Anti-Human Immunodeficiency Virus (HIV) Activity, Safety, and Pharmacokinetics of Adefovir Dipivoxil (9-[2-(bis-pivaloyloxymethyl)-phosphonomethoxyethyl]adenine) in HIV-Infected Patients


A randomized, double-blind, placebo-controlled, dose-escalation study of adefovir dipivoxil, an oral prodrug of adefovir, was conducted in 36 human immunodeficiency virus (HIV)-infected subjects to evaluate its anti-HIV activity, safety, and pharmacokinetics. Subjects received placebo or one of three dosages of adefovir dipivoxil daily for 14 days. Median decreases in serum p24 antigen of 31% (P = .02), 25% (P = .31), and 30% (P = .01) occurred in each drug-treated group, respectively, compared with an increase of 17% in the placebo group. Median decreases in serum HIV RNA of 0.4–0.6 log10 copies/mL occurred in the drug-treated groups (P = .03), compared with no change in the placebo group. Gastrointestinal complaints and reversible liver transaminase elevations were the most frequently noted adverse events. Decreases in serum free carnitine occurred in each drug-treated group during treatment. After 14 days of dosing, adefovir dipivoxil demonstrated anti-HIV activity and was best tolerated at the lowest dosage studied, 125 mg daily.

The acyclic adenine phosphonate compound, 9-(2-phosphonomethoxyethyl)adenine (adefovir), has demonstrated a broad spectrum of antiviral activity in both in vitro and animal models [1, 2]. Activity has been demonstrated against several RNA and DNA viruses, including human immunodeficiency virus (HIV) types 1 and 2, herpes simplex virus types 1 and 2, human herpesvirus 6, human cytomegalovirus, Epstein-Barr virus, and hepatitis B virus [3–6]. The ED50 of adefovir for inhibition of HIV-1 ranges from 0.006 to 7.0 μM depending on the cell culture system and assay type used [7, 8]. The active intracellular metabolite, adefovir diphosphate, an inhibitor of reverse transcriptase, persists in cells, with a half-life ranging from 16 to 18 h [9].

Previously, adefovir has been administered intravenously to patients with HIV infection in two clinical trials. In patients with advanced HIV infection (n = 8, median CD4 cell count, 42/mm3) who received 1 mg/kg/day adefovir, the median p24 antigen concentration decreased from 150 to 76 pg/mL after 4 weeks of treatment [10]. In another trial in which subjects received 1 mg/kg/day adefovir (n = 10, mean CD4 cell count, 200/mm3), the mean p24 antigen concentration decreased from 209 to 103 pg/mL after 6 weeks of treatment [11].

Adefovir, however, demonstrated poor bioavailability when administered orally as a solution to 5 HIV-infected subjects [12]. The oral bioavailability at 3.0 mg/kg/dose was <12% (n = 5) on the basis of serum levels [12] and was consistent with the degree of bioavailability observed in several animal species in preclinical studies [13].

The low oral bioavailability of adefovir was attributed to the charged nature of the phosphonate group at physiologic pH, which may limit intestinal cellular uptake [14]. Therefore, to improve bioavailability, the bis-pivaloyloxyethyl ester of adefovir was synthesized to mask the negative charges of the phosphonate group and increase the lipophilicity of the compound (figure 1). In vitro studies of radiolabeled bis-pivaloyloxymethyl adefovir (adefovir dipivoxil) suggested a 100-fold increase in cellular uptake compared with adefovir and showed that the active diphosphorylated metabolite of adefovir was still formed [15]. The oral bioavailability of adefovir after administration of adefovir dipivoxil was shown to be ~25% in cynomolgus monkeys [16].

After oral administration of single doses of a suspension of adefovir dipivoxil to 16 HIV-infected persons, adefovir was detected in the systemic circulation with mean peak levels of 0.64 ± 0.08 μg/mL following a 500-mg dose [17]. Neither the mono-pivaloyloxyethyl nor di-pivaloyloxyethyl esters of adefovir were detected in the blood, suggesting that the prodrug was rapidly hydrolyzed to adefovir. When single oral doses of
500 mg of adefovir dipivoxil were given as a tablet to 10 HIV-infected people, mean bioavailability was found to be ~33% greater when administered after a meal (41.2% ± 13%) than when administered after fasting (30.1% ± 12%, P = .004) [17]. The mean area under the adefovir serum concentration-time curve (AUC) following oral administration of the 500-mg tablet was 6.85 (± 2.0) μg/h/mL; this was equivalent to the AUC expected after intravenous administration of a single 1.6-mg/kg dose of adefovir [12]. In this same study, single doses of adefovir dipivoxil up to and including 500 mg were found to be well tolerated.

