ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1995, p. 2309–2315 Vol. 39, No. 10
0066-4804/95/$04.00+0

Population Pharmacokinetics of Stavudine (d4T) in Patients with AIDS or Advanced AIDS-Related Complex

CYNTHIA M. HORTON,[1]† MICHAEL N. DUDLEY,[1]* SANJEEV KAUL,[2] KENNETH H. MAYER,[3] KATHLEEN SQUIRES,[4]‡ LISA DUNKLE,[2] AND ROBERT ANDERSON[2]

Antiinfective Pharmacology Research Unit, University of Rhode Island College of Pharmacy and Roger Williams Medical Center, and Brown University AIDS Program,[3] Providence, Rhode Island; Bristol-Myers Squibb Pharmaceutical Research Institute, Syracuse, New York and Wallingford, Connecticut[2]; and New York Hospital-Cornell Medical Center, New York, New York[4]

Received 2 June 1994/Returned for modification 29 January 1995/Accepted 30 June 1995

The population pharmacokinetics and bioavailability of oral stavudine (d4T; 2′,3′-dideoxy-3′-deoxythymidine) was determined in 81 patients with AIDS or AIDS-related complex (ARC) enrolled in phase I and phase I/II dose-ranging trials. Each patient underwent inpatient pharmacokinetic studies following administration of the first oral stavudine dose; 59 patients were restudied after chronic therapy for an average of 19 days. Thirty-three of these patients also received a single intravenous stavudine dose prior to starting an oral regimen. A two-compartment model with first-order absorption and elimination was used as the structural pharmacokinetic model. A basic model provided the following population parameter estimates (interpatient variability expressed in parentheses as percent coefficient of variation): clearance/bioavailability = 30.9 (24.5%) liters/h; volume of distribution/bioavailability = 8.42 (not modeled) liters; volume of distribution at steady state/bioavailability = 68.9 (105%) liters; intercompartmental clearance/bioavailability = 12.4 (26%) liters/h; and first-order absorption rate constant = 1.32 (78.9%) liters/h. In the subset of 33 patients receiving both intravenous and oral doses, the bioavailability of stavudine was estimated to be 99.1% (18.5%). Total body weight, stage of disease (AIDS versus ARC), and an oral stavudine dose of ≥200 mg were found to have a statistically significant but a clinically marginal effect on the estimate of the oral clearance of stavudine. This analysis shows the high degree of bioavailability of stavudine in patients with AIDS and ARC and the relatively low degree of interpatient variability in oral drug clearance compared with those of other nucleosides. Population pharmacokinetic analysis is a useful tool for assessing the combined effects of several patient variables on the pharmacokinetic properties of drugs in human immunodeficiency virus-infected patients.

Nucleoside antiretroviral therapy currently remains the cornerstone of drug therapy of human immunodeficiency virus (HIV) infection. Unfortunately, most of the currently available agents exhibit significant interpatient variability in their pharmacokinetic properties, which leads to variability in in vivo drug exposure (11). This can result in modulation of the therapeutic as well as the toxicological responses to these agents (3, 4, 9, 13). For example, the development of opportunistic infections and hematological toxicity has been linked to the mean concentrations of zidovudine in serum (4, 13), and suppression of p24 antigen and changes in children's intelligence quotient scores have been correlated with didanosine exposure (3, 9). Careful consideration of the pharmacokinetic properties of drugs and elucidation of the sources of variability are important early in the dose-defining process for future testing in large-scale clinical trials.

Recent emphasis in drug development has been placed on population-based methods for describing the dispositions of drugs in patients. Nonlinear mixed-effects modeling (NONMEM) and nonparametric expectation maximization algorithm (NPEM) are examples of techniques that allow for the estimation of population values of pharmacokinetic parameters along with their variabilities (7, 8, 19).

Stavudine (d4T; 2′,3′-didehydro-3′-deoxythymidine) is a pyrimidine nucleoside antiretroviral agent with in vitro activity against HIV similar to that of zidovudine (2). It also appears to retain activity against some zidovudine-resistant strains of HIV (16). Preclinical and clinical studies have also shown stavudine to be less cytotoxic than zidovudine (1, 5); however, the dose-limiting toxicity in humans is peripheral neuropathy (6, 18, 21).

This report summarizes the population pharmacokinetics of stavudine in 81 patients to whom stavudine was administered orally (p.o.) in phase I and phase I/II dose-ranging studies by using nonlinear mixed-effects modeling as implemented in the program NONMEM.

