

Pharmacokinetics of Single-Dose Oral Stavudine in Subjects with Renal Impairment and in Subjects Requiring Hemodialysis

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Two open-label studies assessed the pharmacokinetics of single orally administered doses of 40 mg of stavudine in subjects with renal impairment. In one study (study I), 15 subjects with selected degrees of renal impairment, but not requiring hemodialysis, were stratified into three groups of five subjects each according to creatinine clearance (CL_{CR}) normalized by body surface area (ml/min/1.73 m²): mild (CL_{CR}, 60 to 80), moderate (30 to 50), and severe (≤20) renal impairment. Five healthy subjects (CL_{CR} ≥ 90) were also enrolled. The stavudine area under the curve from 0 h to infinity (AUC_{0-∞}) increased nonlinearly with declining renal function: 1,864, 2,215, 3,609, and 5,928 ng · h/ml for normal renal function and for mild, moderate, and severe renal impairment, respectively (*P* = 0.0001 between renal impairment groups). The following stavudine dosage recommendations for renal impairment were proposed for subjects weighing ≥60 kg: CL_{CR} of >50 ml/min/1.73 m², 40 mg every 12 h; CL_{CR} of 21 to 50 ml/min/1.73 m², 20 mg every 12 h; and CL_{CR} of 10 to 20 ml/min/1.73 m², 20 mg every 24 h. For subjects weighing <60 kg, the proposed doses were 30, 15, and 15 mg, respectively, with the same dosing intervals specified above. In a second study (study II), 12 subjects with end-stage renal disease requiring hemodialysis three times a week were enrolled in a randomized, open-label crossover study (dialysis 2 h after dosing and lasting 4 h or dosing without dialysis). There were no statistically significant differences for AUC_{0-∞}, AUC₂₋₆, time to maximum concentration of drug in serum, half-life, or apparent oral clearance when the two treatment dosage regimens were compared. As a result of study II, the recommended dosing rate for subjects requiring hemodialysis was the same as that proposed for those with severe renal impairment not requiring hemodialysis; however, dosing was recommended to follow hemodialysis and to occur at the same time each day.

Stavudine (ZERIT; d4T; 2',3'-didehydro-3'-deoxythymidine), a synthetic thymidine nucleoside analogue, is indicated for use in the United States for the treatment of human immunodeficiency virus (HIV)-infected patients who have received prolonged prior zidovudine therapy and in the European Union for the treatment of HIV-infected adults and children with progressive or advanced immunodeficiency. The oral pharmacokinetics of stavudine have been reported for both adult and pediatric patients with HIV infection. In a pharmacokinetic study of HIV-infected patients with AIDS or AIDS-related complex, the mean area under the concentration-time curve from 0 h to infinity (AUC_{0-∞}) following a single oral dose was 1,730, 2,320, 4,810, and 6,630 ng · h/ml for 0.67-, 1.33-, 2.67-, and 4-mg doses/kg of body weight, respectively, with 34 to 41% of the oral dose excreted as unchanged drug in the urine (3). Following oral administration of stavudine to patients with HIV infection, the bioavailability of stavudine at doses of 0.1 to 12 mg/kg has been reported to range between 82 and 99% (3, 6, 8).

The relation of stavudine dose to AUC was confirmed in a study of asymptomatic HIV-infected patients in whom 5-, 10-, 20-, and 40-mg capsules of stavudine produced AUC_{0-∞} values of 250, 490, 980, and 1,950 ng · h/ml, respectively (8). In children with HIV, the AUC_{0-∞}s were 628 and 1,629 ng · h/ml

following administration of 1.0- and 2.0-mg/kg doses of stavudine, respectively, and the absolute bioavailability ranged from 61 to 78% (9). Pharmacokinetic parameters are generally the same after single doses and repeated multiple doses (3; S. Kaul, D. A. Dandekar, and R. H. Barbhayia, *Abstr. VII Int. Conf. AIDS*, abstr. B90, 1992). The extent of absorption of stavudine is not affected by food; however, the rate of absorption is slightly decreased (10).

