

Determination of Dosing Guidelines for Stavudine (2',3'-Didehydro-3'-Deoxythymidine) in Children with Human Immunodeficiency Virus Infection

SANJEEV KAUL,^{1*} MARK W. KLINE,² JOSEPH A. CHURCH,³ AND LISA M. DUNKLE^{1†}

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey¹; Texas Children's Hospital, Baylor College of Medicine, Houston, Texas²; and Childrens Hospital Los Angeles, University of Southern California, Los Angeles, California³

Received 22 September 1999/Returned for modification 23 January 2000/Accepted 29 November 2000

The results of the development of dosing guidelines for stavudine in human immunodeficiency virus (HIV)-infected children are summarized. Included in the integrated analyses were 21 and 33 HIV-infected pediatric and adult patients, respectively, from three phase I-II studies. Data for 21 children and 18 adults who received intravenous doses of 0.125 to 2 and 0.5 to 1 mg/kg of body weight, respectively, were used for the determination of dosing guidelines; exposure data for 16 children and 15 adults who received oral doses of 1 to 2 and 0.5 to 1 mg/kg/day, respectively, were used to validate the dosing recommendations for children. Significant relationships were observed between total body clearance (in milliliters per minute) in children and adults combined and demographic parameters of age, body weight, and body surface area ($R^2 = 0.77$ to 0.80 ; $P = 0.0001$). Models of approximated pediatric dose based on clearance values and direct adult exposure yielded a stavudine dosage of 2 mg/kg/day for children of ≤ 30 kg of body weight and 1 mg/kg/day (adult dose) for children of >30 kg of body weight.

Stavudine is a nucleoside analog reverse transcriptase inhibitor that is currently recommended as a first-line option in triple-drug combinations intended to produce maximal suppression of the viral load in individuals with human immunodeficiency virus (HIV) infection (2). Initial investigations of stavudine monotherapy for pediatric HIV infection indicated that the agent was safe, well tolerated, and associated with clinical and immunologic benefits at least equivalent to those observed with zidovudine monotherapy (16, 17). Current recommendations for treatment of pediatric HIV disease favor the use of potent and aggressive combination therapy to maximally reduce the viral burden (3).

Several clinical studies with HIV-infected adults have investigated the pharmacokinetics and demonstrated the *in vivo* activity of stavudine against HIV. Stavudine exhibits linear pharmacokinetics following oral administration, it is rapidly absorbed with an absolute bioavailability of 82 to 99%, renal elimination of unchanged drug accounts for about 40% of the administered dose, and there is no significant accumulation of stavudine with a repeated twice-daily dosing regimen (5, 12, 24).

Three dose-ranging phase I trials that evaluated stavudine dosages of 0.5 to 12.0 mg/kg of body weight/day demonstrated that stavudine was well tolerated at doses below 4.0 mg/kg/day but that unacceptably higher rates of peripheral neuropathy were observed at higher doses (1, 22, 28).

These trials supported a phase II trial of stavudine with dosages of 0.5 to 2.0 mg/kg/day. Results from the phase II study suggested that the most favorable therapeutic index was seen at 0.5 mg/kg/day when that dosage was compared to dosages of 0.1 and 2.0 mg/kg/day (23). However, two studies that directly compared 20 and 40 mg twice daily (0.5 and 1.0 mg/kg/day, respectively) found no significant differences between the two dose groups in terms of increases in CD4⁺-cell counts and lower HIV RNA levels and comparable survival rates. The higher dose was associated with greater body weight gain, improved hematological findings, and fewer hospitalizations (18). Finally, a phase III trial demonstrated that the 1.0-mg/kg/day dose of stavudine was well tolerated and delayed progression of HIV disease in patients who had previously received zidovudine treatment for 6 or more months (29).

In a pediatric study, oral stavudine has been shown to exhibit consistent and predictable pharmacokinetics over a dose range of 0.125 to 4 mg/kg/day, with an absence of dose-related adverse events and variable central nervous system penetration (16). Dose-related adverse events have been reported in the adult population (1, 18, 22, 23, 28).

Objective. The phase I study described here was designed in part to assess the intravenous pharmacokinetics and the safety, anti-HIV activity, and pharmacokinetics of orally administered stavudine when given at doses that range from 0.125 to 4.0 mg/kg. The results of this primary objective were reported previously (16). A secondary objective was to identify a suitable recommended dosage of stavudine for children by comparing the pharmacokinetic results obtained in the study with values predicted on the basis of data from studies with adults and on the developmental metrics of age, body weight (BWT), and body surface area (BSA). Summarized here are the results

* Corresponding author. Mailing address: Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000. Phone: (609) 252-5124. Fax: (609) 252-7035. E-mail: sanjeev.kaul@bms.com.

† Present address: Achillion Pharmaceuticals, New Haven, CT 06511.