MATERIALS AND METHODS

Patients. Data from three phase I and phase I/II protocols of stavudine were obtained from Bristol-Myers Squibb; the clinical results from those studies have been described elsewhere (6, 18, 20). The patients enrolled in the protocols were ≥12 years of age and had either AIDS as defined by the Centers for Disease Control and Prevention (CDC) or AIDS-related complex (ARC; CDC stage IV-A or IV-C-2), a CD4 cell count of ≤500/mm^3, no active AIDS-defining opportunistic infections, and no previous hematological intolerance to zidovudine. In addition to the above, patients had the following characteristics at the time of entry into the study: hemoglobin concentration of ≥8.5 g/liter; neutrophil count of ≥950/mm^3; platelet count of ≥75,000/mm^3; alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin levels less than three times the upper limit of normal; and a serum creatinine level of ≤1.5 mg/dl. All patients gave informed consent according to the guidelines of the respective institutions.

Study design. The allocation of 81 patients among the different regimens of stavudine in the three protocols is provided in Table 1. Capsules of stavudine for p.o. administration were administered to patients in dosages ranging from 0.1 to

* Corresponding author. Mailing address: Antiinfective Pharmacology Research Unit, University of Rhode Island College of Pharmacy, Roger Williams Medical Center, 5th Floor-Elmhurst Campus, 825 Chalkstone, Ave., Providence, RI 02908. Phone: (401) 456-2261. Fax: (401) 456-6590.

† Present address: University of Wisconsin, Madison.

‡ Present address: University of Alabama at Birmingham.

TABLE 1. Stavudine dosage regimens for 81 patients included in population pharmacokinetic analysis

Oral dosage (mg/kg/day)	No. of patients-regimen by study site[a]			Total no. of patients (no. of patients receiving single i.v. dose)
	Providence	New York	Multicenter	
12	6-TID	5-QID		11 (9)
8	6-TID	6-QID		12 (1)
4	6-TID	4-BID, 4-QID		14 (4)
2	1-BID, 6-TID	2-BID, 5-QID	3-TID	17 (3)
1	5-BID	3-BID		8 (8)
0.5	4-BID	4-BID	5-TID	13 (8)
0.1			6-TID	6 (0)

[a] BID, twice daily; TID, three times daily; QID, four times daily.

12 mg/kg of body weight per day divided into two, three, or four doses per day. The combined data set represented more than a 100-fold range in daily dosages of stavudine that were fractionated into administration two, three, or four times daily. A single intravenous (i.v.) dose was also given to a subset of patients prior to the p.o. administration of stavudine, thus allowing for estimation of the absolute bioavailability (F) in these patients.

All blood samples were collected as part of pharmacokinetic studies. Pharmacokinetic studies were conducted in an inpatient setting after administration of the first p.o. dose to all 81 patients. Repeat inpatient sampling for pharmacokinetic analysis was performed for 59 (73%) of these patients after a mean of 19 days (range, 8 to 59 days) of stavudine therapy. Thirty-three patients also received a single i.v. dose (one-quarter of the p.o. dose) prior to receipt of the first p.o. dose of stavudine.

Patients were admitted to an inpatient unit the evening prior to administration of the study doses of stavudine and fasted overnight until 2 h following administration of the morning study dose. Blood samples (3 ml) were collected from an indwelling i.v. catheter before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 8 h after administration of a p.o. dose in all protocols and up to 12 or 24 h in the phase I studies. The single i.v. dose was delivered via a constant-rate infusion pump over 60 min; blood samples were drawn before the infusion and at 0.25, 0.5, 0.75, 1, 1.1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 h after the start of the infusion. Blood samples were collected in potassium EDTA-containing Vacutainer tubes, placed on ice, and centrifuged at 3,000 × g at 4°C within 1 h of collection. The plasma was placed in screw-cap polypropylene tubes, and the tubes were stored at −90°C.

Plasma stavudine concentrations in 71 patients were assayed by a previously described high-pressure liquid chromatography (HPLC) method (14). The precision of the HPLC assay was <9% (coefficient of variation × 100%). In patients receiving stavudine at dosages of ≤2 mg/kg/day, a more sensitive radioimmunoassay was used to assay the stavudine concentrations in plasma samples. The total number of samples assayed by this method comprised ca. 10% of the total number of samples. This assay used 10 μl of sample combined with 185 μl of total of antibody and control plasma. The mixture was combined and was stored overnight at 4°C, and then 200 μl of ^{125}I-labeled histamine-stavudine conjugate was added. This mixture was refrigerated at 4°C for 4 h; this was followed by the addition of 1 ml of a 7.5% polyethylene glycol solution containing 1% goat anti-rabbit gamma globulin. The samples were then centrifuged, and the supernatant was decanted and discarded. The remaining pellet was resuspended in scintillation fluid to measure the radioactivity. The lower limit of quantitation of the radioimmunoassay was 2.5 ng/ml (standard curve range, 2.5 to 100 ng/ml). Accuracy (as the percent deviation of the nominal value) and precision (as the percent coefficient of variation [CV]) for quality control samples were 5 and 8%, respectively. Selected plasma samples were assayed by both HPLC and radioimmunoassay, and the results obtained by both methods were in agreement (data not shown).