In vivo metabolism studies using ¹⁴C-labeled stavudine in rhesus and cynomolgus monkeys have shown that fecal elimination (biliary excretion) is negligible (1). Hepatic impairment does not necessitate a change in stavudine dosage. When healthy human controls were compared with HIV-negative volunteers with cirrhosis of the liver, there were no significant differences in the pharmacokinetic parameters (13).

Renal clearance is a major route of elimination for stavudine. Since renal dysfunction occurs in patients with AIDS, secondary to HIV disease or to intravenous drug abuse (5), an assessment of the effect of renal impairment on the disposition of stavudine is warranted. Two studies are reported here. The first study was performed to assess the acute safety and pharmacokinetics of stavudine in subjects with mild, moderate, or severe renal impairment. Based on these results, a second study was conducted to determine the effects of hemodialysis on stavudine pharmacokinetics.

MATERIALS AND METHODS

Study I: subjects with mild, moderate, or severe renal impairment. (i) **Subjects and study design.** In an open-label, nonrandomized, single-center study, 20 male and female subjects were enrolled and stratified according to their individual

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24-h creatinine clearance (CL_{CR}) values. Each subject's CL_{CR} was determined on the basis of two 24-h urine collections obtained at least 5 days apart and no more than 1 month before enrollment. The body surface area, in square meters, for each subject was calculated by the equation proposed by Dubois and Dubois (2): body surface area (m^2) = (weight in kilograms)^{0.425} · (height in centimeters)^{0.725} · 71.84. Fifteen subjects with renal impairment, none requiring hemodialysis, were stratified into three groups of five subjects each: mild (CL_{CR} of 60 to 80 ml/min/1.73 m^2), moderate (CL_{CR} of 30 to 50 ml/min/1.73 m^2), or severe ($CL_{CR} \leq 20$ ml/min/1.73 m^2). Five subjects with normal renal function ($CL_{CR} \geq 90$ ml/min/1.73 m^2) were also enrolled. Following an overnight fast, each subject received a single 40-mg oral dose of stavudine administered as two 20-mg capsules. The subjects were ≥ 18 years of age, with body weights of ≥ 60 kg and no more than 15 below or 40% above ideal body weight. Except for renal disease, they were in good health. Subjects were excluded from the trial if they had renal impairment requiring hemodialysis. Also excluded were nursing or pregnant females or females of childbearing potential, unless an acceptable contraceptive method was being used. In addition, subjects could not be enrolled if they required concomitant medication known to affect renal tubular function (e.g., probenecol, beta-lactam antibiotic, or trimethoprim-sulfamethoxazole) or hepatic metabolism (e.g., cimetidine, fluconazole, phenytoin, phenobarbital, rifampin, or rifabutin) or if they had recent exposure to investigational drugs. The protocol was approved by the investigator's Institutional Review Board prior to study initiation; each subject provided written informed consent for participation in the study prior to the performance of any study-related procedures.

(ii) Pharmacokinetic methods. Twenty-four-hour urine collections were made beginning immediately before dosing. Blood samples were then collected just before and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after stavudine administration. Stavudine concentrations were measured in both plasma and urine samples by a validated high-performance liquid chromatographic method (7). Pharmacokinetic parameters were calculated from plasma concentration-versus-time and urinary-excretion data using noncompartmental methods (4, 11).