TABLE 1. Demographic characteristics of patients

Patient population	No. of patients		Age (yr) ^a	BWT (kg) ^a	HT (cm) ^{a,b}	BSA (m ²) ^a
	Males	Females				
Children ^c	13	8	5.8 (0.1–15.0)	19.3 (2.1–43.4)	104.2 (44.0–151.2)	0.73 (0.16–1.29)
Adults ^d	33		38 (31–46)	72 (53–89)	178 (166–191)	1.89 (1.66–2.12)

^a Values are means (ranges).

^b HT, height.

^c Intravenous pharmacokinetic data were obtained for 21 patients, 16 of which provided oral pharmacokinetic data.

^d Intravenous pharmacokinetic data were obtained from 18 patients, and a separate cohort of 15 patients provided oral pharmacokinetic data

of the investigation used to develop dosing guidelines for stavudine in HIV-infected children.

MATERIALS AND METHODS

Design. Phase I-II studies evaluating the pharmacokinetics of stavudine in HIV-infected adults and children have previously been described in detail (1, 5, 12, 16; S. Kaul, K. A. Dandekar, K. A. Pittman, H. Murray, and W. Weiss, Program abstr. VIth Int. Conf. AIDS, abstr. S.B. 455, 1990). The clinical trial with children was a randomized study, whereas the two trials with adult patient populations were nonrandomized studies. Data for children who received 60-min intravenous infusion doses of 0.125, 0.5, 1, and 2 mg/kg and from adults who received 60-min intravenous infusion doses of 0.5, 0.75, and 1 mg/kg were used for the determination of dosing guidelines. For the validation of the dosing guidelines, exposure data for children who received oral doses of 1 and 2 mg/kg/day and for adults who received 0.5 and 1 mg/kg/day were used. The oral dose of stavudine was administered as two equally divided doses 12 h apart (twice-daily regimen).

Patients. Eligible patients were required to have documented HIV infection with no acute opportunistic infection, no intractable diarrhea, no grade 1 or greater peripheral neuropathic symptoms, and no clinically significant laboratory values at the time of enrollment. Patients were required to have received no prior treatment with zidovudine, they could not have been treated with didanosine or zalcitabine within 3 months prior to enrollment, nor could they have received any agents known to have been potent inducers of drug-metabolizing enzymes within 2 weeks prior to enrollment. Patients were furthermore excluded if they had had previous myelosuppressive, neurotoxic, or cytotoxic anticancer therapy within 3 months prior to enrollment or if they were expected to require such therapy. Patients were required to have normal serum creatinine or creatinine clearance values and were required not to take drugs that would affect renal tubular secretion. Adults had performance status of at least 60% on the Karnofsky scale and entry CD4-cell counts of ≤ 500 cells/ml.

Pharmacokinetic study procedures. After dose administration, 10 to 13 blood samples were collected over an 8- and/or 24-h period and plasma samples were analyzed for intact stavudine by validated high-performance liquid chromatography (HPLC) or radioimmunoassay (RIA) methods (13, 14). The lower limits of quantitation of the HPLC and RIA methods were 25 and 2.5 ng/ml, respectively. The plasma concentration-time data were analyzed by using a noncompartmental method (7, 25). The following pharmacokinetic parameters were used in the current analyses: total body clearance (CL), steady-state volume of distribution (V_{SS}), elimination half-life ($t_{1/2}$), maximal concentration in plasma (C_{max}), the area under the curve (AUC) extrapolated to infinity after administration of the first oral dose ($AUC_{0-\infty}$), and AUC over a dosing interval of 12 h after the administration of multiple doses (AUC_{τ}).

Determination of dosing guidelines. The following methodology was used as a means to predict appropriate dosing guidelines for pediatric patients. Pediatric

patients were categorized as being either adolescents, children, or infants according to the classification of Skaer (27). (i) Fiftieth percentile values of BWT (in kilograms) and BSA (in square meters) were obtained from standard growth tables and charts (9) for each age from 3 months to 18 years. BSA values were calculated from weight and height by the method of Dubois and Dubois (4). (ii) The relationship between the CL (in milliliters per minute) of stavudine and the demographic characteristics of age, BWT, and BSA were determined by using simple linear regression. In these analyses, BWT was used instead of ideal or lean body weight because none of the patients were overweight. (iii) These linear regression equations were used to calculate the predicted CL for children (CL_{C-P}) and adults (CL_{A-P}) on the basis of age, BWT, and BSA. CL_{A-P} reference values were used by assuming the following constant values: BWT of 60 kg and BSA of 1.69 m². The latter was calculated by the method proposed by Freireich et al. (6). (iv) CL_{C-P} values were used to calculate the predicted total daily dosage for children (TDD_{C-P} ; in milligrams per day) required for each age by the following formula: $TDD_{C-P} = TDD_A \times (CL_{C-P}/CL_{A-P})$, where TDD_A is the total daily dosage for adults (a constant value of 80 mg for body weight ≥ 60 kg) (20). TDD_{C-P} values were calculated according to each of the dependent variables of age, BWT, and BSA. (v) Finally, TDD_{C-P} values were divided by the 50th percentile BWT for a given age to determine the recommended dose (in milligrams per kilogram per day) for that age on the basis of the associated dependent variable of age, BWT, or BSA.

