Pharmacokinetics and Safety of a Single Dose of Stavudine (d4T) in Patients with Severe Hepatic Impairment

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Received 18 December 1996/Returned for modification 24 May 1997/Accepted 17 September 1997

This open-label study enrolled five subjects with biopsy-proven cirrhosis and moderate to severe hepatic impairment (Child-Pugh classification grade B or C) and five age- and gender-matched controls. All subjects received a single 40-mg oral dose of stavudine (d4T). Stavudine pharmacokinetics in subjects with hepatic impairment were similar to those in age- and gender-matched control subjects and were not substantially different from those previously observed in human immunodeficiency virus-infected patients. Based on these findings, stavudine use does not require modification of the dose or dosing interval for patients with liver disease.

Stavudine (2',3'-didehydro-3'-deoxythymidine; also called d4T) is a thymidine nucleoside analog with potent in vitro activity against human immunodeficiency virus (HIV) type 1 at levels which are generally 100-fold below those that are cytotoxic. Biochemical studies indicate that stavudine, like related nucleoside analogs, acts on the reverse transcriptases of HIV type 1 and other retroviruses. Stavudine triphosphate, produced by phosphorylation by cellular kinases, preferentially inhibits viral reverse transcriptase, with relatively little inhibition of host cell DNA polymerase (6). In clinical studies, stavudine has been shown to exert a significant antiviral effect with acceptable safety; the principal toxic effect is peripheral neuropathy (10, 14).

The pharmacokinetics of stavudine have been described (4, 8). Following oral administration to HIV-infected patients with normal renal and hepatic function, stavudine was rapidly absorbed, with an apparent bioavailability (mean ± standard deviation [SD]) of 86% ± 18%. Peak concentrations in plasma (Cmax) increased in a dose-related manner and occurred within 1 h after dosing. Area under the plasma concentration-time curve from 0 h to infinity (AUC0–∞) also increased in proportion to dose. Apparent volume of distribution (V_app/F) and apparent oral clearance (CLp/F) were independent of dose, with values of 66 ± 22 liters and 33.5 ± 10 liters/h, respectively. Renal clearance accounted for about 40% of the overall clearance and was about twice the creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. Urinary recovery (UR) was 39% ± 23% of the administered dose. The terminal elimination half-life (t1/2) was also independent of dose, with a value of 1.15 ± 0.35 h. Plasma protein binding of stavudine was negligible. Since nonrenal clearance is a major route of elimination for stavudine, assessment of the safety and pharmacokinetics of stavudine in subjects with hepatic impairment was warranted.

The purposes of this open-label study were (i) to estimate the single-dose pharmacokinetics of stavudine in patients with moderate to severe hepatic impairment, (ii) to compare the pharmacokinetics in these subjects with the pharmacokinetics in age- and gender-matched controls, and (iii) to assess the safety and tolerance of a single dose of stavudine administered to subjects with hepatic impairment.

(This work was presented in part at the Second National Conference on Human Retroviruses and Related Infections, Washington, D.C., 1 February 1995.)

Male and nonpregnant, nonnursing female patients with hepatic impairment were eligible if they were at least 18 years old, if their body weight was >50 kg and no more than 15% below or 40% above Metropolitan Life standards, and if they had the following test results: hemoglobin, >10.0 g/dl; polymorphonuclear leukocytes, >1,000/mm3; platelets, >39,000/mm3; prothrombin time, <10 s longer than that of the control; aspartate aminotransferase and alanine aminotransferase, <10 times the upper limit for healthy persons; total bilirubin, <12 mg/dl; and creatinine clearance as calculated by the Cockcroft-Gault formula (3), >50 ml/min. Other requirements were as follows: no simultaneous acute illness or chronic organ dysfunction except hepatic disease; no stage 3 or 4 encephalopathy, severe ascites or edema, or bleeding from esophageal varices within 2 months of enrollment; no history of clinically significant malabsorption or gastrointestinal surgery which could alter drug absorption; and no medication known to inhibit or induce hepatic enzyme activity or inhibit renal tubular secretion. Other patients excluded were those undergoing concomitant therapy with zidovudine, dideoxynosine, or dideoxycytosine; patients with a history of neuropathy or seizures; or who had received neurotoxic drugs within 4 weeks before enrollment; those with a positive urine test for drugs of abuse; patients with a history of allergy to nucleoside analogs; and patients exposed to investigational agents within 1 month of enrollment. Essential medications (e.g., insulin and loop diuretics) were administered at the prescribed doses and times throughout the study, but no medications were administered within 2 h before and after stavudine administration. Histologic evidence of cirrhosis and a modified Child-Pugh score of B or C (1, 12) were required. Age- and gender-matched control subjects were required to have all laboratory values within normal limits. Written informed consent was obtained from all patients and control subjects.