The maximum observed plasma drug concentration was defined as C_{max} , which occurred at time T_{max} . A least-squares linear regression analysis without weighting was used to determine the best-fit log-linear portion of the concentration-versus-time data. The log-linear portion was defined as the portion yielding the smallest mean-square error; the slope was used to calculate the terminal elimination rate constant (k), and the terminal elimination half-life ($t_{1/2}$) was defined as $0.693/k$. The $AUC_{0-\infty}$ was determined using a combination of linear and log-trapezoidal summations, where the log-trapezoidal summation was applied to the log-linear portion of the plasma concentration-versus-time profile and the linear-trapezoidal summation was applied elsewhere. Apparent oral clearance (CLT/F) was calculated as $dose/AUC_{0-\infty}$. Renal clearance (CL_R) was estimated by the equation $CL_R = UR_{0-T}/AUC_{0-T}$, where UR is urinary recovery estimated directly from urinary concentration-versus-time data and T is a specified time point after dosing. The apparent volume of distribution (Vd_{area}/F) was calculated as $Dose/k \cdot AUC_{0-\infty}$.

(iii) Statistical analysis. A one-way analysis of variance (ANOVA) was used to test the effect of renal function on stavudine pharmacokinetics. All statistical tests were performed at an α of 0.05 (two tailed). When the overall F test for group differences was statistically significant, Fisher's least-significant-difference test was performed for group comparisons. A test for linearity across groups was performed for the $AUC_{0-\infty}$ values, and a linear regression model [$AUC_{0-\infty} = \beta_0 + \beta_1(CL_{CR}) + \epsilon$, where β_0 is the intercept, β_1 is the slope of the line, and ϵ is the error term] and an exponential model [$AUC_{0-\infty} = \alpha + \beta_0 \cdot \exp(-\beta_1 \cdot CL_{CR}) + \epsilon$, where α is the asymptote, β_0 is the intercept, β_1 is the slope of the line, and ϵ is the error term] were fitted to the individual stavudine $AUC_{0-\infty}$ -versus- CL_{CR} data. Ninety-five percent confidence intervals about the model-predicted values were determined.

Safety data were summarized from clinical adverse events, clinical laboratory tests (urine and blood samples collected before and during the 24 h after dosing), vital signs measured predose and before the 12- and 24-h blood draws, and physical examinations performed predose and at 24 h after dosing prior to discharge. Clinical adverse events were defined as any study staff-observed or subject-reported (either spontaneously or solicited by study staff) illnesses, signs, or symptoms that appeared or worsened during the course of the study regardless of whether they were believed to be related or unrelated to study drug administration.

Study II: subjects with severe renal impairment requiring hemodialysis. (i) Subjects and study design. Twelve male and female subjects with severe renal impairment requiring maintenance hemodialysis three times a week were enrolled in an open-label crossover study. The subjects were randomized for a dialysis day-no-dialysis day sequence. Subjects were not allowed to enter the study if they were nursing or pregnant females or females of childbearing potential (unless an acceptable contraceptive method was being used). They were also excluded if they had a history of peripheral neuropathy or significant liver disease (liver transaminases of >2 times the normal upper limit, bilirubin at >30 μ mol/liter, or clinical evidence of ascites or hepatic encephalopathy) or evidence of organ dysfunction other than renal impairment. In addition, subjects could not be enrolled if they required concomitant medication known to affect renal tubular function (e.g., cimetidine, penicillin, or trimethoprim-sulfamethoxazole) or if they had recent exposure to investigational drugs or medications which could cause peripheral neuropathy. Although it was not required by the protocol, all

subjects were anuric, and none were taking concomitant medications known to have an impact on drug metabolism. On 2 days (study days 1 and 2), separated by a 7- to 28-day washout period, each subject received a single 40-mg oral dose of stavudine administered as two 20-mg capsules following an overnight fast.

