Oral Bioavailability and Pharmacokinetics of Trovafloxacin in Patients with AIDS

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Trovafloxacin pharmacokinetics were evaluated in 12 subjects with AIDS. By using a randomized design, single 200-mg doses of oral trovafloxacin and intravenous alatrofloxacin were administered. The mean absolute bioavailability was 91%. The pharmacokinetics of trovafloxacin when administered orally as the active form or intravenously as the prodrug (alatrofloxacin) are not altered in subjects with AIDS compared to those in healthy adults.

Malabsorption of nutrients and medications has been documented in patients with human immunodeficiency virus (HIV) infection; however, the pathogenesis of malabsorption for many of these patients is poorly understood (6, 7, 9, 27). Additionally, decreased absorption of orally administered medications may occur without gross evidence of gastrointestinal disease.

Trovafloxacin, a fluoroquinolone antibiotic, has good oral bioavailability in healthy subjects and a pharmacokinetic profile which allows for once-daily dosing (24). The purpose of this study was to evaluate the pharmacokinetics of trovafloxacin in subjects with AIDS.

(This research was presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, 28 September to 1 October 1997 [15].)

This was a single-dose, open-labeled, randomized, two-treatment, two-period crossover study with an interval of at least 7 days. Enrollment criteria were as follows: the subjects (i) were ≥18 years of age, (ii) had documented HIV infections, (iii) met the Centers for Disease Control and Prevention’s revised AIDS surveillance definition (a CD4 cell count of <200 cells/mm3 and/or a medical history of a clinical category C opportunistic infection [3]), and (iv) had normal renal and hepatic functions. Subjects were excluded for any of the following: (i) having a history of hypersensitivity to quinolones, (ii) taking antacids, sucralfate, dideoxyinosine, or iron or zinc supplements or having had enteral feeding, (iii) having documented gastroenteritis due to infectious pathogens, (iv) having a positive serum pregnancy test, or (v) having a history of convulsive disorders or epilepsy.

A medical history and physical examination were undertaken at enrollment, while blood chemistry, hematology, and urinalysis were obtained pre- and poststudy. HIV test documentation and baseline CD4 counts were also obtained. Female volunteers were screened for pregnancy by a direct latex agglutination test. The institutional review board at Hartford Hospital approved the study, and all subjects gave written informed consent prior to participation.

Study sample size was determined by using an alpha value of 0.05, a power of 80% to detect a 30% difference in the area under the concentration-time curve (AUC) of the dosage forms, and available data from healthy subjects (25). Sample size was calculated to be 9 subjects per dosage form; however, 12 subjects were enrolled to provide sufficient data should subject withdrawal occur. Comparisons between groups were evaluated by using the paired Student t test.

Subjects were randomized to receive either a single 200-mg (two 100-mg tablets) oral dose of trovafloxacin (Pfizer Laboratories, New York, N.Y.) or an equivalent intravenous dose of alatrofloxacin. Oral doses were given with 240 ml of water, and intravenous doses were diluted in a 200-ml solution of 5% dextrose in water and administered over 1 h. Subjects fasted 8 h before to 4 h after administration. After an interval of 7 days, subjects were administered the dosage formulation not given during the first study period.

Subjects were required to discontinue medications that were determined to be unnecessary for the treatment of their HIV infections; however, no medications which could have impacted the subjects’ clinical conditions (such as those for antiretroviral therapy) were terminated during the study. Concurrent medication use was monitored throughout the study. Caffeinated beverages were not allowed throughout the study periods.

Blood samples (5 ml) were collected with an indwelling intravenous catheter prior to drug administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 h postdose. Serum trovafloxacin concentrations were determined by reverse-phase high-pressure liquid chromatography with UV detection, as previously described (26). The assay was linear within a range of 0.1 to 20 μg/ml, and the intra- and interassay coefficients of variation were less than 10%. Alatrofloxacin concentrations were not determined.

Pharmacokinetic parameters were derived individually for each subject. The maximum concentration of drug in serum (Cmax) was obtained directly from a plot of concentration-time data, while Tmax was defined as the time Cmax occurred. The terminal elimination rate constant (kα) was estimated by least-squares regression analysis of the terminal phase of the log-linear plot of concentration-time data. Individual half-life (t1/2) values were calculated as 0.693/kα. The AUC from time zero to infinity (AUC0→∞) was calculated by using the linear trapezoi-
dal rule with extrapolation to infinity. The values for $C_{\text{max}}$ and AUC provided in this report are geometric means.

Systemic clearance (CL) was estimated as dose/AUC$_{0-\infty}$, assuming that the alatrofloxacin was completely converted to trovafloxacin. The volume of distribution at steady state ($V_{\text{ss}}$) was estimated as $CL / AUMC_{0-\infty}$. Where $AUMC_{0-\infty}$ is the area under the first moment curve from time zero to infinity and $T$ is the infusion time. Both CL and $V_{ss}$ have been corrected for the weights of the individual subjects. The absolute bioavailability of trovafloxacin was determined by the ratio $AUC_{0-\infty}$oral/$AUC_{0-\infty}$intravenous.