The study was conducted from February to November 1994 at the General Clinical Research Center of The Johns Hopkins Hospital. It was a nonrandomized, open-label study of five

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TABLE 1. Stavudine pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Group status and subject no.</th>
<th>C_{max} (ng/ml)(^a)</th>
<th>T_{max} (h)(^b)</th>
<th>AUC_{0–\infty} (ng · h/ml)(^d)</th>
<th>CL_{T/F} (liters/h)(^c)</th>
<th>CL_{V/(CL/F)} (liters/h)(^c)</th>
<th>V_{area/F} (liters)(^e)</th>
<th>t_{1/2} (h)(^b)</th>
<th>UR (%)(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic impairment</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>586</td>
<td>0.75</td>
<td>1,957</td>
<td>20.5</td>
<td>11.1</td>
<td>89</td>
<td>3.0</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>744</td>
<td>0.50</td>
<td>1,767</td>
<td>22.6</td>
<td>11.6</td>
<td>54</td>
<td>1.7</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>505</td>
<td>1.50</td>
<td>1,414</td>
<td>28.3</td>
<td>14.1</td>
<td>74</td>
<td>1.8</td>
<td>49</td>
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<tr>
<td>7</td>
<td>822</td>
<td>0.25</td>
<td>2,461</td>
<td>16.3</td>
<td>7.6</td>
<td>51</td>
<td>2.2</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>1,621</td>
<td>0.25</td>
<td>1,788</td>
<td>22.4</td>
<td>10.9</td>
<td>39</td>
<td>1.2</td>
<td>49</td>
</tr>
<tr>
<td>Mean ± SD (CV)</td>
<td>856 ± 446 (52)</td>
<td>0.65 ± 0.5 (77)</td>
<td>1,877 ± 381 (20)</td>
<td>22.0 ± 4.3 (20)</td>
<td>11.1 ± 2.3 (21)</td>
<td>62 ± 20 (17)</td>
<td>2.0 ± 0.7 (34)</td>
<td>51 ± 4 (8)</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
<td>614</td>
<td>0.75</td>
<td>1,480</td>
<td>27.0</td>
<td>17.1</td>
<td>72</td>
<td>1.8</td>
<td>63</td>
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<tr>
<td>4</td>
<td>1,076</td>
<td>0.75</td>
<td>1,774</td>
<td>22.6</td>
<td>15.3</td>
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<td>6</td>
<td>1,305</td>
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<td>2,342</td>
<td>17.1</td>
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<td>45</td>
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<td>8</td>
<td>1,649</td>
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<td>1,432</td>
<td>27.9</td>
<td>15.6</td>
<td>56</td>
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<td>59</td>
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<tr>
<td>10</td>
<td>1,432</td>
<td>0.5</td>
<td>3,408</td>
<td>11.8</td>
<td>7.6</td>
<td>31</td>
<td>1.8</td>
<td>62</td>
</tr>
<tr>
<td>Mean ± SD (CV)</td>
<td>1,215 ± 395 (32)</td>
<td>0.60 ± 0.1 (17)</td>
<td>2,087 ± 822 (39)</td>
<td>21.2 ± 6.8 (32)</td>
<td>13.0 ± 4.2 (32)</td>
<td>52 ± 13 (20)</td>
<td>1.7 ± 0.2 (11)</td>
<td>63 ± 4 (6)</td>
</tr>
</tbody>
</table>