(ii) Pharmacokinetic methods. Blood and dialysate (for the hemodialysis arm of the study) samples were collected before and during the 24-h periods after dosing on study day 1 and/or 2. Blood samples were taken just before and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 h after stavudine dosing. Dialysate fluid was taken every 30 min during the 4-h dialysis. As all subjects were anuric, UR and CL_R were assumed to be zero. Stavudine levels in plasma and dialysate were measured by validated high-performance liquid chromatographic methods. The dialysis period began 2 h after dosing and lasted 4 h. During hemodialysis, blood was pumped at the rate of 250 ml/min through the extracorporeal circuit. The molecular weight cutoff for the cellophane membrane was 1,000 Da. An estimate of the amount of stavudine eliminated by hemodialysis was obtained from the concentration of stavudine (in nanograms per milliliter) at the midpoint of each 30-min period during hemodialysis times the estimated volume of dialysis fluid (directly measured [in milliliters] from collected samples) used in the same period. In addition to $AUC_{0-\infty}$, C_{max} , T_{max} , $t_{1/2}$, and CLT/F, defined for study I above, other parameters were calculated in study II. AUC_{2-6} was defined as the AUC in the period 2 to 6 h after dosing. %DIAL was defined as the percentage of the administered dose recovered as unchanged stavudine in the dialysate fluid. The clearance of unchanged stavudine during hemodialysis, CL_{HD} , was determined as previously described: $CL_{HD} = [Q_P \cdot C_A - (Q_P - Q_{UF}) \cdot C_V]/C_A$, where C_A and C_V were the plasma concentrations before and after dialysis, respectively; Q_P was the plasma flow entering the dialyzer; and Q_{UF} was the preset ultrafiltration rate of the dialyzer (i.e., 10 ml/min).

(iii) Statistical analysis. All statistical tests were performed at an α of 0.05 (two tailed). For each pharmacokinetic parameter, a two-way crossover design was analyzed by a mixed model, including the period of study day 1 versus study day 2, treatment (dialysis versus no dialysis) fixed effects, and a random subject effect. $AUC_{0-\infty}$, AUC_{2-6} , C_{max} , and CLT/F were prior log transformed. For T_{max} and $t_{1/2}$, the nonparametric Wilcoxon rank sum test was used.

Safety data were summarized from clinical adverse events, clinical laboratory tests (blood samples collected before and during the 24 h after each dose), vital signs measured predose and before the 12- and 24-h blood draws, and electrocardiograms (ECGs) and physical examinations performed predose and at 24 h after dosing.

RESULTS

Study I. (i) Demographics. Twelve male and 8 female subjects (18 white and 2 black) were enrolled and completed the study. The ages of the subjects ranged from 18 to 84 years (mean, 51 years), heights ranged from 133 to 198 cm (mean, 169 cm), and weights ranged from 61 to 120 kg (mean, 78 kg). Demographic characteristics are provided in Table 1.

(ii) Pharmacokinetics. Systemic exposure to stavudine increased in a nonlinear manner as CL_{CR} decreased. As shown in Table 2, the mean $AUC_{0-\infty}$ values for the normal renal function group and the mild, moderate, and severe renal impairment groups were 1,864, 2,215, 3,609, and 5,928 ng · h/ml, respectively. The overall ANOVA demonstrated a statistically significant difference ($P = 0.0001$) between renal impairment groups; pairwise comparisons showed statistically significant differences among the mild, moderate, and severe groups but not between the normal renal function group and the mild renal impairment group.

Also as presented in Table 2, $t_{1/2}$ also increased significantly ($P = 0.01$) across groups with decreasing CL_{CR} (increasing severity of renal impairment). In addition, there were significant overall differences for CLT/F, CL_R , and percent UR with decreasing values for CL_{CR} . There was no statistically significant overall group mean difference for C_{max} , T_{max} , or Vd_{area}/F .

The results of this study provide a basis for stavudine dosing adjustments in individuals with renal impairment by establishing a relation between CL_{CR} and AUC. The relationship between $AUC_{0-\infty}$ and CL_{CR} is best described by the model in Fig. 1, which shows both the estimated exponential curves (see Materials and Methods) and observed data. Based on estimated data, a set of dosing guidelines were proposed for the administration of stavudine in subjects with renal impairment (Table 3). These recommendations set treatment criteria ac-