Twelve subjects with AIDS (7 male and 5 female) were enrolled, and 10 completed the study. Two subjects (one male and one female) were withdrawn after developing hives at the infusion site immediately after the initiation of the intravenous dose. Median (range) values for age, weight, and CD4 count in our population were 40 years (23 to 50 years), 73 kg (54 to 103 kg), and 240 CD4 cells/mm$^3$ (16 to 485 CD4 cells/mm$^3$), respectively. Of the 10 subjects that completed the study, nine took the following concurrent medications (number of subjects): zidovudine (6), stavudine (2), zalcitabine (2), lamivudine (6), saquinavir (1), indinavir (3), farnoslovir (1), fluconazole (1), trimethoprim-sulfamethoxazole (4), and sertraline (1). One subject was not taking medications at the time of the study.

Mean serum trovafloxacin concentrations following the administration of the oral and intravenous formulations are presented in Fig. 1. Pharmacokinetic data for both dosage forms are displayed in Table 1. Between the two formulations, no significant differences were observed in AUC$_{0-\infty}$ or $t_{1/2}$ values. The adjusted geometric mean values for AUC$_{0-\infty}$ were 25.0 and 27.6 mg·h/ml for the oral and intravenous administrations, respectively. With these values, the absolute bioavailability of trovafloxacin was 91% (range, 52 to 124%).

While this study was not designed to evaluate potential interactions between trovafloxacin and antiretroviral or other medications, no overt interactions were observed based upon an inspection of the trovafloxacin concentration-time profiles for our subjects. However, this needs to be confirmed in other studies since the possibility of a drug interaction cannot be ignored, and the generalization of these data may be limited to subjects not receiving current standards of treatment.

The administration of trovafloxacin was generally well tolerated, and all adverse events were mild. The majority of these events resolved within 12 h after dosing. The most common events (number of episodes) were lightheadedness (8), head-

**TABLE 1. Pharmacokinetic parameters of trovafloxacin after a 200-mg oral or intravenous dose in subjects with AIDS**

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>$C_{\text{max}}$ ($\mu$g/ml)$^a$</th>
<th>$T_{\text{max}}$ (h)$^b$</th>
<th>$t_{1/2}$ (h)</th>
<th>AUC$_{0-\infty}$ ($\mu$g·h/ml)</th>
<th>CL (ml·kg/min)</th>
<th>$V_{ss}$ (liter/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>2.1 ± 0.9</td>
<td>1.6 ± 1.1</td>
<td>9.4 ± 1.8</td>
<td>24.1 ± 10.5</td>
<td>94.2 ± 12.0</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Intravenous</td>
<td>2.8 ± 0.5</td>
<td>1.0</td>
<td>9.6 ± 1.7</td>
<td>27.7 ± 4.7</td>
<td>94.2 ± 12.0</td>
<td>1.3 ± 0.1</td>
</tr>
</tbody>
</table>

$^a$ Administered as alatrofloxacin at a dose equivalent to 200 mg of trovafloxacin.

$^b$ Values are reported as means ± standard deviations.

$^c$ Values are significantly different ($P < 0.05$).

$^d$ Time to $C_{\text{max}}$. 

FIG. 1. Mean trovafloxacin concentrations ± standard deviations following the administration of intravenous (IV) alatrofloxacin ($n = 10$) and oral (PO) trovafloxacin ($n = 12$) to patients with AIDS.
ache (13), and nausea (6). As mentioned previously, 2 of the 12 subjects (17%) experienced infusion-related adverse events and were subsequently withdrawn from the study. This incidence was higher than the 5% rate for the 200-mg intravenous dose reported by the drug manufacturer. (21) No clinically significant alteration in laboratory values compared to the baseline was noted at the conclusion of the study for any subject. Adverse-event severity was determined by the subject’s description of the event and the level of discomfort and by the investigator’s clinical judgement. Subjects were provided with 24-h contact information and were told to notify the study investigators if they experienced any adverse events or physical discomfort between study periods.

The etiology of alterations in the gastrointestinal tracts of those infected with HIV is likely multifactorial (1, 7, 9, 10, 14). Since the primary site of absorption for most orally administered agents is the small intestine, and since medication malabsorption has been reported in patients with AIDS (2, 18–20, 22), several studies have been conducted to assess the pharmacokinetics and bioavailability of commonly utilized antibiotics in this population (4, 17, 24, 25). In conclusion, trovafloxacin is well absorbed when administered by the oral route in subjects with AIDS, and this route is a suitable treatment option in the absence of infectious gastroenteritis and severe diarrhea.

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REFERENCES