Data sets. A total of 1,742 plasma stavudine concentrations were divided into two data sets. Data on the concentration of drug in plasma for all 81 patients (1,326 plasma samples) following the administration of the first or multiple p.o. doses comprised the p.o. data set. An average of 16.4 (range, 4 to 24) plasma stavudine levels were contributed by each patient. A second data set (entitled the i.v./p.o. data set) consisted of 826 plasma samples collected after the first i.v. and p.o. (first and multiple) doses for a subset 33 patients who received a single i.v. dose of stavudine prior to studies of the pharmacokinetics of stavudine administered p.o.

Plasma stavudine concentrations versus time and clinical and demographic data were obtained from databases generated from case report forms supplied by Bristol-Myers Squibb. Plasma stavudine concentrations less than the lower limit of quantitation were not used in this analysis. The translator portion of NONMEM (NM-TRAN) uses data in a specific format in which dosing events at time zero are followed by observation events (i.e., plasma drug concentrations or CD4 cell counts) at relative time points for each individual. The data obtained from Bristol-Myers Squibb were merged with the dosing information and were configured in the NM-TRAN format by using a microcomputer for input into NONMEM.

Pharmacostatistical model. Nonlinear mixed-effects modeling was performed by using NONMEM version 3.0 (double precision, level 1.2) on an International Business Machines ES-9000 computer (19). This version uses the first-order approximation in generating function evaluations. Program-supplied PRED routines were used. Preliminary runs of several models established that a two-compartment open model with first-order rate constants (K_a's) for absorption and elimination (ADVAN4 TRANS3) was optimal for describing the data. The structural model was parameterized as follows: p.o. clearance divided by F (CL/F); volumes of distribution of the central compartment and at steady-state both divided by F (V_1/F and V_{ss}/F, respectively); intercompartmental clearance divided by F (Q/F); and K_a. Since previous pharmacokinetic studies have shown that the half-life of stavudine is approximately 1.1 h (12), steady-state conditions were assumed to exist in those patients undergoing repeat pharmacokinetic studies following the administration of multiple doses. The same structural model with a separate term for bioavailability ($F1$) was used for the subset of 33 patients who received both the i.v. and the p.o. formulations of stavudine.

Models for interpatient variability and residual error terms were determined by changes in objective function and the increased precision of the pharmacokinetic parameter estimates. Interpatient variability in CL/F, V_{ss}/F, Q/F, and K_a were modeled by using a constant coefficient of variation (proportional) term, or $\theta_j = \theta'_j(1 + \eta\theta_j)$, where θ_j is the estimate or typical value for a pharmacokinetic parameter in the jth individual, θ'_j is the predicted pharmacokinetic parameter, and $\eta\theta_j$ represents the random difference (with mean = 0 and variance = σ^2) between the true value of the pharmacokinetic parameter for the individual and the value predicted by the pharmacostatistical model.

Since a wide range of stavudine concentrations was observed, the residual error was modeled as having both constant and proportional elements: $C_{ij} = [C_{ij}(1 + \varepsilon 2_{ij})] + \varepsilon 2_{ij}$, where C_{ij} is the observed concentration in serum for the jth individual at time i, C'_{ij} is the model-predicted concentration in serum for the jth individual at time i, and $\varepsilon 1_{ij}$ and $\varepsilon 2_{ij}$ are components of residual error. This design allowed for the model to be additive at low drug concentrations and proportional at higher concentrations. Fits that used models in which residual error was strictly proportional, additive, or exponential were inferior (data not shown).

Model-building procedure. The minimum value of the objective function (−2 × log likelihood) along with plots of weighted residuals versus predicted concentrations in plasma aided in determination of the appropriate pharmacostatistical models for analysis of the data. After the basic model was constructed, additional fixed effects (i.e., patient characteristics or variables) were introduced into the model on the basis of the selection of variables or outcomes of clinical importance and previous observations with nucleoside antiretroviral agents. Absolute values for patient-specific variables such as total body weight or CD4

TABLE 2. Characteristics of 81 patients in population pharmacokinetic analysis of stavudine given p.o.