TABLE 1. Demographic characteristics of subjects in studies I and II

Study	Renal function group	Parameter	Ht (cm)	Wt (kg)	Age (yr)	Sex	Race
I	Normal	Mean	167	76.2	25	2 males, 3 females	5 white
		Range	133–185	62.3–85.5	18–38		
		<i>n</i>	5	5	5		
	Mild	Mean	168	84	64	4 males, 1 female	5 white
		Range	157–177	75.7–92.2	58–74		
		<i>n</i>	5	5	5		
	Moderate	Mean	173	80.2	62	2 males, 3 females	4 white, 1 black
		Range	163–198	60.9–120	50–81		
		<i>n</i>	5	5	5		
	Severe	Mean	168	73.3	53.5	4 males, 1 female	4 white, 1 black
		Range	165–172	60.9–92.3	30–84		
		<i>n</i>	5	5	5		
Overall	Mean	169	78	51	12 males, 8 females	18 white, 2 black	
	Range	133–198	61–120	18–84			
	<i>n</i>	20	20	20			
II	Hemodialysis	Mean	174	68	34	9 males, 3 females	12 white
		Range	165–185	48–90	20–52		
		<i>n</i>	12	12	12		

cording to CL_{CR} normalized by body surface area (>50 , 21 to 50, and 10 to 20 ml/min/1.73 m²). These adjustments should provide exposure to stavudine, as reflected by AUC, for individuals with renal impairment which matches that for patients with normal renal function.

(iii) **Safety data.** There were no deaths, other serious adverse events, or discontinuations in this study. Twelve clinical adverse events were reported by 8 (40%) of 20 subjects. The incidence of adverse events was not related to CL_{CR} , and all adverse events resolved. Two subjects with severe renal impairment had adverse events possibly related to treatment. One subject had severe pedal edema and liver enlargement, which resolved following treatment with diuretics; the second subject had mild stomach discomfort, mild headache, and moderate emesis. All other adverse events were determined by the investigator to be unrelated to stavudine. There were no clinically significant laboratory abnormalities and no clinically significant deviations in vital signs or ECGs.

Study II. (i) Demographics. Nine male and three female white subjects were enrolled and completed the study. Of the 12 subjects, 9 had hemodialysis on study day 1, and the remaining 3 had hemodialysis on study day 2. Their ages ranged from 20 to 52 years (mean, 34 years), their heights ranged from 165 to 185 cm (mean, 174 cm), and their weights ranged from 48 to 90 kg (mean, 68 kg) (Table 1). There were no statistically

significant differences in these demographic parameters between the subjects who had hemodialysis on study day 1 and those who had hemodialysis on study day 2.

(ii) **Pharmacokinetics.** As shown in Table 4, the ratios of geometric mean values for the day with hemodialysis and those for the day without hemodialysis were not statistically significant for either $AUC_{0-\infty}$ or AUC_{2-6} . The geometric mean values with and without hemodialysis were 5,365 and 6,326 ng · h/ml, respectively, for $AUC_{0-\infty}$ and 1,934 and 2,184 ng · h/ml, respectively, for AUC_{2-6} . There was a statistically significant ratio of geometric means for C_{max} with and without hemodialysis (ratio, 0.821; means, 822.8 and 1,002 ng/ml, respectively; $P = 0.04$). There was no statistically significant ratio of geometric means for CLT/F with and without hemodialysis, and there were no statistically significant differences in median T_{max} or $t_{1/2}$. The CL_{HD} was 7.19 liters/h (range, 4.84 to 8.48 liters/h), and %DIAL was 30.5% (range, 21.2 to 40.1%).

There were technical problems in the plasma assay for one subject on the day without hemodialysis; therefore, $n = 12$ for the day with hemodialysis and $n = 11$ for the day without hemodialysis. Another subject had unexpectedly higher C_{max} , $AUC_{0-\infty}$, and AUC_{2-6} values with hemodialysis than without, differing from all of the other subjects. However, as there was no reason to question the integrity of this subject's pharmacokinetic parameters, his data were included for both days. How-

TABLE 2. Mean pharmacokinetic parameter values in normal subjects and subjects with renal impairment based on CL_{CR} normalized by body surface area in study I

