Pharmacokinetics of Stavudine (2′,3′-Didehydro-3′-Deoxythymidine) in the Neonatal Macaque (Macaca nemestrina)

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Our objective was to determine whether age affects the pharmacokinetics of stavudine (2′,3′-didehydro-3′-deoxythymidine) in the neonatal pig-tailed macaque (Macaca nemestrina). The drug (5 mg/kg of body weight) was administered serially as a single intravenous bolus to the same four macaques at the ages of <1 week, 1 month, and 4 months. Plasma clearance at <1 week of age was significantly lower (P < 0.05) than the corresponding values at 1 month and 4 months. Our data indicate that the pharmacokinetics of stavudine change significantly with age in M. nemestrina.

Heterosexual transmission of the human immunodeficiency virus (HIV) now outranks all other means of transmission. Consequently, the number of children born worldwide to mothers infected with HIV is on the rise. The virus is now the fifth leading cause of death among children in the United States (19). Zidovudine is the drug recommended for administration to the pregnant woman infected with HIV, as well as to her infant for 6 weeks after birth (6). However, administration of zidovudine to the pregnant woman and her offspring may not always represent the best therapeutic strategy because of drug intolerance or because of zidovudine-resistant HIV strains. Therefore, there is considerable interest in investigating other dideoxynucleosides with different toxicity and activity profiles in the treatment of pregnant women and infants with HIV.

Stavudine (2′,3′-dideoxy-3′-deoxythymidine; d4T) is a dideoxynucleoside active against reverse transcriptase and zidovudine-resistant HIV isolates (12). Data from phase 1 clinical trials of d4T indicate that the rate of decline in serum p24 antigen is comparable to that seen with zidovudine (5). However, in contrast to zidovudine, the dose-limiting toxicity of d4T is peripheral neuropathy (5), not anemia and neutropenia.

To optimize d4T therapy of the neonate infected with HIV, the age-related changes in the pharmacokinetics of d4T need to be evaluated. For this reason, we have determined, as part of an ongoing series of investigations, the age-dependent change in the pharmacokinetics of d4T in the neonatal macaque (Macaca nemestrina). We have chosen M. nemestrina for our studies because this species has proven to be an excellent animal model for the study of dideoxynucleoside disposition. Previous studies in our laboratory with zidovudine (14, 15) and dideoxynosine (ddI) (20, 21) in the adult and infant M. nemestrina have shown that the pharmacokinetics of these drugs, including metabolic clearance and renal clearance, are comparable to those in human adults (10, 11) and infants (4).

Materials. The drug d4T was a gift from Bristol-Myers Squibb (Syracuse, N.Y.). All other chemicals used were of reagent grade.

Animals. The same four infant M. nemestrina monkeys were studied serially at ages <1 week (5.75 ± 1.26 days; weight, 0.45 ± 0.054 kg), 1 month (30.7 ± 0.6 days; weight, 0.62 ± 0.14 kg), and 4 months (119.5 ± 1.9 days; weight, 1.10 ± 0.16 kg). The animals were administered a single intravenous (i.v.) bolus dose of d4T (5.0 mg/kg of body weight) through a catheter placed in the cephalic vein while under sedation with ketamine (5 mg/kg, intramuscular). Blood samples were drawn from the femoral vein by venipuncture before and at 5, 10, 15, 30, 60, 90, 120, and 180 min after drug administration; plasma was separated by centrifugation. The total volume of blood drawn did not exceed 3.8 ml in any study. Cerebrospinal fluid (CSF) samples (200 μl) were drawn when possible, and blood-contaminated samples were discarded. CSF samples were collected at 60 min (1 week of age, n = 3; 1 month of age, n = 3; 4 months of age, n = 4) and at 90 min (<1 week of age, n = 3; 4 months of age, n = 2), by cisternal puncture under sedation with ketamine. Because most of our 90-min CSF samples contained blood, they were not analyzed; only the 60-min time points were used to determine the CSF/plasma ratios.

Analytical methods. Concentrations of d4T in plasma (100 μl) and CSF (100 μl) were determined by a high-performance
The pharmacokinetic parameters of d4T in the neonatal M. nemestrina are presented in Table 1. The clearance (CL) of d4T increases significantly with age, from 5.93 ± 1.06 ml/min/kg at 1 week of age to 13.6 ± 1.78 ml/min/kg at 4 months of age. The steady-state volume of distribution (Vss) also increases with age, from 451 ± 87.5 liters/kg at 1 week of age to 662.4 ± 177.9 liters/kg at 4 months of age. The elimination half-life (t1/2) and mean body residence time (MBRT) decrease with age, from 0.22 ± 0.02 at 1 week of age to 0.02 ± 0.01 at 4 months of age.