Adefovir dipivoxil was considered an excellent candidate for further development on the basis of its ability to provide adefovir exposure (AUC) values that exceeded those shown to have anti-HIV activity after intravenous dosing of adefovir [12, 17]. Therefore, a study was designed to evaluate the anti-HIV activity, safety, tolerance, and pharmacokinetics of adefovir dipivoxil when administered as a single daily dose for 14 consecutive days. Because significant decreases in serum carnitine levels have been reported in patients treated with other pivaloyloxymethyl side chain–containing compounds, such as pivalic acid esterified with carnitine, and the resulting complex is renally excreted.

Methods

Study design. This study was a 14-day randomized, double-blind, placebo-controlled, dose-escalation study of three dose tiers of adefovir dipivoxil: 125 mg, 250 mg, and 500 mg daily. Within each tier of 12 subjects, 9 were randomly assigned to receive adefovir dipivoxil and 3 to receive placebo. The study was designed so that enrollment into the next sequential tier could occur only after all subjects in the previous tier had been observed for at least 1 week after the completion of dosing. All subjects were hospitalized in the General Clinical Research Center Inpatient Unit at Johns Hopkins Hospital during the dosing portion of the study.

Study population. Eligible subjects included HIV-infected persons with CD4 cell counts of at least 100/mm³ and immune-complex–dissociated p24 antigen concentration of at least 50 pg/mL at the time of screening. To be eligible, at the time of screening, subjects must have had hepatic transaminases (aspartate aminotransferase and alanine aminotransferase) ≤100 IU/L (normal: ≤35 IU/L); lipase ≤260 IU/L (normal: ≤200 IU/L); an absolute neutrophil count of ≥1000/mm³; and preserved coagulation function. Subjects were excluded if they were pregnant or lactating, undergoing parenteral treatment for an active serious infection, or lactose-intolerant. Subjects were allowed to continue approved prophylaxis for Pneumocystis carinii pneumonia. All subjects discontinued antiretroviral therapy at least 2 weeks prior to receiving the first dose of adefovir dipivoxil. Nephrotoxic agents, systemic azoles, and rifamycins were contraindicated.

Study drug. Each subject received 14 consecutive days of adefovir dipivoxil or identical-appearing lactose-containing placebo tablets. Adefovir dipivoxil tablets contained 125 mg each of active drug. Drug was administered every 24 h at ~9 A.M. following consumption of breakfast.

Antiviral activity. Blood was obtained at baseline, day 8, and day 15 (24 h following the last dose of drug) for determination of p24 antigen concentration. Aliquots of serum samples obtained at baseline and day 14 for pharmacokinetic analyses were analyzed by quantitative HIV RNA–based polymerase chain reaction (PCR). Samples for immune complex–dissociated p24 antigen and quantitative HIV RNA were assayed in duplicate and in one batch at the end of the study. p24 determinations were done by use of a kit (Immune Complex Disruption Kit; Abbott, Abbott Park, IL) and PCR determinations were done by Laboratory Corporation of America (formerly Roche Biomedical Laboratories; Research Triangle Park, NC) [21, 22]. Duplicates were averaged for analysis purposes. Blood for CD4 lymphocyte counts was obtained at baseline and day 15 of the study. CD4 cell counts were measured by use of flow cytometry (Coulter, Miami, FL) by Maryland Medical Laboratories (Baltimore).

Safety evaluations. Clinical assessments were performed and blood for safety monitoring was obtained at baseline, day 4, day 8, and day 14 and at poststudy weeks 1 and 4. Safety laboratory testing included measurements of hematology, electrolyte and chemistry panels, serum lipase, and total and free carnitine and avampicillin [18–20], the effect of adefovir dipivoxil on serum and urine samples obtained at baseline, day 8, and day 15 and at 1 and 4 weeks following completion of dosing. Carnitine was measured by Associated Regional and University Pathologists (Salt Lake City), by the spectrophotometric method of Pearson et al. [23].