Parameter	Value (SD) with CL_{CR} (ml/min/1.73 m ²) of ^a :				ANOVA for group differences (P) ^b
	≥ 90 ($n = 5$)	60–80 ($n = 5$)	30–50 ($n = 5$)	≤ 20 ($n = 5$)	
C_{max} (ng/ml)	836 (196)	845 (101)	834 (170)	1,002 (287)	0.49
T_{max} (h)	0.65 (0.2)	0.95 (0.3)	1.35 (1.0)	1.10 (0.4)	0.23
$AUC_{0-\infty}$ (ng · h/ml)	1,864 (173)*	2,215 (440)*	3,609 (740)†	5,928 (1178)‡	0.0001
CLT/F (ml/min)	360 (32)*	312 (67)*	191 (39)†	116 (25)‡	0.0001
CL_R (ml/min)	201 (77)*	135 (22)†	73 (18)‡	17 (3)§	0.0001
Vd_{area}/F (liters)	48.2 (8)	51.2 (10)	53.4 (26)	45.1 (9)	0.84
$t_{1/2}$ (h)	1.55 (0.24)*	1.94 (0.48)*†	3.51 (2.52)†‡	4.55 (0.88)‡	0.01
UR (%)	58.7 (20)*	44.6 (8)*†	40.0 (11)†	14.0 (4)‡	0.0003

^a ≥ 90 ml/min/1.73 m², normal function; 60 to 80, mild renal impairment; 30 to 50, moderate renal impairment; ≤ 20 , severe renal impairment.

^b Differences among individual group means were assessed by Fisher's least significant-difference test ($P \leq 0.05$). Means with the same symbols are not significantly different.