Characteristic[a]	Value
No. of men/women[b]	71/7
Median age (yr [range])	36 (22–85)
Median total body weight (kg [range])	70 (41–102)
Median lean body weight (kg [range])[c]	70 (30–87)
Risk group (no. of patients)[b]	
IVDU	15
Sexual contact	56
Race (no. of patients)[b]	
White	61
Black	6
Hispanic	9
Disease stage (no. of patients)	
AIDS	26
ARC	50
Unknown	5
Median initial CD4 cell no. (cells/mm^3 [range])	153 (9–580)
Prior zidovudine therapy (no. of patients)	44
GI disease (no. of patients)[d]	16
Tobacco use (no. of patients)	30
Stavudine p.o. dose ≥200 mg (no. of patients)	11
Development of peripheral neuropathy (no. of patients)	34

[a] IVDU, intravenous drug use; GI, gastrointestinal.

[b] Data not available for some patients.

[c] Calculated as 50 kg + 2.3 · (height [in inches] − 60) for men; 5 kg is subtracted from this value for women.

[d] Nonhepatobiliary, noncirrhotic; mainly diarrhea.

TABLE 3. Population pharmacokinetic parameters of stavudine by using a basic model in 81 patients (p.o. data set)

Model parameter	CL/*F* (liters/h)	V_1/F (liters)	V_{ss}/F (liters)	Q/F (liters/h)	K_a (liters/h)	ε1	ε2
Population estimate	30.9	8.42	68.9	12.4	1.32	0.17	0.002
95% CI	28.5, 33.3	4.44, 12.4	44.7, 93.1	6.94, 17.9	1.07, 1.57	0.13, 0.21	0, 0.003
Interpatient variability[a]	24.5	NM[b]	105	26	78.9		
95% CI	17, 30		32, 145	0, 45	63, 92		

[a] CV (in percent).
[b] NM, not modeled.

count (which reflects the degree of disease progression) were included in the model as follows: TVCL = TVCL + $\theta_j \cdot$ TBW, where TVCL is the typical value of CL/*F*, TBW is the total body weight, and θ_j is the factor value for each individual with a known total body weight.

Nominal data describing patient characteristics and categories were fashioned with if-then statements; for example, the effect of oral stavudine doses greater than 200 mg on CL/*F* would be coded as follows: if mg ≥200 then TVCL = TVCL $\cdot \theta_1$, where absolute oral doses of ≥200 mg result in a different estimation of CL/*F* for patients receiving large oral doses.

The criterion for acceptance of a factor into the model was a decrease in the minimum value of the objective function of >3.8 following introduction of a single term (degrees of freedom = 1), and it was considered statistically significant at the 5% ($P < 0.05$) level by using the χ^2 distribution (17, 19). A fixed effect was retained in the model as a weight on a particular variable if the minimum objective function decreased significantly and if the 95% confidence intervals (CIs) for the estimate did not include the null value. If the minimum objective function decreased significantly but the 95% CI for the estimate included the null value, the effect of the variable was considered to be of borderline significance and it was not retained in the final model. Plots of weighted residuals versus predicted concentrations in plasma or variables also guided the selection of fixed effects for inclusion and retention in the model during the model-building procedure.

Single variables that were found to significantly improve the fit of the model to the data were tested together to develop the final model. In order to eliminate covariates, each variable was taken out of the model by setting it equal to its null value. A change in the minimum objective function of >3.8 signified that the variable was important and it was retained in the final model.

RESULTS

The characteristics of the 81 patients included in the analysis are given in Table 2. The population consisted largely of white men in their mid-30s who acquired HIV through homosexual or heterosexual transmission. Most patients had ARC, with the median CD4 cell count being less than 200 cells per mm^3 upon entry into the study. Approximately half of the patients had received previous zidovudine therapy for various intervals. The range of measurable plasma stavudine concentrations ranged between 0.0025 and 7.5 μg/ml.

Basic model. The pharmacokinetic parameter estimates obtained with the basic model are given in Table 3. The CL of stavudine given p.o. was estimated to be ~31 liters/h, with interpatient variability estimated to be 24.5%. The decline in plasma stavudine concentrations as described by a two-compartment model was evident by estimation of a peripheral compartment (represented by $V_{ss}/F - V_1/F$) about sevenfold larger than that of the central compartment. The absorption rate of stavudine given p.o. was typically rapid, with a high estimate for interpatient variability. Interpatient variability (expressed as percent CV) for V_{ss}/F and Q/F were 105 and 26%, respectively. The CV for residual error was estimated to be ~41% for the range of plasma stavudine concentrations measured.

