Safety, Tolerance, and Pharmacokinetics of Atevirdine Mesylate (U-87201E) in Asymptomatic Human Immunodeficiency Virus-Infected Patients

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Atevirdine mesylate (U-87201E) is a new nonnucleoside (bisheteroarylpiperazine) inhibitor of human immunodeficiency virus type 1 reverse transcriptase. In a double-blind, escalating single-dose study the safety, tolerance, and pharmacokinetics of atevirdine mesylate were investigated in 24 asymptomatic human immunodeficiency virus-seropositive male patients. Each patient received one single oral dose of atevirdine mesylate and placebo separated by an interval of 1 to 3 weeks. For each dose level (400, 800, 1,200, and 1,600 mg) six patients received drug and placebo on separate occasions. Blood samples were collected before dosing and at intervals afterward for safety evaluation and estimation of atevirdine and metabolite levels. The concentrations of atevirdine and its principal metabolite (U-89255) in serum were determined by high-performance liquid chromatography. The results of the study showed that atevirdine mesylate is well tolerated at all dose levels. No clinically significant effects on vital signs, electrocardiograms, or laboratory tests were observed. Occasional headache and nausea were reported both in the drug group and in the placebo group. The times to peak values were relatively short (0.5 to 1.0 h), suggesting a rapid absorption. The maximum concentrations of drug in serum were 1.4 μM (400 mg), 4.2 μM (800 mg), 7.3 μM (1,200 mg), and 5.8 μM (1,600 mg). The values of the pharmacokinetic parameters for atevirdine were found to have relatively large intersubject variabilities, and consequently, the study had little power to detect dose-dependent changes in the values of the pharmacokinetic parameters. The oral clearance of atevirdine tended to increase by 90% as the atevirdine mesylate doses increased from 400 to 1,600 mg, but this change in oral clearance was not statistically significant. The values of the pharmacokinetic parameters determined in the study were similar to those found in a previous single-dose study in healthy volunteers.

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Bisheteroarylpiperazines (BHAPs) are potent inhibitors of human immunodeficiency virus type 1 (HIV-1) (12). Atevirdine mesylate (U-87201E; Fig. 1) is the first of this new class of nonnucleoside reverse transcriptase (RT) inhibitors; it is structurally different from the currently available RT inhibitors. RT is responsible for converting the single-stranded RNA genome of the virus into DNA. This conversion is essential for the establishment of provirus (11). Interference with the function of this enzyme has been shown to improve the prognosis of HIV infection and delay the progression of the clinical syndrome (7, 13).

Atevirdine mesylate has been shown to have significant anti-HIV RT activity in vitro. It inhibits HIV-1 replication in infected peripheral blood leukocyte cultures at a 50% inhibitory concentration of 1 nM and a concentration which is cytotoxic to 50% of cells of 100 μM and also inhibits completely the formation of syncytia in human T-cell leukemia virus type III-infected MT-2 cells at 2 μM (1, 12). It acts at a site different from that at which the nucleoside RT inhibitors such as 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI), or 2′,3′-dideoxycytidine (ddC) act. The concomitant use of two RT inhibitors acting at different enzymatic sites may prevent the development of viral resistance. In vitro, the BHAPs exhibit synergy with AZT, ddI, and ddC (3). Furthermore, they are active against AZT-resistant viral strains. The development of HIV-1 resistance to BHAPs has been reported previously (10). Interestingly, however, virus resistant to BHAPs appeared to be more susceptible than the corresponding wild-type strain to other nonnucleoside RT inhibitors (6). Toxicity studies in animals indicate that atevirdine mesylate has lower toxicity than nucleoside analogs. Thus, for a number of reasons atevirdine mesylate appears to be an important new drug for the treatment of HIV-infected individuals.