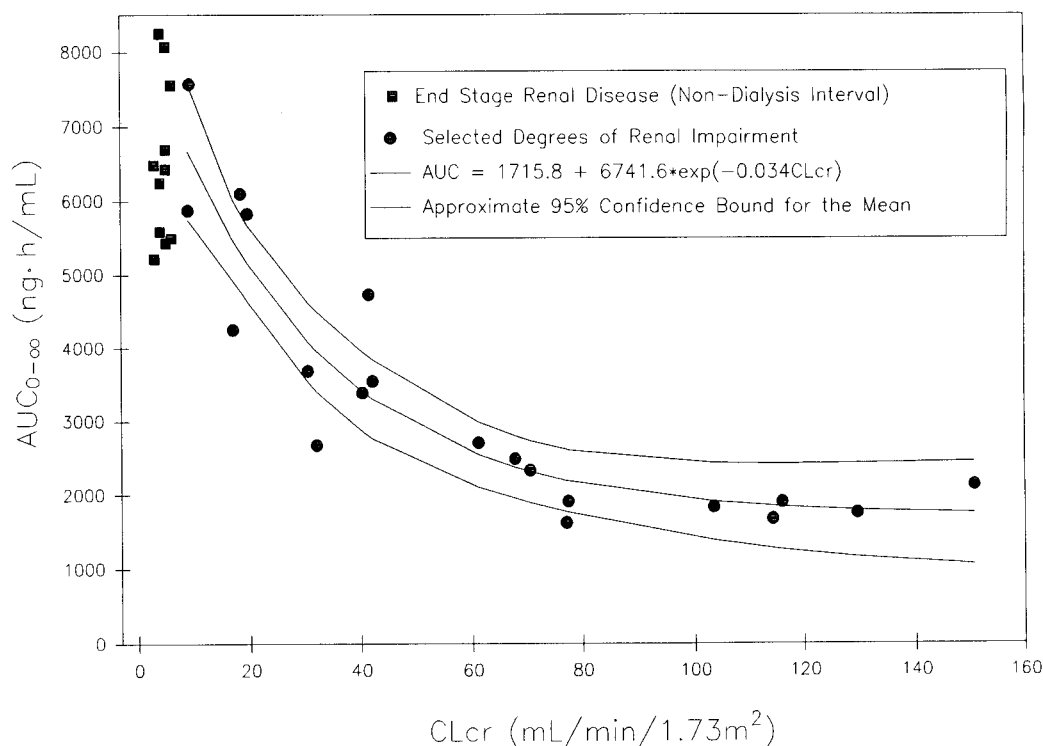


FIG. 1. Relationship between $AUC_{0-\infty}$ and CL_{CR} normalized for body surface area (these values were used in the regression analysis) and a Jitter plot for end-stage renal disease subjects centered around a mean creatinine clearance of 5 mL/min/1.73m^2 and superimposed on the original graph. The predicted regression equation and respective confidence bounds did not include subjects with end-stage renal disease from study II.

ever, a summary of pharmacokinetic parameters excluding results from this subject is provided in Table 5.

The results of this study led to the following proposal: the dosage schedules for subjects with severe renal impairment requiring hemodialysis should be the same as those recommended in study I for subjects with severe renal impairment not requiring hemodialysis (20 mg every 24 h for subjects with body weights of $\geq 60 \text{ kg}$ and 15 mg every 24 h for subjects with body weights of $< 60 \text{ kg}$). However, doses should be administered after scheduled hemodialysis and at the same time each day.

(iii) **Safety.** There were no serious clinical adverse events and no discontinuations. Only one adverse event was reported: moderate hypotension in a subject during hemodialysis. Dialysis was discontinued after 3.25 h of the 4.0-h dialysis session, and the hypotension quickly resolved. The subject was not dropped from the study, and the event was not considered to be related to stavudine. In general, vital signs in individual subjects were essentially unchanged during the study. No un-

usual pattern of out-of-range clinical laboratory parameters was seen. As expected, hemoglobin, erythrocyte, and hematocrit levels were consistently low and creatinine values were consistently high for all subjects. There were no clinically significant changes in ECGs.

DISCUSSION

The results of study I suggest that as creatinine clearance declines, exposure to stavudine increases for a given dose. After a single 40-mg dose, mean $AUC_{0-\infty}$ values ranged from $1,864 \text{ ng} \cdot \text{h/ml}$ in subjects with normal renal function to $5,928 \text{ ng} \cdot \text{h/ml}$ in subjects with severe renal impairment, representing a 3.2-fold increase in $AUC_{0-\infty}$ with decreasing renal function.

TABLE 4. Mean pharmacokinetic parameter values in end-stage renal disease subjects with and without hemodialysis

Parameter	Value (SE)		P value
	With hemodialysis (n = 12)	Without hemodialysis (n = 11)	
C_{\max}^a (ng/ml)	822.8 (0.066)	1,002 (0.068)	0.041
T_{\max}^b (h)	1.3 (0.3, 3.0)	1.0 (0.3, 2.0)	0.061
$AUC_{0-\infty}^a$ (ng · h/ml)	5,365 (0.078)	6,326 (0.080)	0.083
AUC_{2-6}^a (ng · h/ml)	1,934 (0.068)	2,184 (0.069)	0.104
$t_{1/2}^b$ (h)	5.7 (3.9, 11.6)	5.3 (3.6, 8.4)	0.630
CLT/F^c (liters/h)	7.456 (0.078)	6.323 (0.080)	0.083
$CLHD^c$ (liters/h)	7.19 (1.05)	Not applicable	Not applicable
%DIAL ^c	30.5 (5.3)	Not applicable	Not applicable

^a Geometric mean (standard error of mean in log scale).

^b Median (minimum, maximum).

^c Arithmetic mean (standard deviation).

TABLE 3. Stavudine dosing recommendations for subjects with renal impairment based on CL_{CR}

CL_{CR} (ml/min/1.73 m ²)	Recommendations dose for body weight of:	
	$\geq 60 \text{ kg}$	$< 60 \text{ kg}$
> 50	40 mg every 12 h	30 mg every 12 h
21–50	20 mg every 12 h	15 mg every 12 h
10–20	20 mg every 24 h	15 mg every 24 h
Hemodialysis ^a	20 mg every 24 h	15 mg every 24 h

^a The recommended dose is to be administered after completion of hemodialysis and at the same time each day.

