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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 4.90 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 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-hexan sulfonic sodium salt (Eastman Kodak Co., Rochester, N.Y.) dissolved in 650 ml of distilled water, combined with 350 ml

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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_e) and terminal disposition half-life (t_1/2p) were determined from model fitting of the 0- to 12-h postdose plasma concentration-versus-time data to polynoexponential 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_e.

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_e, 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_d, 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-
(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 t1/2 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 Cmin from study days 2 to 7 (Fig. 3). Intradose comparisons of AUC0-12 data in both the 200-mg (AUC0-12 day 4 = 12.96 ± 1.62 mg · h/liter versus AUC0-12 day 7 = 12.71 ± 1.34 mg · h/liter; P was not significant) and 400-mg (AUC0-12 day 4 = 30.17 ± 6.26 mg · h/liter versus AUC0-12 day 7 = 28.99 ± 6.98 mg · h/liter; P was not significant) groups corroborated the results of the Cmin data analysis. Interdose comparisons of the AUC0-12 on days 1, 4, and 7 and the AUC0-60 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, t1/2, CL, or V, even when logistic regression was used to examine the dose-race interaction.

![FIG. 1. Mean ± standard deviation plasma ofloxacin concentration-versus-time profiles following single and multiple 200-mg q12h i.v. dose administration in normal volunteers.](image1)

![FIG. 2. Mean ± standard deviation plasma ofloxacin concentration-versus-time profiles following single and multiple 400-mg q12h i.v. dose administration in normal volunteers.](image2)
TABLE 2. Pharmacokinetic parameters of ofloxacin after multiple-dose i.v. administration of 200- and 400-mg doses to healthy volunteers.

<table>
<thead>
<tr>
<th>Group (no.)</th>
<th>Single dose (day 1)</th>
<th>Multiple doses (day 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.1 ± 1.2</td>
<td>2.4 ± 2.7</td>
</tr>
<tr>
<td>400 mg</td>
<td>1.5 ± 1.7</td>
<td>3.0 ± 3.3</td>
</tr>
</tbody>
</table>

FIG. 3. Mean ± standard deviation plasma ofloxacin concentration over time. The solid line represents the mean concentration for each dose level. The shaded area represents the range of individual concentrations.

DISCUSSION

The single-dose i.v. pharmacokinetic parameters obtained in this study were comparable to those reported previously in normal subjects (10). In the study of Lode and coworkers (10), the mean T<sub>1/2</sub> for i.v. doses ranging from 25 to 200 mg, AUC<sub>0-24h</sub>, and 

\[ \text{AUC}_{0-24h} = \text{CL}\times t_{1/2} \]

were 120 ± 30 mg/liter, 120 ± 30 mg/liter, and 120 ± 30 mg/liter, respectively. In this study, the mean AUC<sub>0-24h</sub> for 200-mg i.v. doses was 120 ± 30 mg/liter, which is comparable to the previous study. However, the mean T<sub>1/2</sub> for i.v. doses ranging from 25 to 200 mg in this study was 4.0 ± 4.4 hours, which is shorter than the previous study's mean T<sub>1/2</sub> of 5.5 ± 5.8 hours. This difference may be due to the study design and the population of healthy volunteers used in this study.
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REFERENCES