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Bioavailability of Once- and Twice-Daily Regimens of Didanosine in Human Immunodeficiency Virus-Infected Children

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The bioavailability of didanosine at 180 mg/m^2 once daily was compared to that at 90 mg/m^2 twice daily in 24 children with advanced human immunodeficiency virus infection. Children were studied at steady state using optimal sampling and prior pharmacokinetic parameter estimates. Relative bioavailability was 0.95 ± 0.49, supporting the potential clinical adequacy of once-daily dosing.

The active form of didanosine has an extended intracellular half-life, suggesting its potential for once-daily administration (10). Pediatric experience suggested that didanosine doses of 90 to 180 mg/m^2 were less well absorbed than those of 20 to 60 mg/m^2. However, no difference in the bioavailability of didanosine at 90 mg/m^2 (13%; range, 2 to 29%) and 180 mg/m^2 (14%; range, 12 to 17%) was observed (1). Reevaluation of once-daily didanosine combined with hydroxyurea (J. Rusnak, A. Berry, K. Sharkey, B. Stinnette, K. Dyall, S. Zhou, and M. A. Vahey, Program Abstr. 12th World AIDS Conf., abstr. 12352, 1998) or other long-acting antiretrovirals (A. Haberl, P. Gute, A. Carlebach, M. Mosch, Y. Miller, and S. Staszewski, Program Abstr. 12th World AIDS Conf., abstr. 22398, 1998) is under way, and preliminary results with adults suggest the potential utility of these regimens (5, 6, 11; Haberl et al., Program Abstr. 12th World AIDS Conf.; Rusnak et al., Program Abstr. 12th World AIDS Conf.). The objective of this study was to determine the relative bioavailability of didanosine when it was administered as a single daily dose of 180 mg/m^2 and in a standard regimen of 90 mg/m^2 given twice daily to children with advanced human immunodeficiency virus (HIV) infection.

HIV-infected children at the Pediatric Institute of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, in 1996 were invited to participate, and informed consents were signed by their legal guardians. An independent ethics committee of the Federal University of Rio de Janeiro approved this trial. Inclusion criteria were symptomatic HIV infection and the receipt of buffered didanosine tablets, alone or in combination with zidovudine. Children with active opportunistic infections, pancreatitis, or peripheral neuropathy were excluded.

The didanosine suspension was prepared by the Pediatric Institute pharmacist at study entry and monthly with Videx pediatric powder for solution and Maalox Plus. The reconstituted suspension was usable for 1 month. Children received didanosine twice daily (90 mg/m^2 every 12 h) during the first 45 days of the study and then once daily (180 mg/m^2) during the remaining 45 days of the study. Medication was shaken before being used and stored at 2 to 8°C; doses were taken on an empty stomach.

Three optimally spaced blood samples, at 0.5, 1, and 3 h postdose, were obtained following the morning dose on day 45 of each of the two regimens; plasma was separated and stored at −20°C until analysis, 7 months later. Plasma samples were analyzed by Analytical Solutions, Inc., using a validated radioimmunoassay with a lower limit of quantitation of 0.003 mg/liter. Inter- and intraday coefficients of variation were less than 10% across the range of 8 to 160 ng/ml.

Didanosine pharmacokinetic parameters were determined by Bayesian estimation with a one-compartment oral absorption model and no lag time. A priori estimates for the mean pediatric clearance (1,278 ml/min/m^2), half-life (0.95 h), and time to maximum concentrations in plasma (C_{max}) (0.5 h) were obtained from the literature (2, 7). All modeling was performed using WinNonlin (version 1.0; Scientific Consulting, Inc.) with unity weighting. Relative bioavailabilities of the once- and twice-daily regimens were determined by dose-normalized ratios of areas under the steady-state concentration-time curves (AUCs). Pharmacokinetic parameters between the two treatment regimens were compared using a repeated-measure one-way analysis of variance. Bioequivalency was assessed by evaluation of the means and 90% confidence intervals of the differences between the logarithmic transformed dose-normalized AUCs determined for the once-daily and twice-daily regimens.

Twenty-four children were evaluated. Most children had advanced HIV infection; 16 children had CD4 percentages of less than 30%, and 20 children were receiving concurrent zidovudine. Thirteen children were male, and the mean (standard deviation [SD]) age and body surface areas were 4.8 (2.9) years and 0.68 (0.16) m^2, respectively.

Data from two subjects, numbers 11 and 23, were excluded from analysis; the former had uniformly low concentrations in plasma, and the latter did not complete the study. Mean (SD) concentrations in plasma observed for the twice-daily and once-daily regimens were 0.508 (0.347) and 0.971 (0.693) mg/liter at 1 h and 0.090 (0.085) and 0.167 (0.108) mg/liter at 3 h. Table 1 summarizes the pharmacokinetic parameters observed for the once- and twice-daily regimens.