Pharmacokinetic evaluations. Blood was obtained before dosing (0 h) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 6, 8, 12, and 24 h after dosing on day 1 and day 14 (last day of dosing) for determination of pharmacokinetic parameters. Urine samples were obtained over the intervals 0–4, 4–8, 8–12, and 12–24 h following dosing on days 1 and 14. Adefovir concentrations were quantified in serum and urine by a validated reverse-phase ion-pair high-performance liquid chromatography procedure with fluorescent derivatization [12]. Both procedures involved sample preparation by use of strong anion-exchange solid-phase extraction columns (Whatman; VWR Laboratory Supply, San Francisco). Serum samples were derivatized with 200 μL of 43 mM chloroaacetalddehyde in 640 mM sodium acetate. Urine samples were derivatized with 15 μL of 50% (wt/wt) chloroaacetalddehyde in water. The serum method was linear over the range 250–15,000 ng/mL, and the

Figure 1. Structures of adefovir and adefovir dipivoxil. Arrows denote positions of pivaloyloxymethyl groups.
lower limit of quantitation for serum samples was 250 ng/mL. The urine method was linear over the range 1000–20,000 ng/mL.

Pharmacokinetic parameters were assessed by application of the nonlinear curve-fitting software package PCNONLIN (Statistical Consultants, Lexington, KY) by use of noncompartmental methods. The parameters estimated included maximum serum concentration ($C_{max}$), the time to $C_{max}$ ($T_{max}$), AUC extrapolated to infinity, and the half-life of the terminal elimination phase ($t_{1/2}$). For the 250-mg and 500-mg dose groups, oral bioavailability was estimated by comparing the serum AUC data obtained following oral administration with the serum AUC data obtained following intravenous administration of adefovir in previous clinical trials [12]. For the 125-mg dose group, mean bioavailability was calculated on the basis of urinary recovery data. Mean urinary recovery following single-dose administration of intravenous adefovir had been shown to be ~98% [12].

Statistics. Homogeneity of variance among treatment groups at baseline was evaluated by use of one-way analysis of variance and one-way analysis of variance of ranks (Kruskal-Wallis) [24]. For evaluation of differences among groups in safety monitoring parameters and antiviral activity, similar testing procedures were used. For further evaluation of changes in virus load, pairwise comparisons were made between each adefovir dipivoxil dose group and the placebo group by use of the Mann-Whitney U test. Resulting $P$ values were adjusted for multiple comparisons with Bonferroni’s adjustment [25]. Additional testing of changes in virus load included evaluation of the differences among all groups, taking into account the ordered nature of the adefovir dipivoxil dose groups, by use of the Jonckheere-Terpstra test [24]. Differences between day 1 and day 14 pharmacokinetic parameters within a given dose group were evaluated by using paired $t$ test analyses. Differences between dose groups were evaluated by using unpaired $t$ test analyses, which were not corrected for multiple groups.

Results

Study subjects. Thirty-six subjects entered and completed the study. Patient demographic data are shown in table 1. The median age in each dose group ranged from 33 to 36 years. There was a predominance of males in all but the 250-mg dose group. Although there were differences between groups at study entry for median CD4 cell count, p24 antigen concentration, and HIV RNA concentration, these differences did not reach statistical significance. About two-thirds of the subjects had a history of antiretroviral use.

Antiviral activity. At day 15, significant median decreases in serum p24 antigen of 31% ($P = .02$) and 30% ($P = .01$) occurred in the 125-mg and 500-mg groups, respectively, compared with an increase of 17% in the placebo group (figure 2). Although of similar magnitude, the median decrease (25%) in the 250-mg group was not statistically significant ($P = .31$).

At day 14, the median $\log_{10}$ difference in HIV RNA PCR result was not significantly different among the groups by non-parametric analysis of variance: placebo $= -0.1 \log_{10}$ U/mL; 125 mg $= -0.4 \log_{10}$ U/mL; 250 mg $= -0.6 \log_{10}$ U/mL; 500 mg $= -0.6 \log_{10}$ U/mL. However, when the Jonckheere-Terpstra statistical test was used, which takes into account the ordered nature of the doses of adefovir dipivoxil across groups, a significant drug effect on reduction in HIV RNA was seen ($P = .03$). When the placebo group was removed from the analysis and only the dose groups of adefovir dipivoxil were compared, no significant dose-dependent effect was seen.