Statistical methods. A one-way analysis of variance model was used to evaluate comparisons based on sex (26). The intravenous parameters evaluated were CL, V_{SS} , and $t_{1/2}$. Such an analysis was permissible because the demographics by sex were reasonably comparable (age for males, 0.1 to 15.0 years; age for females, 0.6 to 12.4 years; BWT for males, 2.1 to 39.2 kg; BWT for females, 6.7 to 43.4 kg; BSA for males, 0.16 to 1.27 m²; BSA for females, 0.34 to 1.29 m²). A significance level of P equal to 0.05 was used for all hypothesis testing.

RESULTS

Demographics and patient disposition. Data for 21 HIV-infected children and 33 HIV-infected adults were used in this evaluation. For children, intravenous pharmacokinetic data were obtained for 21 patients (doses of 0.125 [$n = 1$], 0.5 [$n = 8$], 1 [$n = 6$], and 2 [$n = 6$] mg/kg), 16 (doses of 0.5 [$n = 8$] and 1 [$n = 8$] mg/kg) of which also provided oral pharmacokinetic data. Intravenous and oral pharmacokinetic data were obtained from two separate cohorts of 18 (doses of 0.5 [$n = 7$], 0.75 [$n = 5$], and 1 [$n = 6$] mg/kg) and 15 (doses of 0.25 [$n = 5$] and 0.5 [$n = 10$] mg/kg) adult patients, respectively. Demographic data for the patients are shown in Table 1. There were

TABLE 2. Intravenous pharmacokinetics of stavudine in pediatric and adult patients^a

Patient group	CL			V_{SS}			$t_{1/2}$ (4)
	ml/min	ml/min/kg	ml/min/m ²	liters	liter/kg	liter/m ²	
Children ($n = 21$)	188.0 (189.1 \pm 115.5)	10.3 (9.92 \pm 3.71)	265.3 (246.9 \pm 94.6)	14.80 (14.34 \pm 10.88)	0.70 (0.74 \pm 0.33)	18.89 (18.49 \pm 9.19)	1.09 (1.11 \pm 0.28)
Adults ($n = 18$)	570.0 (602.0 \pm 140.6)	8.36 (8.46 \pm 2.16)	321.9 (319.9 \pm 77.7)	39.00 (43.89 \pm 16.32)	0.55 (0.60 \pm 0.17)	20.75 (23.04 \pm 7.60)	1.04 (1.13 \pm 0.41)

^a The data are medians, with means and standard deviations in parentheses.

TABLE 3. Relationships of CL and V_{SS} with demographic data

Dependent variable	Equation	R^2	P	No. of patients
BWT (kg) ^a	$BWT = 0.62 \cdot BWT_{50\%} + 6.35$	0.96	0.0001	21
BSA (m ²) ^a	$BSA = 0.82 \cdot BSA_{50\%} + 0.07$	0.99	0.0001	21
CL (ml/min) ^b	$CLT = 12.89 \cdot AGE + 114.3$	0.77	0.0001	39
	$CLT = 7.58 \cdot BWT + 45.7$	0.80	0.0001	39
	$CLT = 339.1 \cdot BSA - 52.3$	0.79	0.0001	39

^a Relationship derived for children only.

^b Relationship derived by using CL values for children ($n = 21$) and adults ($n = 18$) and used in the determination of dosing guidelines.

3 infants, 14 children, and 4 adolescents. The ages of the infants, children, and adolescents ranged from 0.1 to 0.8, 1.1 to 10.4, and 12.4 to 15.0 years, respectively; BWTs ranged from 2.1 to 10.2, 9.6 to 23.9, and 37.0 to 43.4 kg, respectively; heights ranged from 44.0 to 72.5, 73.2 to 131.5, and 145.9 to 151.2 cm, respectively; and BSAs ranged from 0.16 to 0.43, 0.42 to 0.95, and 1.27 to 1.29 m², respectively. The pediatric sample was 38% female. As is the case with reported epidemiological data (2), the predominant HIV risk factor was perinatal transmission (80%), with blood transfusion due to hemophilia or other injury or disease accounting for the remainder of the cases. Eighty-nine percent of the adults had homosexual or bisexual activity as a risk factor, and 11% were intravenous drug users.