The current study was designed, first, to investigate the safety and tolerance of escalating single doses of atevirdine mesylate up to 1,600 mg in HIV-seropositive individuals and, second, to investigate whether the safety and tolerance profiles and the pharmacokinetics of the drug were altered by the presence of an HIV infection. A previous single-dose clinical study in healthy volunteers did not reveal any adverse effects that would preclude the further development of atevirdine (15). In this first single-dose study, approximate dose proportionality was observed and the concentrations of the inactive N-dealkyl metabolite of atevirdine, U-89255 (Fig. 1), in serum were found to be similar to those of the parent drug. In multiple-dose clinical studies subsequent to the study discussed in this report, the pharmacokinetics of atevirdine were found to
capsules of identical appearance containing 100 mg of lactose (95% microcrystalline cellulose and 5% powder mix) were provided in identical containers as the active drug. Doses were ingested with 250 ml of tap water.

**Evaluation and follow-up.** Vital signs (blood pressure and pulse rate) were measured at regular times postdosing. In addition, patients were frequently questioned about any medical events in a non-directed fashion. Blood and urine samples for general laboratory assessments (safety parameters) were obtained before and at 24 and 48 h postdosing and 7 days after administration of the last dose. Blood samples for determinations of atevirdine and metabolite levels in serum were taken before dosing and at 0.5, 1, 1.5, 2, 3, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 h postdosing.

The concentrations of atevirdine and its circulating N-dealkyl metabolite, U-89255, in serum were assayed by a high-performance liquid chromatographic procedure with a lower limit of quantitation for atevirdine of 0.02 μM (8). Replicate assays were performed on a few samples, and for those samples the average concentrations were generally used in the calculation of pharmacokinetic parameters. The maximum concentrations ($C_{\text{max}}$) of atevirdine and its metabolite and the times of their occurrence ($T_{\text{max}}$) were tabulated. The area under the concentration-time curve for parent drug and metabolite from time zero to the time of the last quantifiable concentration ($AUC_{\text{0–∞}}$) was estimated by the linear trapezoidal rule. The apparent terminal disposition rate constant ($\lambda_e$) for each species was estimated from a log-linear regression of the time points apparently within the terminal disposition phase. The total area under each concentration-time curve ($AUC_{\text{0–∞}}$) was then estimated by adding the extrapolated component to $AUC_{\text{0–η}}$. The elimination clearance of atevirdine mesylate was calculated by dividing the dose by the atevirdine mesylate $AUC_{\text{0–∞}}$. The area under the concentration-time curve for atevirdine and metabolite from time zero to 48 h ($AUC_{\text{0–48h}}$) was estimated by the linear trapezoidal rule. In this calculation, concentration extrapolations beyond the quantitation limit of the assay were not used. If $AUC_{\text{0–48h}}$ could not be calculated, $AUC_{\text{0–∞}}$ was used to estimate CL/FR. The area under the first moment curve to the last quantifiable concentration ($AUMC_{\text{0–η}}$) was calculated for each species by the linear trapezoidal rule. The total area under the first moment curve ($AUMC_{\text{0–∞}}$) was calculated by dividing the $AUC_{\text{0–∞}}$ for the metabolite by the corresponding $AUC_{\text{0–∞}}$ for the parent drug.

**Statistical analysis.** Descriptive statistics were calculated for the pharmacokinetic parameters which were derived from each species and from each dose level. The values for the pharmacokinetic parameters which might be dose-dependent (e.g., $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{\text{0–∞}}$, CL/FR) were compared for each species in a one-way analysis of variance (ANOVA), with dose as a classification variable and with an alpha value of 0.05. Pharmacokinetic parameters which might be dose independent were compared using a two-way ANOVA with dose as a classification variable. Pair-wise comparisons were performed in these ANOVAs by Fisher’s least significant difference tests at an alpha value of 0.05. Linear regressions were performed for $C_{\text{max}}$ and $AUC_{\text{0–∞}}$ versus dose (and also dose per kilogram of body weight and dose per square meter of body surface area). In these regressions, a weighting function of $1/y$ was used.

The values for the pharmacokinetic parameters from the study were compared by t tests with the values which were obtained from healthy volunteers in a previous study (5). All of the calculations of the pharmacokinetic parameters and statistical analysis of those values were performed with SAS version 5 in a mainframe environment.