All study groups had a rise in mean CD4 cell count; however, there was no significant difference between the change in the placebo group and with the changes seen in the adefovir dipivoxil-treated groups (data not shown).

Safety and tolerance. All subjects completed 14 days of dosing. Gastrointestinal complaints were the most frequently reported adverse events (table 2). Although no subject was withdrawn from the study because of gastrointestinal complaints, 6, 8, and 9 subjects in the 125-mg, 250-mg, and 500-mg adefovir dipivoxil treatment groups, respectively, experienced one or more gastrointestinal side effects that were graded as mild (grade I) or moderate (grade II). The gastrointestinal side effects most commonly reported by subjects receiving adefovir dipivoxil included loose stools (52%), nausea (52%), vomiting (22%), anorexia (22%), abdominal discomfort (19%), and eructation or flatulence (19%). The frequency and severity of gastrointestinal events were dose-related. One or more grade II gastrointestinal events were reported in 6 subjects in the 500-mg group compared with 3 in the 250-mg group and 2 in the 125-mg group.

During dosing, 5 subjects in the 250-mg dose group and 4 subjects in the 500-mg group experienced reversible elevations of hepatic transaminases. These increases were graded as mild (grade I: 40–150 IU/L) or moderate (grade II: 151–300 IU/L). In all subjects, transaminase levels returned to baseline within 2 weeks following discontinuation of therapy. Only two of the elevations were of grade II severity (table 2).

One subject in the 500-mg group, with a history of asymptomatic hyperlipasemia (400–1137 IU/L) prior to study entry, was noted to have serum lipase concentrations between 1000 and 1309 during the 14 days of drug therapy. He had no symptoms suggestive of pancreatitis.

One subject in the 500-mg group, with a history of both atrial fibrillation and presumed Gilbert’s syndrome (bilirubin, 1.4 mg/dL at baseline), reported nausea, decreased appetite, and intermittent vomiting while receiving drug. During the last day of drug administration, he experienced a 6-h episode of asymptomatic atrial fibrillation that resolved spontaneously. At the 1-week follow-up visit he was noted to have an elevated bilirubin measurement of 2.6 mg/dL, which decreased to 1.8 mg/dL 10 days later.

One subject in the 125-mg dose group, with a history of untreated hyperglycemia (blood glucose, >300 mg/dL and elevated hemoglobin A1C) and a baseline blood glucose level of 211 mg/dL, was noted to have blood glucose concentrations in the range of 300–600 mg/dL at 1 week and 4 weeks following the completion of drug administration. These findings were consistent with untreated type II diabetes mellitus.
Table 1. Baseline characteristics for study groups (adefovir dipivoxil at 125, 250, or 500 mg or placebo).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 9)</th>
<th>125 mg (n = 9)</th>
<th>250 mg (n = 9)</th>
<th>500 mg (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>34 (26–44)</td>
<td>33 (29–52)</td>
<td>36 (28–49)</td>
<td>34 (21–48)</td>
</tr>
<tr>
<td>Sex (no. male/no. female)</td>
<td>7/2</td>
<td>7/2</td>
<td>4/5</td>
<td>7/2</td>
</tr>
<tr>
<td>Median p24 antigen, pg/mL</td>
<td>306 [260; 1014]</td>
<td>188 [106; 277]</td>
<td>458 [211; 951]</td>
<td>178 [73; 329]</td>
</tr>
<tr>
<td>Median HIV RNA copies x 10³/mL</td>
<td>153 [50; 194]</td>
<td>42 [35; 70]</td>
<td>71 [27; 193]</td>
<td>69 [54; 121]</td>
</tr>
<tr>
<td>No. with prior antiretroviral use</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. Nos. in brackets are upper and lower boundaries of interquartile ranges.