Results of the analysis of data for the subset of 33 patients who received stavudine both i.v. and p.o. (i.v./p.o. data set) are given in Table 4. The estimate of absolute *F* was 99.1%, with an interpatient variability of 18.5% (CV). When all data for the patients who received stavudine by the p.o. and i.v. routes were analyzed together (i.e., levels in plasma of all 81 patients given drug by the i.v. and p.o. routes), the estimate of *F* was similar to this value (data not shown). The estimates of CL and V_{ss} for this subset of patients were similar to those obtained with the full (p.o.) data set. Estimates of V_1 and *Q* (after accounting for *F*) were different for this subset of 33 patients compared with those for all 81 patients, likely because of improved estimation of values for these parameters with the availability of plasma samples collected during the i.v. infusion.

Model building. The patient characteristics and variables (fixed effects) tested individually for inclusion in the model of CL/*F* for the p.o. data set are given in Table 5. The fixed effects found singly to significantly influence the estimates of CL/*F* were p.o. stavudine doses of ≥200 mg, total body weight, a diagnosis of AIDS, receipt of prior zidovudine therapy, and calculated lean body weight. However, the 95% CIs for the magnitude of the effect for the latter two factors included the null value. Models that used different stavudine dose breakpoints (e.g., ≥150 mg) had no effect on estimates of CL. Therefore, only a p.o. stavudine dose of ≥200 mg, total body weight, and a diagnosis of AIDS versus ARC were tested further in the full model.

The fixed effects found to significantly influence the estimates of V_{ss}/F were total body weight and calculated lean body weight. Although statistically significant, the 95% CI for estimates of the magnitude of the effect of lean body weight included the null value (as it did with the CL of drug given p.o.), and therefore it was not included in the full model.

TABLE 4. Population pharmacokinetic parameters for subset of 33 patients who received stavudine both i.v. and p.o. (i.v./p.o. data set)

Model parameter	*F* (% of dose)	CL (liters/h)	V_1 (liters)	V_{ss} (liters)	*Q* (liters/h)	K_a (liters/h)	ε1	ε2
Population estimate	99.1	34.6	23.9	56.1	20.3	2.38	0.13	0.003
95% CI	82.3, 116	28.9, 40.3	18.8, 29.0	47.3, 64.9	16.3, 24.3	1.8, 3.0	0.09, 0.17	0, 0.006
Interpatient variability[a]	18.5	20.6	NM[b]	NM	48	103		
95% CI	1, 36	0, 43			0, 71	31, 175		

[a] CV (in percent).
[b] NM, not modeled.

TABLE 5. Summary of analyses of the effects of single patient variables on stavudine population pharmacokinetic parameters by using the p.o. data set[a]

Hypothesis	Null value	Factor value (95% CI)[b]	Change in MOF[c]	*P* value	Conclusion
Do the following affect CL/*F*?					
High dose[d]	1	1.41 (1.18, 1.64)	−41.17	<0.001	Test in full model
TBW	0	0.17 (0.04, 0.3)	−32.72	<0.001	Test in full model
AIDS	1	1.23 (1.01, 1.45)	−19.47	<0.001	Test in full model
Prior ZDV therapy	1	1.12 (0.9, 1.34)	−7.83	<0.01	Borderline effect
LBM	0	0.05 (−0.03, 0.13)	−6.91	<0.01	Borderline effect
Smoking	1	0.93 (0.74, 1.12)	−3.11	>0.05	No effect
GI disease[e]	1	0.94 (0.54, 1.35)	−1.19	>0.2	No effect
Age	0	0.01 (−0.22, 0.25)	−0.06	>0.3	No effect
Starting CD4 cell no.	1	0.99 (0.75, 1.23)	−0.02	>0.3	No effect
Development of PN	1	0.99 (0.76, 1.22)	−0.12	>0.3	No effect
Do the following affect V_{ss}/F?					
TBW	0	0.689 (0.207, 1.17)	−5.34	<0.05	Test in full model
LBM	0	−0.589 (−1.399, 0.221)	−10.616	<0.01	Borderline effect
Age	0	−0.076 (−0.706, 0.554)	−0.04	>0.3	No effect

[a] MOF, minimum objective function; TBW, total body weight (in kilograms); ZDV, zidovudine; LBM, lean body mass (in kilograms); GI, gastrointestinal; CD4, CD4 cell count (in cells per cubic millimeter); PN, peripheral neuropathy.
[b] When the null value is equal to 1, the factor is a multiplier of CL/*F*; when the null value is equal to 0, the factor is a multiplier on the variable tested.
[c] Relative to basic model.
[d] Dose of ≥200 mg of stavudine given p.o.
[e] Nonhepatobiliary, noncirrhotic; mainly diarrhea.

