and coworkers (10) reported $t_{1/2\beta}$ of 5.71 \pm 0.73 h, V of 132 \pm 19 liters, CL of 15.6 \pm 3.0 liters/h, and $AUC_{0-\infty}$ of 27.1 \pm 4.11 mg \cdot h/liter after a single 400-mg i.v. dose.

The present study extends these previous observations to include multiple-dose i.v. administration. Data from this study demonstrate that steady state is achieved by day 2 of a multiple dose i.v. ofloxacin regimen in normal volunteers. In addition, interdose comparisons of $t_{1/2\beta}$, AUC, CL, and V suggest that ofloxacin exhibits dose-independent pharmacokinetics over the dosage range studied. Similar dose-independent pharmacokinetics over a lower i.v. dosage range (25 to 200 mg) were demonstrated by Lode et al. (4).

Parenteral ofloxacin appeared to be reasonably well tolerated in recipients of the two dosage regimens studied, with the exception of a high incidence of i.v. infusion site skin reactions. Whether the frequency of i.v. infusion site skin reactions can be reduced by prolonging the infusion time or diluting the drug concentration from the 2 to 4 mg/ml used in this study warrants further investigation. In any case, ofloxacin should be administered via the oral route whenever possible to avoid this potential complication.

Results of this study demonstrate that parenteral ofloxacin in dosage regimens of 200 and 400 mg q12h provides concentrations in serum in excess of the MICs for most susceptible pathogens (MIC for 90% of isolates, \leq 0.5 to 1 mg/liter) over the entire dosing interval. However, for less susceptible pathogens such as *Pseudomonas aeruginosa* (MIC range for 90% of isolates, 1 to 8 mg/liter), such regimens may provide substantial periods of time that the drug is present at concentrations below the MIC for the organism. Further studies of higher or more frequently administered i.v. doses may be warranted.

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TABLE 2. Pharmacokinetic parameters of ofloxacin after multiple-dose q12h i.v. administration of 200- and 400-mg doses to healthy volunteers^a

Group (no. of subjects)	Single dose (day 1)		Multiple dose (day 4)				Multiple dose (day 7)				
	AUC_{0-12} (mg \cdot h/liter)	$t_{1/2\beta}$ (h) ^b	AUC_{0-12} (mg \cdot h/liter)	$t_{1/2\beta}$ (h) ^b	CL (liters \cdot h/kg)	V (liters/kg)	AUC_{0-12} (mg \cdot h/liter)	AUC_{0-60} (mg \cdot h/liter)	$t_{1/2\beta}$ (h) ^b	CL (liters/h/kg)	V (liters/kg)
200 mg (10)	9.31 \pm 0.80 (8.48-10.94)	4.28 (3.67-5.49)	12.96 \pm 1.62 (11.09-15.64)	4.91 (4.05-5.83)	0.207-0.028 (0.172-0.260)	1.46 \pm 0.11 (1.34-1.57)	12.71 \pm 1.34 (10.35-15.38)	17.31 \pm 3.03 (13.60-24.37)	4.98 (4.40-6.63)	0.210 \pm 0.027 (0.164-0.259)	1.15 \pm 0.14 (1.30-1.78)
400 mg (12)	19.78 \pm 3.46 (14.38-25.86)	5.06 (3.90-7.12)	30.17 \pm 6.26 (22.82-43.54)	6.00 (4.24-9.32)	0.187 \pm 0.043 (0.106-0.272)	1.63 \pm 0.17 (1.35-2.00)	28.99 \pm 6.98 (20.54-42.35)	41.83 \pm 12.36 (29.84-69.16)	6.67 (5.48-9.69)	0.195 \pm 0.040 (0.100-0.246)	1.92 \pm 0.50 (1.30-3.14)

^a Abbreviations are defined in the text. Values are means \pm standard deviations (ranges), unless indicated otherwise.
^b Harmonic mean.

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