Pharmacokinetic results. There were no statistically significant differences in CL, V_{SS} , and $t_{1/2}$ between male and female pediatric patients ($P > 0.05$). The key intravenous pharmacokinetic parameters for stavudine by patient population are summarized in Table 2. As expected, significant relationships (Table 3 and Fig. 1) were observed between CL in children and adults combined (as expressed in milliliters per minute) and demographic parameters of age ($R^2 = 0.77$; $P < 0.05$), BWT ($R^2 = 0.80$; $P < 0.05$), and BSA ($R^2 = 0.79$; $P < 0.05$). Predicted CL (in milliliters per minute per kilogram) decreased with increasing body weight (in kilograms) in pediatric patients, as shown in Fig. 2. At body weights greater than 30 kg, predicted CL appeared to level off, suggesting that dosage

recommendation in pediatric patients with BWTs of >30 kg may be similar to the clinically recommended dose for adult patients.

Determination of dosing guidelines. As expected, significant relationships were observed between BWT and age and between BSA and age for the pediatric patients (data not shown). When the BWT and BSA values for the HIV-infected children enrolled in this study were independently submitted to linear regressions with the corresponding measures obtained from the 50th percentiles of growth charts ($BWT_{50\%}$ and $BSA_{50\%}$), the values were highly correlated ($R^2 \geq 0.96$). However, the slopes of the linear regression lines deviated from the line of identity by -38 and -18% , respectively (Table 2). This observation is in line with the expectation that HIV-infected pediatric patients will tend to have lower than average BWTs and, correspondingly, lower than average BSAs. The model calculated as a means of approximating the appropriate dosing guideline for children, which was based on the estimated CL and the corresponding stavudine doses when age, BWT, or BSA was used as an independent variable, is shown in Table 4. It is evident from Table 4 that within the age range estimated, younger children require a larger dose (in milligrams per kilogram per day) of stavudine in order to achieve exposures that are equivalent to the exposures observed in adults following administration of the recommended dosage of 1.0 mg/kg/day (i.e., 80 mg/day for a 60-kg adult), which has been proven to

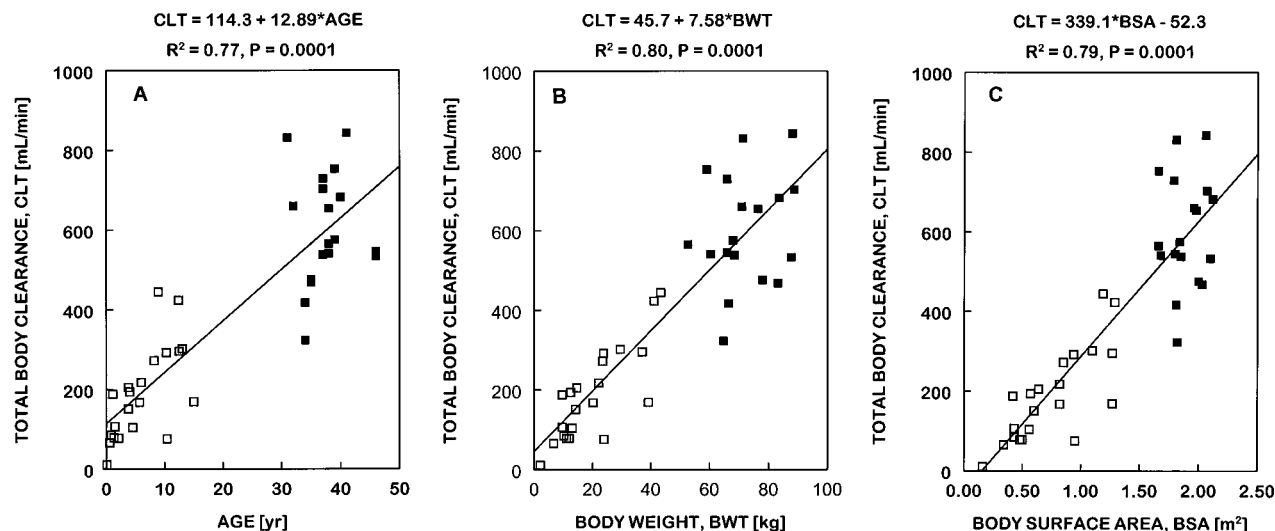


FIG. 1. Scattergrams showing stavudine clearance as a function of age (A), BWT (B), and BSA (C) for pediatric (\square) and adult (\blacksquare) patients with HIV infection. The solid lines are the linear regression lines. The correlations between CL and age, BWT, and BSA are statistically significant.

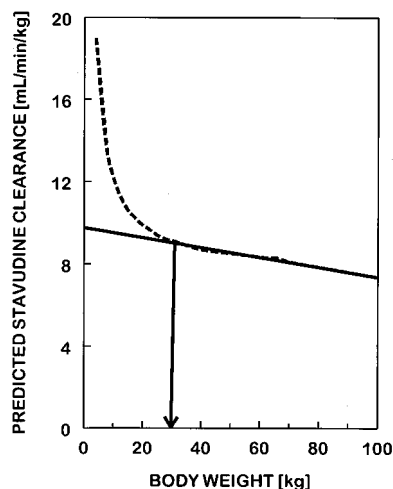


FIG. 2. Relationship between predicted stavudine CL and BWT in HIV-infected pediatric patients. The dashed line represents the predicted CL values, and the solid line is the linear regression line of the terminal datum points. The arrow represents the body weight of 30 kg, where the two curves appear to diverge.

offer clinical benefit in HIV-infected adult patients. The data in Table 4 suggest that children with body weights of ≤ 30 kg should be given 2 mg/kg/day (twice-daily regimen); for children with body weights of >30 kg, the daily adult dose (60 mg/day

for body weights of <60 kg and 80 mg/day for body weights of ≥ 60 kg) is recommended.