In rhesus and cynomolgus monkeys, only 40 to 50% of the radioactivity after a single oral or i.v. dose (25 mg/kg) of radiolabeled d4T is recovered in the urine. The vast majority (>90%) of this recovered radioactivity is unchanged d4T. The remaining 50 to 60% of the radiolabeled dose is not recovered in urine or feces up to 30 days after drug administration (7). Likewise, studies with human adults have found that 30 to 40% of the dose is recovered as unchanged d4T in the urine (8). These data indicate that renal excretion plays an important role in the elimination of d4T in humans and monkeys. Since renal function is poorly developed at birth, it is not surprising that the clearance of d4T in the neonatal macaque changes with age. This change in clearance with age is remarkably similar to that observed by us for neonatal M. nemestrina with both zidovudine and ddI (Fig. 2) (15, 21).

The rates of increase in clearance of d4T and ddI with age, as percentages of their 4-month values, are virtually parallel, suggesting that for both drugs the same mechanism is responsible for this change. Since both these drugs are significantly cleared by renal excretion, maturation of renal function is the most likely explanation. That is, this parallel change in clearance suggests that the nonrenal clearance of d4T does not change with age. For zidovudine, although the profile of increase in clearance with age is similar to that of the other two drugs, the rate of increase is different. Very likely, the basis for this difference is the fact that zidovudine is cleared almost equally by two pathways, metabolism by glucuronidation and renal excretion (16). Both these pathways are poorly developed in the neonate (15).

We observed that the value of steady-state volume of distribution of d4T did not significantly increase with age in neonatal macaques (Table 1). Since half-life and mean body residence time are parameters determined by both clearance and volume of distribution, the values at 1 week of age would be expected to be larger than those at 4 months. Surprisingly, only the change in mean body residence time reached statistical significance.

The CSF/plasma concentration ratio of d4T increased with age from 0.17 ± 0.02 at <1 week of age to 0.22 ± 0.02 at 4 months (Table 2). These ratios are similar to those reported for adult rhesus monkeys (0.15) at 1 h after drug administration (22). We also have observed an age-dependent change in CSF/plasma drug concentration ratios for zidovudine and ddI in neonatal macaques (13, 21). The small but significant changes in the CSF/plasma drug concentration ratios for d4T, zidovudine, and ddI in the neonatal macaque may be attributed to age-related permeability changes in the blood-brain barrier. However, the degree of change observed is unlikely to be of clinical importance. While the CSF/plasma ratios for zidovudine, ddI, and d4T in adult and infant macaques are similar, the octanol/water partition coefficient values for zidovudine (0.98 [3]), ddI (0.07 [1]), and d4T (0.18 [3]) are very different. We have previously reported that the steady-state

![FIG. 2. Changes in d4T (●), ddI (○), and zidovudine (□) clearances with age in neonatal M. nemestrina.](http://aac.asm.org/)

**TABLE 1. Pharmacokinetic parameters of d4T in the neonatal M. nemestrina**

<table>
<thead>
<tr>
<th>Age</th>
<th>CL (ml/min/kg)</th>
<th>Vss (liters/kg)</th>
<th>t1/2 (min)</th>
<th>MBRT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wk</td>
<td>5.93 ± 1.06*</td>
<td>451 ± 87.5</td>
<td>54.4 ± 10.3</td>
<td>76.8 ± 13.3</td>
</tr>
<tr>
<td>1 mo</td>
<td>9.74 ± 2.15*</td>
<td>432.3 ± 106</td>
<td>32.2 ± 13.4</td>
<td>45.5 ± 14.4</td>
</tr>
<tr>
<td>4 mo</td>
<td>13.6 ± 1.78</td>
<td>662.4 ± 177.9</td>
<td>42.2 ± 8.22</td>
<td>48.1 ± 7.28</td>
</tr>
</tbody>
</table>

* The data are means for four animals ± standard deviations, with ranges in parentheses. CL, plasma drug clearance; Vss, steady-state volume of distribution; t1/2, elimination half-life; MBRT, mean body residence time.

* Significantly different (P < 0.05) from the corresponding values at 1 and 4 months of age.
concentration of dideoxynucleosides in the CSF is independent of the lipophilicity of the drug and is determined primarily by active efflux of the drug out of the CSF (2, 23).

In summary, we have shown that the pharmacokinetics for d4T change significantly with age in the neonatal M. nemestrina. On the basis of these data we predict that the pharmacokinetics of d4T will change significantly with age in human neonates. Pharmacokinetic studies should be conducted with human neonates prior to initiation of large-scale clinical trials in this population.

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REFERENCES