\(^a\) Overall ANOVA for group differences, P = 0.123; ratio of means, 0.68; 95% confidence interval, 0.39 to 1.18.
\(^b\) Overall ANOVA for group differences, P = 1.000.
\(^c\) Overall ANOVA for group differences, P = 0.782; ratio of means, 0.94; 95% confidence interval, 0.50 to 1.75.
\(^d\) Overall ANOVA for group differences, P = 0.879; ratio of means, 1.08; 95% confidence interval, 0.55 to 1.96.
\(^e\) Overall ANOVA for group differences, P = 0.458; ratio of means, 1.15; 95% confidence interval, 0.70 to 1.96.
\(^f\) Overall ANOVA for group differences, P = 0.003; ratio of means, 0.81; 95% confidence interval, 0.73 to 0.90.

\(^\text{CV}\) coefficient of variation (percent).

FIG. 1. Curves for concentration in plasma versus time for cirrhotic patients and control subjects. No significant difference was observed. Vertical bars represent SDs.

FIG. 2. CL_{T/F} versus measured creatinine clearance in cirrhotic patients (n = 5) and control subjects (n = 5). There is a statistically significant correlation (r^2 = 0.54; P < 0.05).

patients with moderate to severe hepatic impairment and biopsy-proven cirrhosis and five age- and gender-matched controls. The subjects were admitted to the ward the day before dosing. A history was taken, a physical exam was performed, and the laboratory evaluation was completed. The patients were not permitted to consume food or beverages for 8 h prior to dosing. Drug administration was supervised by a study nurse, and the dose of 40 mg of stavudine had to be taken with at least 120 ml of water. No food was allowed until 1 h after dosing; water was allowed ad libitum.

Laboratory evaluations were performed at admission (day 0) and at discharge (day 2). Vital signs were determined during screening and baseline (day 0) assessment, as well as throughout the 24 h after dosing.

Blood samples to assess stavudine pharmacokinetics were collected prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after dosing. Urine was collected immediately predose and in the intervals from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after the dose. Plasma and urine stavudine levels were assessed by standard high-performance liquid chromatography methods (7). Creatinine clearance was calculated from creatinine measurements obtained during the fractioned 24-h urine collection.

Pharmacokinetic parameters for stavudine were estimated from data for concentration in plasma versus time by using noncompartmental methods (13) and the MENU program (5). C_{max} was defined as the highest observed concentration in plasma. The time at which C_{max} occurred was defined as T_{max}.

The terminal elimination rate constant (k_{el}) was determined by log linear regression of at least the final three data points which yielded a minimum mean square error. The extrapolated area was the final concentration divided by k_{el}. CL_{T/F} was estimated as dose/

\[ 1500 \]
Renal clearance was estimated by dividing the UR of stavudine over a given time (UR_{0–T}) by the corresponding AUC. UR was calculated from urinary drug concentrations and the volume. \( V_{\text{arc}}F \) was calculated as dose/(AUC_{0–\infty} \cdot k_{\text{e}}).

An analysis of variance (ANOVA) was performed with terms for status of hepatic impairment and age- and gender-matched pairs of subjects. The 95% confidence intervals were calculated for the means, the differences between means, and the corresponding ratios of means. \( C_{\text{max}} \) and AUC_{0–\infty} were log transformed in advance, and the resulting estimates of means and mean differences were exponentiated to express the results as geometric means and ratios of geometric means on the original scale of measurement. The confidence intervals for the ratios of the untransformed variables were obtained by Feiler’s method as described by Locke (9). For \( T_{\text{max}} \), the nonparametric Wilcoxon signed-rank procedure was performed for the differences between values within each matched pair. All tests of statistical hypotheses were carried out at the 5% significance level, and all treatment comparisons were two sided. All statistical analyses were carried out with SAS/STAT version 6.07.

We recruited four male and one female Caucasian patients aged 34 to 54 years. Three subjects had grade B and two had grade C hepatic cirrhosis, according to the modified Child-Pugh classification system (1, 12). The paired Caucasian control subjects were 30 to 51 years old. The average difference in age was 3.6 years. The patients’ body weights (range, 53.6 to 96.8 kg; average, 84.5 kg) were slightly higher than the body weights of control subjects (range, 54.0 to 95.0 kg; average, 77.6 kg). The average difference in body weight was 7.0 kg.