At baseline, all subjects’ total and free serum carnitine levels were within the normal range (free: 2.3–7.0 μmol/dL; total: 2.6–8.1 μmol/dL). After 14 days of dosing (day 15), there were dose-related decreases in free and total carnitine levels in the adefovir dipivoxil–treated groups. At day 15, in the 125-mg group, the median decrease in serum free carnitine was 12% (P = .02), compared with a median increase in the placebo group of 6% (figure 3). Despite the median decrease in the 125-mg dose group, no subject in this group had free (or total) carnitine levels that fell below the normal range. The median serum free carnitine reductions in the 250-mg and 500-mg groups at day 15 were −58% (P = .009 vs. placebo) and −66% (P = .0009 vs. placebo), respectively. In these groups, about one-half of subjects had free and total carnitine levels that fell below the normal range during the 14-day dosing period. Serum carnitine levels returned toward baseline after discontinuation of study drug dosing. At 1 week following completion of study drug administration (day 21), only 2 subjects (1 in each of the 2 highest dose groups) had a carnitine level below the normal range; carnitine levels in the adefovir dipivoxil–treated groups were not significantly different from those in the placebo group. No study subject experienced symptoms suggestive of a carnitine deficiency syndrome, such as myopathy or encephalopathy.

Pharmacokinetics. Adefovir serum concentration curves for days 1 and day 14, normalized by subject weight, are shown in figure 4. Mean adefovir Cmax values in the 125-mg and 250-mg dose groups were proportional to dose on study days 1 and 14 (table 3). However, on day 14, the mean Cmax for the 500-
Table 2. Total no. of subjects experiencing most frequently observed adverse events or laboratory changes during adefovir dipivoxil administration.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>125 mg</th>
<th>250 mg</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>2 (0)</td>
<td>6 (2)</td>
<td>8 (3)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (0)</td>
<td>2 (0)</td>
<td>4 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Transaminase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elevation</td>
<td>1 (0)</td>
<td>0</td>
<td>5 (1)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

NOTE. Nos. in parentheses are no. of subjects experiencing grade II event.

mg dose group was 24% lower than on day 1 (P = .02). Serum AUC values could not be calculated for subjects in the 125-mg dose group because there were too few detectable serum adefovir levels at the time points sampled. For the 2 highest dose groups, mean AUC values were approximately dose-proportional on both day 1 and day 14 of the study (table 3).

When the mean AUC values were compared between day 1 and day 14 for the 500-mg group, a small (8%) but statistically significant decrease was seen (P = .04). Bioavailability values (determined by comparison to intravenous adefovir data) also decreased on day 14 compared with day 1 for the 500-mg dose group only (P = .005) (table 3). For the 500-mg dose group, mean T\text{max} also increased, from 1.8 h at day 1 to 3.0 h at day 14 (P = .001). Elimination half-life of adefovir dipivoxil, calculated for the 2 highest dose groups, was \( \sim 5.0 \) h.

Significant differences were seen when the urinary recoveries of adefovir in the 125-mg and 250-mg group values on day 1 were compared (\( P = .047 \)) and when the 125-mg and 500-mg group values on day 14 were compared (\( P = .021 \)). One subject in the 500-mg group was not included in the analysis because of an incomplete urine collection. There were no significant differences in urinary recovery within any dose level when day 1 and day 14 values were compared. Urinary recovery values at the 250-mg and 500-mg dose levels approximated the bioavailability values determined from the serum data.

Discussion

In this study, adefovir dipivoxil was administered for 14 consecutive days at doses of either 125, 250, or 500 mg to people with HIV infection. Anti-HIV activity was demonstrated after 14 days of adefovir dipivoxil administration, based on significant decreases in p24 antigen and plasma viral RNA concentrations in the drug-treated groups. At the dosing regimens studied, a dose-dependent reduction in virus load was not seen. Although the magnitude of reduction in p24 antigen concentration (median: 25%–31%) after 14 days of zidovudine monotherapy (mean reduction: 60%) [26], the reduction seen in viral RNA levels (median: 0.4–0.6 log_{10} U) is similar [26]. Furthermore, preliminary reports from a study in which subjects received 125 mg of adefovir dipivoxil daily for 12 weeks show that this magnitude of RNA decrease is sustained over the 12-week period [27]. Ultimately, it will be
congenital carnitine depletion syndromes (i.e., muscle stores depleted to 1.5% of normal) have been associated with no signs or symptoms in some patients but have been associated with cardiomyopathy, skeletal muscle myopathy, encephalopathy, intolerance of fasting, hypoketotic hypoglycemia, and a Reye’s-like syndrome in others [28–33]. In patients receiving courses of therapy with pivampicillin, serum carnitine levels were reported to be depleted to ~15% or less of baseline values [18–20]. In a group of AIDS patients who had been receiving zidovudine for at least 8 weeks, mean free and total carnitine levels were reported as ~1.0 μmol/dL (20%) lower than the mean level for the control (HIV-negative) group [34]. Decreased muscle carnitine has also been reported in patients with zidovudine-induced mitochondrial myopathy [35].