Comparison of pediatric and adult pharmacokinetics after oral administration. In order to validate the dosing guideline recommendation for HIV-infected children, the exposures observed in HIV-infected children after oral administration of stavudine were compared to those observed in HIV-infected adults. The exposures to stavudine in pediatric patients at the 1.0- and 2.0-mg/kg/day dose levels were comparable to those in adults given doses of 0.5 and 1.0 mg/kg/day (Table 5).

DISCUSSION

The pharmacokinetic properties of stavudine appear to be comparable in HIV-infected pediatric and adult patients. However, the bioavailability of stavudine in children (61 to 78%) (16) is slightly lower than that in adults (82 to 99%) (5, 12). When CL was independently subjected to linear regression analysis with demographic parameters of age, BWT, and BSA, significant relationships were observed, which were expected or anticipated. When the measure of predicted CL was adjusted for BWT, a nonlinear relationship emerged. A previous investigation (12) reported that for patients with BWTs of between 40 and 100 kg, a small component of stavudine clearance was related to BWT.

Selection of a correct dose for children is a process fraught with variability, both interindividual variability within a given age and intraindividual variability across ages, with significant

TABLE 4. Age, BWT, BSA, CL, and stavudine doses in the pediatric population

Patient group	Age (yr)	BWT (kg) ^a	BSA (m ²) ^b	CL (ml/min) ^c			Stavudine dose						Median dose	
				Age	BWT	BSA	mg/day ^d			mg/kg/day			mg/kg/day	mg/m ² /day
							Age	BWT	BSA	Age	BWT	BSA		
Adult ^e		≥ 60	1.69	372	501	521	80	80	80	1.3	1.3	1.31	1.3	47
Adolescent	18	70	1.85	346	569	575	74	91	88	1.1	1.3	1.3	1.3	48
	17	66	1.81	333	546	561	72	87	86	1.1	1.3	1.3	1.3	48
	16	62	1.75	321	516	541	69	82	83	1.1	1.3	1.3	1.3	47
	15	57	1.65	308	478	507	66	76	78	1.2	1.3	1.4	1.3	46
	14	51	1.53	295	432	467	63	69	72	1.2	1.4	1.4	1.4	45
	13	45	1.41	282	387	426	61	62	65	1.4	1.4	1.4	1.4	44
Child	12	40	1.30	269	349	389	58	56	60	1.5	1.4	1.5	1.5	45
	11	35	1.19	256	311	351	55	50	54	1.6	1.4	1.5	1.5	45
	10	31	1.11	243	281	324	52	45	50	1.7	1.4	1.6	1.6	45
	9	28	1.04	230	258	300	49	41	46	1.7	1.5	1.6	1.6	44
	8	25	0.95	217	235	270	47	38	41	1.9	1.5	1.7	1.7	44
	7	23	0.89	205	220	249	44	35	38	1.9	1.5	1.7	1.7	43
	6	21	0.82	192	205	226	41	33	35	2.0	1.6	1.7	1.7	43
	5	19	0.76	179	190	205	38	30	31	2.0	1.6	1.7	1.7	42
	4	17	0.69	166	175	182	36	28	28	2.1	1.6	1.6	1.6	41
	3	15	0.62	153	159	158	33	25	24	2.2	1.7	1.6	1.7	40
2	12	0.53	140	137	127	30	22	20	2.5	1.8	1.6	1.8	42	
Infant	1	10	0.44	127	122	97	27	19	15	2.7	1.9	1.5	1.9	43
	0.5	8	0.37	121	106	73	26	17	11	3.3	2.1	1.4	2.1	46
	0.25	4	0.26	118	76	36	25	12	6	6.3	3.0	1.5	3.0	46

^a The 50th percentile BWT for children from growth tables (9).

^b BSA was calculated from the 50th percentile weight and height.

^c Predicted from the relationships given in Table 3.

^d Stavudine dose predicted by the equation $TTD_{C-P} = TDD_A \times (CLT_{C-P}/CLT_{A-P})$; see text for details.

^e The stavudine dosage recommendation for an adult was obtained from reference 20.