Final model. The parameter estimates generated in the final model are given in Table 6. The final model included terms for total body weight, stage of HIV infection (AIDS versus ARC), and receipt of a high dose (≥200 mg per dose) of stavudine. Figure 1 shows the plasma stavudine concentrations in a 70-kg patient with AIDS or ARC. Total body weight in the estimation of V_{ss}/F was dropped from the full model because its effect became statistically insignificant when all factors were included in the final model for CL/*F*. When the parameters for high p.o. stavudine doses, total body weight, and AIDS were individually restricted to their null values, significant increases (141, 25, and 13, respectively) in the minimum objective function resulted. Therefore, all three fixed effects were retained within the final model for the CL of stavudine given p.o.: $CL/F = (18.8 + 0.13 \cdot TBW) \cdot (1.2 - stage) \cdot (1.5 - dose)$, where CL/*F* is in liters per hour, TBW is total body weight in kilograms, stage is 0.2 if the patient has ARC and 0 if the patient has AIDS, and dose is 0.5 if the patient ingests a p.o. dose of <200 mg and 0 if the patients ingests a p.o. dose of ≥200 mg. The estimates of V_1/F, V_{ss}/F, Q/F, and K_a and their respective CIs were essentially unchanged from those from the basic model, as were the estimates of interpatient variability. Residual error was also unchanged from that from the basic model. A comparison of the plots of weighted residuals versus predicted plasma stavudine concentrations in the basic and final models showed some improvement for the predicted plasma stavudine concentrations in the higher range (Fig. 2).

DISCUSSION

Therapy of HIV infection with currently available nucleoside antiretroviral agents is frequently frustrated by a high degree of variability between patients in in vivo drug exposure following the administration of fixed doses of drug. This is particularly problematic for zidovudine, for which there may be more than a 10-fold range in the area under the concentration-time curve among patients because of differences in the *F* and CL of the drug (11). The differences in drug exposure may have a marked impact on the observed antiviral effects, as well as the tolerance to drug during therapy (9–11). Therefore, development of newer nucleosides with improved *F* and a low degree of interpatient variability would be desirable in the long-term management of patients with HIV infection.

The present study extends previous observations concerning

TABLE 6. Population pharmacokinetic parameters for 81 patients given stavudine p.o. for final model with p.o. data set

Model parameter	CL/*F* (liters/h)	V_1/F (liters)	V_{ss}/F (liters)	Q/F (liters/h)	K_a (liters/h)	ε1	ε2
Population estimate (95% CI)	[18.8 (11.6, 26) + 0.13 (0.03, 0.24) · TBW] · [1.2 (1.0, 1.38) − stage] · [1.5 (1.12), 1.86) − dose]	8.18 (4.68, 11.7)	70 (44.9, 95.2)	13.1 (7.7, 18.5)	1.35 (1.13, 1.57)	0.17 (0.13, 0.21)	0.002 (0, 0.003)
Interpatient variability[b]	20	NM[c]	89	30	82		
95% CI	11, 25		24, 123	0, 46	67, 94		

[a] $CL/F = [18.8 + 0.13 \cdot TBW] \cdot [1.2 - stage] \cdot [1.5 - dose]$, where TBW is total body weight, stage is equal to 0.2 if the patient has ARC and 0 if the patient has AIDS, and dose is equal to 0.5 if the patient ingests p.o. dose of <200 mg and 0 if the patient ingests ≥200 mg.
[b] CV (in percent).
[c] NM, not modeled.