After receiving 14 days of 125 mg of adefovir dipivoxil daily, no subject in this study had a free or total serum carnitine level that fell below the normal range, although this dose group showed a median decrease of 12% in free carnitine. In the 2 higher dose groups, the decrease in serum carnitine (median, 58%–66%) was greater than in the 125-mg group but was less than that reported following courses of pivampicillin therapy [18]. It will be important to see if a further decrease occurs during longer periods of adefovir dipivoxil administration at any dose level.

At the dose regimens studied, adefovir dipivoxil generally showed dose-proportional increases in adefovir $C_{\text{max}}$ and $AUC$

<table>
<thead>
<tr>
<th>Parameter, time point</th>
<th>125 mg</th>
<th>250 mg</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.211 ± 0.131</td>
<td>0.436 ± 0.73</td>
<td>0.831 ± 0.143</td>
</tr>
<tr>
<td>Day 14</td>
<td>0.237 ± 0.082</td>
<td>0.449 ± 0.136</td>
<td>0.635 ± 0.134*</td>
</tr>
<tr>
<td>AUC (μg/h/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>ND</td>
<td>3.76 ± 1.28</td>
<td>6.65 ± 1.44</td>
</tr>
<tr>
<td>Day 14</td>
<td>ND</td>
<td>3.22 ± 0.85</td>
<td>6.15 ± 1.31*</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>45.1 ± 15.9</td>
<td>39.1 ± 8.6</td>
<td>36.5 ± 6.5</td>
</tr>
<tr>
<td>Day 14</td>
<td>41.7 ± 11.5</td>
<td>31.9 ± 6.7</td>
<td>32.2 ± 5.9*</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>2.2 ± 1</td>
<td>2.4 ± 0.8</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>Day 14</td>
<td>1.8 ± 0.8</td>
<td>2.4 ± 0.6</td>
<td>3.0 ± 0.0*</td>
</tr>
<tr>
<td>Urine recovery (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>44.4 ± 15.6</td>
<td>32.8 ± 6.1*</td>
<td>29.6 ± 12.2</td>
</tr>
<tr>
<td>Day 14</td>
<td>41.0 ± 11.3</td>
<td>31.0 ± 8.0</td>
<td>27.5 ± 10.2*</td>
</tr>
<tr>
<td>Serum $t_{\frac{1}{2}}$ (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>ND</td>
<td>5.0 ± 1.7</td>
<td>5.4 ± 0.8</td>
</tr>
<tr>
<td>Day 14</td>
<td>ND</td>
<td>4.2 ± 1.0</td>
<td>5.8 ± 1.1</td>
</tr>
</tbody>
</table>

**NOTE.** Data are means ± SEs. ND, not determined. $C_{\text{max}}$, maximum serum concentration; $T_{\text{max}}$, time to $C_{\text{max}}$; $t_{\frac{1}{2}}$, half-life of terminal elimination phase. $P$ values are given in text.

* Significantly different from day 1 values.

† Significantly different from 125-mg group values.
parameters. The decrease in mean $C_{\text{max}}$ and AUC and increase in mean $T_{\text{max}}$ after administration of 500 mg once daily for 14 days suggest a decrease in the rate and extent of intestinal absorption of adefovir dipivoxil. These findings were evident only in the 500-mg dose group, the group in which gastrointestinal adverse events were most frequent. Potential changes in gastrointestinal motility accompanying these symptoms may explain the decrease in rate of absorption that was seen at day 14. Adefovir dipivoxil diffuses passively into cells [14], unlike adefovir, which depends on an active transport system. Thus, transit time through the gastrointestinal tract may influence the extent of adefovir dipivoxil absorption.

Adefovir dipivoxil demonstrated a favorable pharmacokinetic profile in this study. The mean oral bioavailability of the prodrug was ~35% at the two highest dose levels. On the basis of the excellent tolerability, once-daily dosing, and anti-HIV activity observed with the administration of 125 mg of adefovir dipivoxil, this agent may be a useful addition to current anti-HIV therapies. Also, in vitro data suggest that HIV resistance to adefovir develops more slowly than to other nucleosides [36]. Whether this is true in vivo will be determined in studies of longer use.

Acknowledgments

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References