TABLE 5. Pharmacokinetics of stavudine in pediatric and adult patients with HIV infection following oral administration of various doses^a

Patient population	Total dose [mg/kg/day] (regimen)	Single dose			
		C _{max} (ng/ml)	AUC _{0-∞} (ng · h/ml)	CL/F ^b (ml/min)	t _{1/2} (h)
Children	1.0 (0.5 mg/kg)	333 [353 ± 104] (n = 8)	671 [642 ± 231] (n = 8)	181 [196 ± 103] (n = 8)	0.90 [0.90 ± 0.28] (n = 8)
	2.0 (1.0 mg/kg)	692 [743 ± 146] (n = 5 ^c)	1,063 [1,270 ± 467] (n = 5)	258 [265 ± 83] (n = 5)	0.96 [0.96 ± 0.16] (n = 5)
Adults	0.5 (0.25 mg/kg)	414 [385 ± 140] (n = 5)	484 [472 ± 52] (n = 5)	689 [714 ± 86] (n = 5)	1.28 [1.24 ± 0.17] (n = 5)
	1.0 (0.5 mg/kg)	771 [720 ± 324] (n = 9 ^d)	1,201 [1,073 ± 414] (n = 9)	555 [659 ± 326] (n = 9)	1.39 [1.33 ± 0.40] (n = 9)

^a The data are medians, with means and standard deviations in brackets. Single-dose pharmacokinetic parameters were derived after administration of the first oral dose; steady-state pharmacokinetic parameters were derived for adults after at least 6 days of oral dosing and for children after at least 12 weeks of dosing. *n*, number of patients.

^b *F*, bioavailability.

^c Data were not available for three patients.

^d Data were not available for one patient.

sources of variability arising from growth and development, concomitant pathophysiology, and other therapeutic regimens (15). Of the several independent variables that have been used to determine an appropriate drug dosage in children (age, BSA, BWT), drugs have generally been prescribed on the basis of BWT (drugs with wide therapeutic windows) or, to a lesser extent, BSA (drugs with narrow therapeutic windows) (19). In most cases, BWT is appropriate to height and so should very closely match measures of BSA; therefore, in most cases it is appropriate to use BWT as the independent variable of choice to estimate an appropriate drug dosage when one is administering drugs that do not possess a narrow therapeutic window. BWT scaling principles have also been recommended for calculation of dosages for children (30).

For stavudine, the determination of dosing guidelines for pediatric patients was based on the goal of achieving an exposure (i.e., AUC) in children equivalent to that achieved in adults receiving a dose with proven efficacy. Since CL relates dose to exposure, our strategy involved correlation of CL to age, BWT, and BSA, followed by prediction of the dose for a child by using the estimated 50th percentile of BWT and BSA at a given age for healthy children. Use of the predicted CL for a child based on age, BWT, and BSA resulted in three values for a dose, the median value of which was selected as the appropriate dose for a given BWT. This approach gave equal weights to the contributions of the three demographic parameters to dose calculation and an unbiased selection of stavudine dose at a given BWT. CL after intravenous administration was used in these estimations in order to avoid confounding due to variability in the extent of absorption. For convenience in clinical practice, the dose estimated for children was in milligrams per kilogram per day; the dose in milligrams per square meter per day was used to ascertain further whether a child would be under- or overdosed.

In this study, the method of estimating an appropriate dose to achieve an equivalent drug exposure (i.e., AUC) compared with that from a 1.0-mg/kg/day regimen in a 60-kg adult demonstrated that children require a higher dosage, typically twice the adult dosage, to achieve equal exposure to stavudine. This is similar to the case for lamivudine, a compound that is primarily renally eliminated with an age-dependent CL (20). Accordingly, on the basis of these predictions and on the basis of a comparison of the actual results for identical dose regimens, the appropriate dose regimen for children of ≤ 30 kg of body

weight is proposed to be 2.0 mg/kg/day; for children whose body weights are >30 kg, the daily adult dose (60 mg/day for those with body weights of <60 kg and 80 mg/day for those with body weights of ≥ 60 kg) is recommended.

When one is dosing pediatric patients with stavudine, the following should be kept in mind. (i) The pediatric powder for oral solution formulation is bioequivalent to the capsule formulation (unpublished data, Bristol-Myers Squibb Company). Therefore, the recommended doses for children are easily achievable by using either of the formulations. (ii) Stavudine distributes in total body water (24). Since total body water correlates very well with lean body mass (or weight) (21), the dosages of stavudine in obese children should be based on lean body weight. In cachectic patients, the dosage of stavudine should be based on the actual BWT of the pediatric patient. (iii) The dosing guidelines for female children are similar to those for male children since there are no sex differences in the pharmacokinetics of stavudine. (iv) Stavudine pharmacokinetics were investigated in only three children who were <1 year of age. Therefore, the data are not sufficient to make definitive recommendations for pediatric patients in this age range. Stavudine CL is dependent on renal and nonrenal mechanisms, but only renal impairment is associated with significant alterations in stavudine CL (18). Since kidney function displays age-dependent increases in functional capacity and approaches the values for adults by 3 to 12 months of life (8, 11), dosing in newborns and infants ages <1 year should account for reduced renal CL in early life.