The analysis for the safety (biochemical and hematological) and demographic data was performed with SAS version 6.07 software in a mainframe environment.

**RESULTS**

**Demographics.** Twenty-four volunteers completed both weeks of the study. The mean age of these volunteers was 34 years (range, 21 to 51 years). Their mean weight and height were 73.3 kg (range, 50.5 to 101.0 kg) and 181 cm (range, 161 to 196 cm), respectively. There were 21 white males, 2 Asian/oriental males, and 1 black male subject in the study.

**Safety and tolerance.** Medical events such as headache and nausea occurred occasionally with equal frequencies during active drug dosing and placebo treatment. Their severities were mild to moderate. There were no serious medical events during this study at any dose level. Two subjects had mild (<1.5 times the upper limit of normal) elevations in their liver enzyme levels. One of them had taken 400 mg of atevirdine mesylate 7 days before; the other had taken placebo 7 days before. In both patients liver function normalized within 4 weeks after the end of the study. No clinically significant differences were identified for any quantitative or qualitative lab-
Pharmacokinetics. The mean concentrations of atevirdine and its metabolite at each dose level are given in Fig. 2 and 3. The median values of the pharmacokinetic parameters for parent drug and metabolite at each dose level are listed in Tables 1 and 2, respectively. The median values of the parameters are listed in Tables 1 and 2 because several pharmacokinetic parameters appeared to have nonnormal distributions. This lack of normality did not adversely affect the ANOVAs of the values of the pharmacokinetic parameters, however, since the residuals from the ANOVAs appeared to be normally distributed. Preliminary nonparametric tests also resulted in the same conclusions obtained by the parametric tests. The results of the parametric tests are therefore discussed in this report. Atevirdine appears to have been rapidly absorbed from the capsule, with median \(T_{\text{max}}\) values ranging from 0.5 to 1.0 h.

The atevirdine \(\lambda_1\) could not be calculated for one patient (subject 11), in whom concentrations declined from the time of \(C_{\text{max}}\) to the sample obtained at 12 h, increased from 16 to 24 h, and were undetectable thereafter. A few other subjects also showed late peaks in their serum atevirdine concentration-time profiles, but none was as pronounced as that for subject 11 (Fig. 4). These late peaks could possibly be related to enterohepatic recycling, prolonged drug absorption, or assay interferences. Attempts to resolve potential interferences by altering the chromatographic mobile phase and detection conditions were unsuccessful.

The atevirdine \(\lambda_1\) values for several patients may have been estimated imprecisely because of relatively small changes in the concentrations during the blood sampling period of the protocol. Of the 23 subjects for whom atevirdine terminal disposition-phase half-lives (\(t_{1/2}\)) were obtained, for 16 subjects \(t_{1/2}\) were less than 24 h, for 6 subjects \(t_{1/2}\) were between 24 and 46 h, and for 1 subject the \(t_{1/2}\) was estimated to be 132 h. There was no apparent relationship between the appearance of a clearly evident late atevirdine peak and a long \(t_{1/2}\). The atevirdine \(\lambda_1\) was independent of dose, with an overall median \(\lambda_1\) of 0.039 h\(^{-1}\); this median \(\lambda_1\) corresponds to a \(t_{1/2}\) of 18 h. The atevirdine MRT was independent of dose, with an overall median MRT of 11 h. Although the dose effect was not statistically significant in the analyses of \(\lambda_1\) and MRT, there was a tendency for shorter \(t_{1/2}\) and MRTs with increasing dose. The median fraction of the atevirdine AUC\(_{0-\infty}\) which was extrapolated was 9%, with values ranging from 0.3 to 57%. For the metabolite, the median fraction of AUC\(_{0-\infty}\) which was extrapolated was 3%, with values ranging from 0.6 to 57%. Any conclusions based on analyses of AUC\(_{0-48}\) values were virtually identical to those based on AUC\(_{0-\infty}\) values, but only the AUC\(_{0-\infty}\) results are discussed in this report.