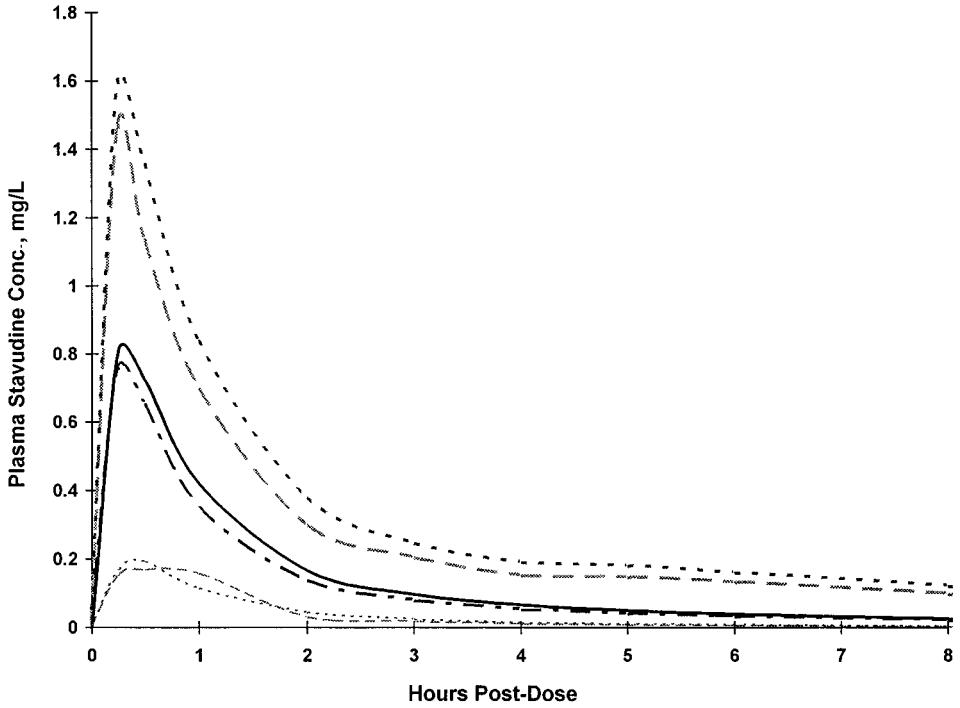

FIG. 1. Simulated plasma stavudine concentration-versus-time curves for a 70-kg patient with ARC or AIDS receiving a 40-mg dose of oral stavudine. Curves were derived from a simulation with 100 patients by using the population values of the pharmacokinetic parameters from the final model and their estimated variances and covariances (i.e., lower triangle of the covariance matrix). Bold lines indicate mean levels in plasma at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h postdose from the simulation for patients with AIDS (— - — -) or ARC (——). The corresponding upper and lower 95% CIs for stavudine levels in the plasma of patients with AIDS (dashed lines) or ARC (dotted lines) are also shown.

the pharmacokinetics of stavudine in patients with HIV infection. The estimate for typical systemic *F* of stavudine in 33 patients was nearly 100%. A previous estimate of *F* in six patients receiving 4-mg/kg oral doses (data for these patients were also included in this population analysis) averaged 82% (12). Since i.v. and p.o. dose studies were performed on different days, drug CL is assumed to be stable over the period of study to allow for an estimation of *F*; changes in drug CL between days would result in erroneous values for drug *F*. Previous comparisons of stavudine pharmacokinetic parameters following administration of the first and multiple p.o. doses showed no changes in the CL of drug given p.o. (12). However, since the i.v./p.o. data set comprised all pharmacokinetic data after p.o. administration (i.e., first and steady-state study doses) as well as pharmacokinetic data after i.v. administration for these patients, we also estimated the *F* of stavudine for these 33 patients using pharmacokinetic data from the first p.o. and i.v. doses only; since these studies were done within 1 day of each other, the possibility of changes in drug CL between days would be highly remote. The estimate of *F* with this stripped i.v./p.o. data set was still approximately 100% (data not shown).

This analysis identified patient characteristics associated with the population estimate of CL of drug given p.o. Information on total body weight, the diagnosis of AIDS (versus ARC), and p.o. stavudine doses of $\geq$200 mg statistically improved the population model for CL/*F* (see final model). The increase in stavudine CL/*F* with the higher dose is consistent with trends reported previously and suggests a slightly lower *F* of drug given p.o. at higher doses. Reduction in the *F* values of certain nucleosides given p.o. has previously been attributed to saturation of carrier-mediated transport of drug across the gastrointestinal mucosa (10, 11, 15).

Although inclusion of some fixed effects resulted in a statistically significant improvement in the model, it appears that some of these associations are of limited clinical significance. The change in the CL of stavudine given p.o. with higher doses is of limited clinical importance since dose-limiting peripheral neuropathy precludes the use of daily exposures associated with this dose, and lower doses have been shown to have acceptable tolerance with clinical benefit (20). The difference in CL/*F* between patients with AIDS and those with ARC was small. As shown in Fig. 1, there is much overlap between the serum stavudine concentrations was for typical patients with either AIDS or ARC. Similarly, the effect that total body weight had on stavudine CL/*F* was of small magnitude; only a 15% variation in the base value of the CL of drug given p.o. (calculated by using the median total body weight of 70 kg for the 81 patients) occurred for the upper and lower extremes of the total body weight in patients enrolled in these studies. These data suggest that stavudine doses do not need to be adjusted for total body weight in adult patients weighing between 40 and 100 kg. However, in patients with AIDS with a combination of extreme values in body weight, dose individualization may be required to achieve maximal antiviral effects.