The nucleoside reverse transcriptase inhibitors are prodrugs, for their active moieties, the triphosphates, are believed to be active against HIV (10). Therefore, doses and/or systemic exposure to the parent compound do not necessarily take into consideration the importance of the cellular metabolism that more directly reflects the pharmacological effects of this class of drugs. The *in vitro* formation of intracellular stavudine triphosphate shows a good dose-response with respect to extracellular concentrations of the drug (10). The latter suggests that the intracellular concentrations of stavudine triphosphate may be easily and predictably modulated by extracellular exposure to stavudine.

In conclusion, the study of the pharmacokinetics of stavudine described here and the prospective identification of appropriate dosing guidelines for children infected with HIV demonstrated that children eliminate stavudine more quickly

TABLE 5—Continued

Steady state			
C_{max} (ng/ml)	AUC_{τ} (ng · h/ml)	CL/F (ml/min)	$t_{1/2}$ (h)
385 [424 ± 189] ($n = 8$)	672 [631 ± 237] ($n = 8$)	176 [198 ± 109] ($n = 8$)	1.07 [1.10 ± 0.23] ($n = 8$)
845 [956 ± 612] ($n = 8$)	1,436 [1,439 ± 521] ($n = 8$)	212 [233 ± 109] ($n = 8$)	1.04 [1.06 ± 0.16] ($n = 8$)
356 [310 ± 92] ($n = 4^d$)	538 [565 ± 103] ($n = 4$)	620 [604 ± 99] ($n = 4$)	1.07 [1.27 ± 0.54] ($n = 4$)
689 [857 ± 606] ($n = 10$)	1,194 [1,173 ± 370] ($n = 10$)	539 [574 ± 150] ($n = 10$)	1.32 [1.45 ± 0.44] ($n = 10$)

than adults and, consequently, require a higher dose to achieve drug exposures equivalent to those achieved in adults. Accordingly, it is recommended that in order to achieve exposure levels in children of ≤ 30 kg of body weight that are consistent with the clinically effective dose level of 1.0 mg/kg/day administered to adults (with a maximum of 80 mg/day), it is necessary to administer a stavudine dose of 2.0 mg/kg/day; the dose for children of >30 kg of body weight is 60 mg/day (with a maximum of 80 mg/day), the clinically recommended adult dose.