There were 12 adverse events reported, 11 for the patients with hepatic impairment and 1 for the control subjects. Seven events were classified as moderate and five as mild in severity. Only 6 of the 12 events were classified as possibly study drug related (three moderate and three mild events), and these occurred in two individuals. One of these patients complained of moderate abdominal cramps and indigestion as well as mild reduction in urinary output without diuretics. He had mild left-lower-quadrant tenderness and moderate epigastric tenderness. These abdominal symptoms and signs remitted in less than 1 day. The other patient observed looser stools than usual (a mild event) that ended 8 h after he received stavudine.

The pharmacokinetic parameters are shown in Table 1. All parameters were comparable for the two groups except UR. The CL_{T/F}s were 22.0 ± 4.3 liters/h in the patients with hepatic disease and 21.2 ± 6.8 liters/h in the healthy controls (\( P = 0.88 \)). The renal clearances were 11.0 ± 2.3 liters/h in the hepatic-disease patients and 13.0 ± 4.2 liters/h in the controls (\( P = 0.48 \)). UR of stavudine was lower in cirrhotic patients (51% ± 4% in cirrhotic patients versus 63% ± 4% in healthy subjects; \( P = 0.003 \)).

Figure 1 shows the curves for mean concentration in plasma versus time for the two study groups. These curves show that the overall pharmacokinetics in plasma were not significantly altered by moderate to severe cirrhosis.

The average creatinine clearance in the patient group was 5.69 ± 3.53 liters/h, whereas the controls had higher values, 6.56 ± 2.98 liters/h. Linear-regression analysis showed a correlation between the creatinine clearance and the CL_{T/F} of stavudine for the groups combined (\( r^2 = 0.54 \), \( P < 0.05 \)) (Fig. 2).

This study shows that patients with cirrhosis and moderate to severe hepatic dysfunction had CL_{T/F}s for stavudine which were not significantly different from those of healthy controls. The significantly lower UR in the subjects with cirrhosis could best be explained by a corresponding reduction in renal function. This reduction in renal function with altered renal blood flow and glomerular filtration is likely related to functional renal impairment typically seen in patients with advanced cirrhosis (11). Also, relative muscle mass is reduced in such patients, and the plasma creatinine concentration may be within normal limits despite reduced renal function (2). The observed correlation of measured creatinine clearance and stavudine CL_{T/F} suggests that the differences in UR are mainly attributable to the differences in renal function. A reduced apparent bioavailability would be another explanation for the diminished UR of stavudine in patients with cirrhosis; this possibility cannot be excluded since absolute bioavailability was not estimated.

Although this was a single-dose pharmacokinetic study, significant accumulation of stavudine following multiple doses is unlikely. The available data provide no evidence of significantly reduced drug elimination in patients with liver disease. These observations suggest that stavudine use does not require adjustment of the dose or dosing interval for patients with liver disease.

In this study, the drug was safe, with no serious adverse events recorded. While there were more events recorded for the patient group than for the controls, we attribute this to the fact that these subjects were seriously ill (most were awaiting liver transplant) and had a higher probability for any type of event, including spontaneous ones.

In conclusion, we have shown the absence of a significant alteration in pharmacokinetics in plasma of a single oral dose of stavudine in patients with moderate to severe hepatic impairment. Thus, stavudine may be given to patients with hepatic disease according to standard dosing recommendations, without dose adjustment.

This study was supported by NIH grant RR-00355, General Clinical Research Center (GCRC) (Osler 5, Adult), The Johns Hopkins Hospital, Baltimore, Md.; by Outpatient GCRC grant 5M01RR00722; and by Bristol-Myers Squibb Company. H.J.S. was partly supported by Janggen-Pöhn Stiftung, St. Gallen, Switzerland.

We appreciate advice on study procedures and review of the manuscript by H. Franklin Herlong and Dennis A. Noc and assistance in manuscript preparation by Mary Williams.

REFERENCES