On the basis of the median values, the \(C_{\text{max}}\) and AUC\(_{0-\infty}\) values for both parent drug and metabolite tended to increase less than proportionately with dose at doses above 800 mg, but these trends were not statistically significant in the ANOVAs of dose-normalized \(C_{\text{max}}\) and AUC\(_{0-\infty}\). Additional normalization of these parameters to either body mass or surface area did not affect the results. The atevirdine CL\(_{\text{PO}}\) was similarly independent of dose, although the median CL\(_{\text{PO}}\) values tended to increase with increasing dose. Although significant dose effects were observed for CL\(_{\text{form}}\)/CL\(_{\text{mest}}\), contrasts of the doses revealed no consistent trends.

There was considerable overlap between dose groups with respect to values of \(C_{\text{max}}\) and AUC\(_{0-\infty}\) for both atevirdine and metabolite; e.g., the atevirdine \(C_{\text{max}}\) values for the 1,600-mg group ranged from 2 to 19.9 \(\mu M\), and the values for the 400-mg

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(C_{\text{max}}) ((\mu M))</th>
<th>(\lambda_1) (h(^{-1}))</th>
<th>AUC(_{0-\infty}) ((\mu M) h)</th>
<th>CL(_{\text{PO}}) (liter/h)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1.0 (0.5–1.5)</td>
<td>1.4 (0.5–4.5)</td>
<td>0.032 (0.008–0.082)</td>
<td>7.9 (1.8–17)</td>
<td>107 (49–457)</td>
<td>18 (8–92)</td>
</tr>
<tr>
<td>800</td>
<td>0.8 (0.5–1.0)</td>
<td>4.2 (2.4–11)</td>
<td>0.034 (0.024–0.091)</td>
<td>14 (8.0–17)</td>
<td>121 (99–211)</td>
<td>13 (5–26)</td>
</tr>
<tr>
<td>1,200</td>
<td>0.5 (0.5–1.0)</td>
<td>7.3 (2.8–9.6)</td>
<td>0.054 (0.023–0.076)</td>
<td>15 (12–26)</td>
<td>170 (96–216)</td>
<td>8.3 (5.9–28)</td>
</tr>
<tr>
<td>1,600</td>
<td>0.8 (0.5–1.0)</td>
<td>5.8 (2.0–20)</td>
<td>0.052 (0.005–0.14)</td>
<td>17 (9.3–53)</td>
<td>202 (63–337)</td>
<td>9.5 (4.2–141)</td>
</tr>
</tbody>
</table>

* Values are medians (ranges).
Table 2. Pharmacokinetic parameters for the atevirdine metabolite after administration of single doses of 400, 800, 1,200, and 1,600 mg of atevirdine mesylate to asymptomatic HIV-seropositive volunteersa

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>T_{max} (h)</th>
<th>C_{max} (µM)</th>
<th>λ_{z} (h⁻¹)</th>
<th>AUC_{0-∞} (µM h)</th>
<th>MRT (h)</th>
<th>CL_{form}/CL_{met}</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1.3 (1.0–2.0)</td>
<td>0.9 (0.3–3.4)</td>
<td>0.25 (0.03–0.55)</td>
<td>4.0 (0.9–28)</td>
<td>3.5 (2.5–27)</td>
<td>0.8 (0.2–1.7)</td>
</tr>
<tr>
<td>800</td>
<td>1.0 (0.5–2.0)</td>
<td>5.4 (1.5–11)</td>
<td>0.14 (0.02–0.20)</td>
<td>24 (9.4–54)</td>
<td>5.6 (3.6–48)</td>
<td>2.2 (0.8–4.1)</td>
</tr>
<tr>
<td>1,200</td>
<td>0.9 (0.5–1.5)</td>
<td>8.0 (4.6–15)</td>
<td>0.14 (0.03–0.19)</td>
<td>26 (20–63)</td>
<td>4.2 (2.7–13)</td>
<td>1.7 (1.5–2.7)</td>
</tr>
<tr>
<td>1,600</td>
<td>1.0 (1.0–1.0)</td>
<td>6.9 (1.8–23)</td>
<td>0.07 (0.008–0.18)</td>
<td>20 (14–96)</td>
<td>4.7 (4.0–88)</td>
<td>1.3 (0.9–1.8)</td>
</tr>
</tbody>
</table>

a Values are medians (ranges).