REFERENCES

- Browne, M. J., K. H. Mayer, S. B. Chafee, M. N. Dudley, M. R. Posner, S. M. Steinberg, K. K. Graham, S. M. Geletko, S. H. Zinner, and S. L. Denman. 1993. 2',3'-didehydro-3'-deoxythymidine (d4T) in patients with AIDS or AIDS-related complex: a phase I trial. *J. Infect. Dis.* **167**:21–29.
- Carpenter, C. C., M. A. Fischl, S. M. Hammer, M. S. Hirsch, D. M. Jacobsen, D. A. Katzenstein, J. S. Montaner, D. D. Richman, M. S. Saag, R. T. Schooley, M. A. Thompson, S. Vella, P. G. Yeni, and P. A. Volberding. 1997. Antiretroviral therapy for HIV infection in 1997: updated recommendations of the International AIDS Society—USA Panel. *JAMA* **277**:1962–1969.
- Centers for Disease Control and Prevention. 1998. Guidelines for the use of antiretroviral agents in pediatric HIV infection. *Morb. Mortal. Wkly. Rep.* **47**(RR-4):1–43.
- DuBois, D., and E. F. DuBois. 1916. A formula to estimate the approximate surface area if height and weight be known. *Arch. Intern. Med.* **17**:863–871.
- Dudley, M. N., K. K. Graham, S. Kaul, S. Geletko, L. Dunkle, M. Browne, and K. Mayer. 1992. Pharmacokinetics of stavudine in patients with AIDS or AIDS-related complex. *J. Infect. Dis.* **166**:480–485.
- Freireich, E. J., E. A. Gehan, D. P. Rall, L. H. Schmidt, and H. E. Skipper. 1966. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chemother. Rep.* **50**:219–244.
- Gibaldi, M., and D. Perrier. 1982. Noncompartmental analysis based on statistical moment theory, p. 409–416. *In* Pharmacokinetics, 2nd ed. Marcel Dekker, New York, N.Y.
- Gladtko, E. 1979. The importance of pharmacokinetics for pediatrics. *Eur. J. Pediatr.* **131**:85–91.
- Hamill, P. V., T. A. Drizd, C. L. Johnson, R. B. Reed, A. F. Roche, and W. M. Moore. 1979. Physical growth: National Cancer Center for Health Statistics percentiles. *Am. J. Clin. Nutr.* **32**:607–629.
- Hitchcock, M. J. M. 1991. 2',3'-Didehydro-2', 3'-dideoxythymidine (D4T), an anti-HIV agent. *Antivir. Chem. Chemother.* **2**:125–132.
- Hook, J. B., and M. D. Baillie. 1979. Perinatal renal pharmacology. *Annu. Rev. Pharmacol. Toxicol.* **19**:607–629.
- Horton, C. M., M. N. Dudley, S. Kaul, K. H. Mayer, K. Squires, L. Dunkle, and R. Anderson. 1995. Population pharmacokinetics of stavudine (d4T) in patients with AIDS or advanced AIDS-related complex. *Antimicrob. Agents Chemother.* **39**:2309–2315.
- Janiszewski, J. S., D. E. Mulvana, S. Kaul, K. A. Dandekar, and R. H. Barbhuiya. 1992. High-performance liquid chromatographic determination of 2',3'-didehydro-3'-deoxythymidine, a new anti-human immunodeficiency virus agent, in human plasma and urine. *J. Chromatogr.* **577**:151–156.
- Kaul, S., B. Stouffer, V. Mummaneni, N. Turabi, S. Mantha, P. Jayatilak, and R. Barbhuiya. 1996. Specific radioimmunoassays for the measurement of stavudine in human plasma and urine. *J. Pharm. Biomed. Anal.* **15**:165–174.
- Kearns, G. L., and M. D. Reed. 1989. Clinical pharmacokinetics in infants and children: a reappraisal. *Clin. Pharmacokinet.* **17**(Suppl. 1):29–67.
- Kline, M. W., L. M. Dunkle, J. A. Church, J. C. Goldsmith, A. T. Harris, M. E. Federici, M. E. Schultze, L. Woods, D. F. Loewen, and S. Kaul. 1995. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics* **96**:247–252.
- Kline, M. W., R. B. Van Dyke, J. C. Lindsey, M. Gwynne, M. Culnane, R. E. McKinney, Jr., S. Nichols, W. G. Mitchell, R. Yogeve, and N. Hutcheon. 1998. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. *AIDS Clinical Trial Group 240 Team. Pediatrics* **101**:214–220.
- Lea, A. P., and D. Faulds. 1996. Stavudine: a review of its pharmacodynamic and pharmacokinetic properties and clinical potential in HIV infection. *Drugs* **51**:846–864.
- Maxwell, G. M. 1989. Paediatric drug dosing: body weight versus surface area. *Drugs* **37**:113–115.
- Medical Economics Co. 1998. Product information for ZERIT® (stavudine) capsules and EPIVIR® (lamivudine) tablets. *In* Physicians' Desk Reference, 52nd ed. Medical Economics Co., Montvale, N.J.
- Morgan, D. J., and K. M. Bray. 1994. Lean body mass as a predictor of drug dosage: implications for drug therapy. *Clin. Pharmacokinet.* **26**:292–307.
- Murray, H. W., K. E. Squires, W. Weiss, S. Sledz, H. S. Sacks, J. Hassett, A. Cross, R. E. Anderson, and L. M. Dunkle. 1995. Stavudine in patients with AIDS and AIDS-related complex: AIDS clinical trials group 089. *J. Infect. Dis.* **171**(Suppl. 2):S123–S130.
- Petersen, E. A., C. H. Ramirez-Ronda, W. D. Hardy, R. Schwartz, H. S. Sacks, S. Follansbee, D. M. Petersen, A. Cross, R. E. Anderson, and L. M. Dunkle. 1995. Dose-related activity of stavudine in patients infected with human immunodeficiency virus. *J. Infect. Dis.* **171**(Suppl. 2):S131–S139.
- Rana, K. Z., and M. N. Dudley. 1997. Clinical pharmacokinetics of stavudine. *Clin. Pharmacokinet.* **33**:276–284.
- Riegelman, S., and P. Collier. 1980. The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. *J. Pharmacokinet. Biopharm.* **8**:509–534.
- SAS Institute, Inc. 1985. SAS user's guide: statistical version, 5th ed. SAS Institute, Inc., Cary, N.C.
- Skaer, T. L. 1991. Dosing considerations in the pediatric patient. *Clin. Ther.* **13**:526–544.
- Skowron, G. 1995. Biological effects and safety of stavudine: overview of phase I and II clinical trials. *J. Infect. Dis.* **171**(Suppl. 2):S113–S117.
- Spruance, S. L., A. T. Pavia, J. W. Mellors, R. Murphy, J. Gathe, Jr., E. Stool, J. G. Jemsek, P. Dellamonica, A. Cross, and L. M. Dunkle. 1997. Clinical efficacy of monotherapy with stavudine compared with zidovudine in HIV-infected, zidovudine-experienced patients. A randomized, double-blind, controlled trial. Bristol-Myers Squibb Stavudine/019 Study Group. *Ann. Intern. Med.* **126**:355–363.
- Wagner, J. G. 1968. Dosage of drugs in infants, children, and adults. *Drug Intell.* **2**:144–151.