This analysis represents one of the most comprehensive evaluations of the pharmacokinetics of an antiretroviral agent in target populations prior to widespread use of the drug. The results show that intersubject variability in the major pharmacokinetic parameters for stavudine that influence systemic exposure (i.e., CL of drug given p.o. and the area under the concentration-time curve) is low. Low variability in CL/*F* between patients suggests that dose is an acceptable controller for exposure to stavudine in vivo. Further studies to evaluate stavudine pharmacokinetics over more prolonged periods of therapy are in progress.

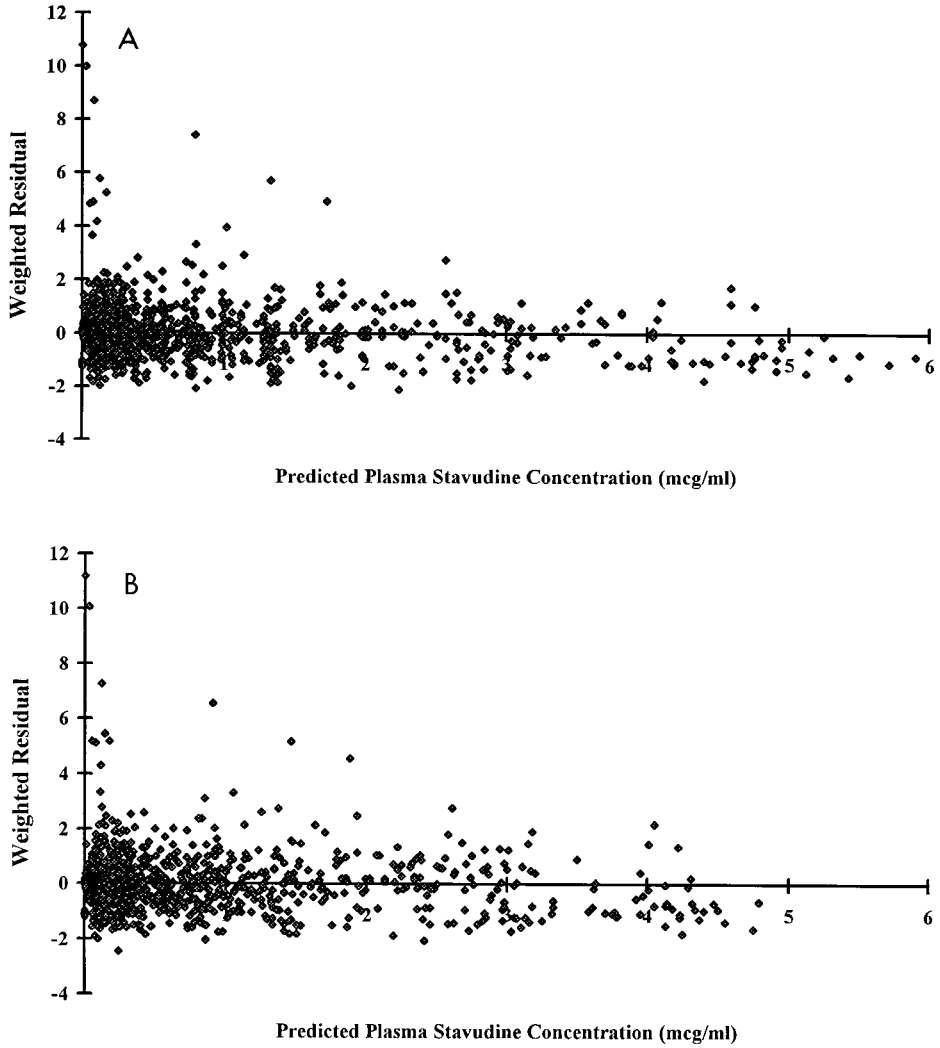

FIG. 2. Scatter plots of weighted residuals versus predicted plasma stavudine concentrations: comparison of basic (A) and final (B) models. The final full model improved the fit of the higher predicted concentrations of stavudine.

ACKNOWLEDGMENTS

We thank Alison Boeckmann of the NONMEM Project Group and Don DiCristoforo for computer assistance and Michael Brown, Mary Ann Messina, and Lisa Pacelli for assistance with the clinical data.

This study was supported in part by a grant from Bristol-Myers Squibb, Wallingford, Conn.

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