Group ranged from 0.5 to 4.5 µM. Intersubject variability in both C_{max} and AUC_{0-∞} also appeared to increase as the dose increased to 1,600 mg, and a weighting function of 1/y was used in the regressions of these parameters versus dose to improve the distributions of weighted residuals. The variabilities in C_{max} and AUC_{0-∞} for both parent drug and metabolite were reduced slightly when the regressions were performed with dose expressed relative to either body mass or surface area, but the R² values typically remained about 0.5. As judged by application of Akaike’s information criterion (17) to fits for both parent drug and metabolite, linear regressions of C_{max} and AUC_{0-∞} versus dose provided better fits than either quadratic or sigmoid models. Plots of atevirdine AUC_{0-∞} and C_{max} as a function of atevirdine mesylate dose are presented in Fig. 5 and 6, respectively.

On the basis of the CL_{form}/CL_{met} values, the serum metabolite concentrations typically exceeded the serum atevirdine concentrations. The T_{max} values for metabolite were similar to those of atevirdine, but the estimates for the t_{1/2} and MRT of the metabolite were consistently shorter than those of the parent drug.

The values for the atevirdine λ_{z}, MRT, and dose-normalized C_{max} were in good agreement with those from the 400- to 1,600-mg dose groups obtained in the previous study (15) with HIV-seronegative volunteers (Table 3). The atevirdine CL_{PO} and dose-normalized AUC_{0-∞} values from the present study differed, however, from those from the study with HIV-seronegative volunteers by about 40%. Preliminary comparisons of the values of the pharmacokinetic parameters obtained in the study with HIV-seronegative volunteers and those obtained in the present study indicated that Wilcoxon rank sum tests and t tests produced similar results; the statistical significance levels in Table 3 are based on the t tests.

Discussion

In the present study atevirdine mesylate was well tolerated at doses up to and including 1,600 mg. The observed medical events occurred with similar frequencies among subjects receiving active drug and placebo and were not related to the concentrations of atevirdine or its metabolite in serum. Such

FIG. 4. Serum atevirdine and metabolite concentrations from representative subjects with various degrees of evidence for a late atevirdine peak. Subject 11 is the volunteer with the largest late peak (400-mg dose), subject 24 had a minor late peak (1,600-mg dose), and subject 15 had no evidence of a late peak (1,600-mg dose). Atevirdine concentrations are represented by closed boxes, and metabolite concentrations are represented by open boxes.

FIG. 5. Atevirdine mesylate AUC_{0-∞} versus dose. The linear regression was statistically significant (P < 0.0001), with an R² of 0.55. The intercept was not significantly different from zero (P > 0.10), and the mean slope was 0.48 with a standard error of 0.09.
TABLE 3. Comparison of pharmacokinetic parameters for atevirdine from single-dose studies in HIV-seropositive individuals and HIV-seronegative volunteers

<table>
<thead>
<tr>
<th>Study group</th>
<th>λ1 (h⁻¹)</th>
<th>MRT (h)</th>
<th>Cmax (µM)</th>
<th>AUC0–∞ (µM h)</th>
<th>CLPO (liter/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV seropositive</td>
<td>0.039 (0.005–0.14)</td>
<td>11 (4–141)</td>
<td>1.9 (0.5–5.3)</td>
<td>6.1 (3–17)</td>
<td>2.0 (0.7–3.7)</td>
</tr>
<tr>
<td>HIV seronegative</td>
<td>0.053 (0.02–0.27)</td>
<td>12 (4–29)</td>
<td>2.2 (0.6–3.7)</td>
<td>10.6 (3–18)</td>
<td>1.1 (0.7–3.5)</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

* Data for HIV-seropositive individuals were obtained from the present study, and those for HIV-seronegative volunteers were obtained from a study described previously (15).