The pharmacokinetic parameters, with the exception of

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TABLE 1. Pharmacokinetic parameters

Parameter[a]	Mean value (SD; 95% confidence interval)	
	Once-daily regimen	Twice-daily regimen
T_{max} (h)	0.63 (0.35; 0.48–0.77)	0.60 (0.57; 0.36–0.84)
C_{max} (mg/liter)	1.45 (1.18; 0.96–1.94)	1.11 (1.03; 0.68–1.54)
$T_{1/2}$ (h)	0.55 (0.21; 0.47–0.64)	0.60 (0.28; 0.49–0.72)
AUC (mg · h/liter)	2.18 (1.35; 1.62–2.74)	1.31 (0.90; 0.93–1.68)[b]
Cl/*F* (ml/min/m^2)	2,076 (1,633; 1,393–2,758)	1,529 (880; 1,161–1,897)

[a] T_{max} is time to maximum concentration in plasma, $T_{1/2}$ is the elimination half-life, and Cl/*F* is the oral clearance.
[b] $P = 0.0003$, by repeated-measure one-way analysis of variance.

AUCs, did not differ between regimens. The substantial variability in C_{max}s precluded observation of a significant difference in C_{max}s between regimens. The bioavailability of the once-daily regimen relative to that of the twice-daily regimen was 0.95 ± 0.49 (range, 0.22 to 1.97), suggesting that the total exposure to didanosine was similar whether the drug was given once or twice daily. There was, however, significant inter- and intrasubject variability in AUCs determined from the two regimens (Fig. 1). This variability resulted in the 90% confidence interval for the transformed AUC (0.65 to 1.01) falling outside the regulatory limits (0.80 to 1.25) for bioequivalence. Thus, although the regimens are likely to perform similarly in a clinical setting, from a Food and Drug Administration perspective, these regimens would not be considered bioequivalent.

The pharmacokinetics of didanosine in both pediatric and adult populations are characterized by significant variability (1–4, 7–10). Factors contributing to this variability between studies can include differences in diet, formulation, concurrent medications, and drug assays. All of our children were receiving a didanosine suspension prepared in a standard fashion by the study pharmacist. The majority of children were also receiving zidovudine. While all parents were given standard instructions concerning the administration of didanosine, the marked intra- and interpatient variability may reflect the variability in the actual administration of the drug that occurs outside a strict research environment.

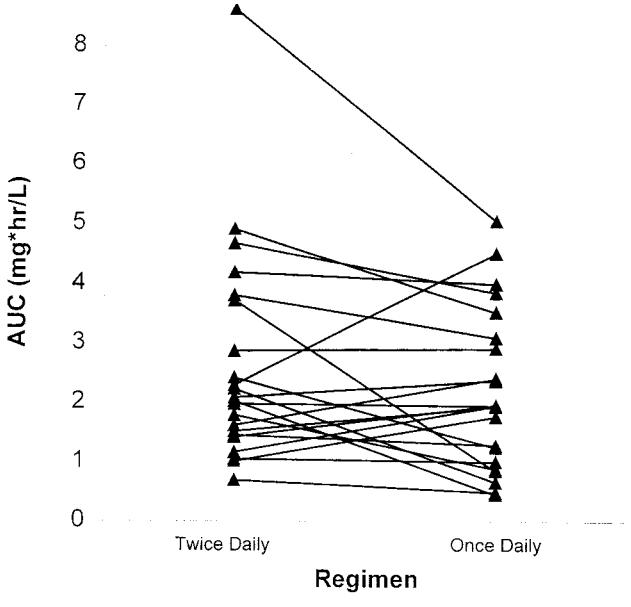

FIG. 1. Comparison of dose-normalized AUCs, by subject, for twice- and once-daily regimens.

Analysis of our data suggests that the extent of absorption of didanosine when it is given as a single daily dose approximates that of the standard, twice-daily regimen, 0.95 ± 0.49. There has been recent interest in prescribing didanosine on a once-daily schedule for adults in an effort to simplify complex antiretroviral regimens. A number of small studies of adults (5, 6, 11; Haberl et al., Program Abstr. 12th World AIDS Conf.; Rusnak et al., Program Abstr. 12th World AIDS Conf.) indicate that both regimens are safe and appear clinically equivalent, as judged by changes in CD4 counts and HIV-1 RNA viral loads. Our study suggests that once-daily dosing of didanosine may be applied in the pediatric setting as well.

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