TABLE 5. Mean pharmacokinetic parameter values in end-stage renal disease subjects with and without hemodialysis excluding subjects with unexpected stavudine levels

Parameter	Value (SE)		P value
	With hemodialysis (n = 11)	Without hemodialysis (n = 10)	
C_{\max}^a (ng/ml)	783.9 (0.071)	1,018 (0.072)	0.023
$AUC_{0-\infty}^a$ (ng · h/ml)	4,985 (0.078)	6,478 (0.079)	0.012
AUC_{2-6}^a (ng · h/ml)	1,799 (0.064)	2,230 (0.065)	0.005
CLT/F ^a (liters/h)	8.024 (0.078)	6.175 (0.079)	0.012

^a Geometric mean (standard error of mean in log scale).

Stavudine exposure in the subjects in this study with normal renal function is consistent with previous data from HIV-infected subjects, where $AUC_{0-\infty}$ was 1,950 ng · h/ml at 40 mg of stavudine (8) and 1,730 ng · h/ml at 0.67 mg/kg (3).

In study I, there was a statistically significant difference for mean $AUC_{0-\infty}$ values among the CL_{CR} groups and a nonlinear relationship between $AUC_{0-\infty}$ and CL_{CR} . In order to develop dosing guidelines based on these results, the following steps were taken: (i) an exponential model was used to predict the stavudine $AUC_{0-\infty}$ for CL_{CR} s from 150 to 5 ml/min/1.73 m² (note that these guidelines are based on CL_{CR} normalized for body surface); (ii) doses of stavudine were estimated that would yield an $AUC_{0-\infty}$ value equal to 1,864 ng · h/ml (the geometric mean value for the normal CL_{CR} group), assuming linear pharmacokinetics and consistent bioavailability for stavudine; and (iii) the predicted doses were then utilized to modify dose levels and intervals so that subjects with differing degrees of renal impairment could be consistently exposed to the drug.

In study II, there were no statistically significant differences between treatments with and without hemodialysis for $AUC_{0-\infty}$, AUC_{2-6} , CLT/F, and $t_{1/2}$. In addition, it should be noted that the values for $AUC_{0-\infty}$ in study II (5,365 and 6,326 ng · h/ml, with and without dialysis, respectively) are similar to the arithmetic mean value for $AUC_{0-\infty}$ of subjects with severe renal impairment in study I (5,928 ng · h/ml). This similarity is further supported in Fig. 1, where the individual $AUC_{0-\infty}$ values for the end-stage renal disease subjects on a nondialysis interval were included on the plot of the original analysis (for graphing purposes, a Jitter subroutine within SAS was used about a mean creatinine clearance of 5 ml/min/1.73 m²). These results suggest that the stavudine dosing guideline for subjects with severe renal impairment is appropriate for subjects who require hemodialysis.

Study II was important because the removal of drugs and their metabolites during hemodialysis would necessitate adjustment of the dose or the schedule of dosing in relation to hemodialysis. Drug clearance during hemodialysis is related to the molecular weight, protein binding, and volume of distribution of the drug (12). During hemodialysis, CL_{HD} was

7.19 liters/h and %DIAL was estimated as 30.5% of the stavudine dose. This degree of stavudine elimination was not unexpected because stavudine has a relatively low molecular weight (224.22), is nonionized at physiological pH, and is only 20% protein bound. While dialysis did not significantly change the $AUC_{0-\infty}$ or AUC_{2-6} when results for all subjects were considered, it is important to note that if more than 30% of a dose or hemodialysis clearance equals or exceeds systemic clearance, extracorporeal removal of the drug may be considered significant, and dosing of the drug should occur following the hemodialysis session. Based on the findings in these two studies, a set of guidelines was recommended for stavudine dosing in renally impaired subjects, including those who require hemodialysis.

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