* Values of the pharmacokinetic parameters were normalized to a dose of 400 mg per 70 kg of body mass.

* NS, not statistically significant (P > 0.05).

minor medical events which occurred are common in persons with HIV infection. Two subjects had transient elevations in their liver enzyme levels, which in one case occurred 7 days after atevirdine mesylate dosing. Although a relationship to the experimental drug cannot be entirely ruled out, it is more likely that this finding is related to the underlying medical condition. In addition, it is unlikely that this event represents a delayed effect of the drug on the liver. No clinically significant effects of atevirdine mesylate on vital signs, electrocardiograms, or general laboratory tests were identified at any dose level.

A major metabolic route for atevirdine mesylate in humans appears to be through the formation of the N-dealkyl metabolite, and the concentrations of this metabolite typically exceeded those of the parent drug. On the basis of the median CLform/CLmet values, the formation and disposition kinetics of the metabolite appear to be linear for single atevirdine mesylate doses up to 1,600 mg. These findings are in agreement with those obtained in the single-dose study with atevirdine mesylate in healthy volunteers (15). The values of the pharmacokinetic parameters for atevirdine were found to have relatively large intersubject variability, and consequently, the present study had little power to detect dose-dependent changes in the values of the pharmacokinetic parameters. On the basis of median values, there was a tendency for CLPO to increase by about 90% as the atevirdine mesylate doses increased from 400 to 1,600 mg, but the change was not statistically significant. Calculations based on the CLPO data indicated that an increase in CLPO of about 110% would have been needed for statistical significance in a parallel group study with six patients per dose group. The tendency for CLPO to increase with increasing dose could be consistent with a decrease in the fraction absorbed as the doses of this insoluble drug increased. The trends in the changes in CLPO, t1/2, and MRT with increasing dose could collectively be indicative of increased systemic clearance with increasing dose. It is likely that data from a crossover dose proportionality study would be required for a definitive conclusion of single-dose pharmacokinetic linearity.

The large CLPO of atevirdine (greater than hepatic blood flow) suggests that atevirdine mesylate is incompletely absorbed or that the drug is susceptible to first-pass metabolism, or both. The finding that the t1/2 and MRT of the metabolite are less than those of the parent drug may also be indicative of the first-pass metabolism of atevirdine. An alternative explanation for the shorter values of t1/2 and MRT might be that the assay for the metabolite is not sensitive enough to allow a determination of the true terminal disposition phase of the metabolite.

The short Tmax values from the present study are consistent with the rapid absorption of atevirdine mesylate from the capsule. A few subjects exhibited late peaks in their atevirdine mesylate concentration-time profiles, however, and these late peaks could be related to intermittent absorption or enterohepatic recycling. Additional bioanalytical work did not reveal any interferences.

Overall, the pharmacokinetics of atevirdine are similar in HIV-seropositive patients and HIV-seronegative healthy volunteers. Table 3 shows a comparison of the results of the current study with those obtained in a single-dose study with atevirdine mesylate in HIV-seronegative healthy male volunteers (15) in more detail. The atevirdine Cmax values from the two studies are nearly identical, and the values of the other pharmacokinetic parameters are in reasonable accord, even though some of them may have been statistically significantly different.

Subsequent to the present study, other studies with atevirdine mesylate showed that the multiple-dose CLPO of atevirdine is generally less than 10% of the single-dose CLPO (2, 5, 9, 14). In addition, CLPO decreased as the atevirdine mesylate doses increased from 200 to 600 mg every 6 h (5). On the basis of the data from the present study, which may be indicative of a decrease in the fractional absorption of atevirdine with increasing dose, the reduction in the multiple-dose CLPO of atevirdine with increasing dose may represent a more profound reduction in presystemic and/or systemic clearance than might be predicted from only the multiple-dose data.

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REFERENCES


