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Transplacental Pharmacokinetics of Dideoxyinosine in Pigtailed Macaques

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To determine whether dideoxyinosine is actively transported across the placenta, four pregnant macaques (*Macaca nemestrina*) near term and their fetuses were infused intravenously in random order with simultaneous doses of dideoxyinosine (42.5 μg/min/kg of body weight) and antipyrine (41.7 μg/min/kg) for 30 h. The infusions took place after the dams had been chronically catheterized at 128 ± 0.8 days of gestation. In a third infusion, the dams alone received a higher dosage of dideoxyinosine (425 μg/min/kg) and the same dosage of antipyrine (41.7 μg/min/kg). Samples of maternal and fetal blood and amniotic fluid were collected at intervals for up to 30 h. The concentrations of dideoxyinosine and antipyrine were determined by high-performance liquid chromatography. The transplacental maternal-fetal drug clearances were compared by the paired Student's *t* test. The ratio (mean ± standard deviation) of the steady-state plasma dideoxyinosine concentration in the fetus to that in the dam was 0.49 ± 0.10 at the low dideoxyinosine infusion rate and 0.51 ± 0.00 at the high dideoxyinosine infusion rate. The clearance associated with maternal-fetal transfer of the drug, CL_{df} (0.38 ± 0.21 ml/min/kg), was not significantly different ($P > 0.05$) from the clearance associated with fetal-maternal transfer of the drug, CL_{fd} (0.56 ± 0.27 ml/min/kg). Also, CL_{df} was not significantly different ($P > 0.05$) from CL_{fd} when normalized with respect to the corresponding transplacental clearance of antipyrine (0.07 ± 0.04 CL_{df} versus 0.09 ± 0.04 CL_{fd}). Our data indicate that passage of dideoxyinosine across the placenta in pregnant *M. nemestrina* near term is passive and constant over the dosage range studied.

Dideoxyinosine (2′,3′-dideoxyinosine; didanosine) is the second dideoxynucleoside to be approved for use in the treatment of AIDS. Although not presently approved for use during pregnancy, dideoxyinosine may be of benefit to pregnant women who cannot tolerate or have become resistant to zidovudine. In addition, data from animal models indicate that dideoxynucleoside therapy of the dam during pregnancy may delay the onset and progression of the disease in offspring infected in utero (15). Thus, information on the extent and mechanisms of transplacental transfer of dideoxynucleosides, including dideoxyinosine, is necessary in the development of therapeutic strategies for the pregnant woman and her potentially infected unborn child. As part of an ongoing series of studies on the dideoxynucleosides, we studied the extent and mechanisms of transfer of dideoxyinosine in vivo across the placenta in a representative nonhuman primate model, *Macaca nemestrina*.

The macaque was chosen because of its anatomical and physiological similarities to humans. It is particularly suitable since it is susceptible to both the simian immunodeficiency virus (12), which produces an AIDS-like syndrome, and the human immunodeficiency virus (1). In addition, the pharmacokinetics of dideoxyinosine in *M. nemestrina* have been shown to be similar to those in humans (13).

MATERIALS AND METHODS

Materials. Dideoxyinosine was supplied by the National Institute of Allergy and Infectious Diseases (Developmental Therapeutics Branch, Division of AIDS). All other chemicals used were of reagent grade.

Animals. Four pregnant macaques were chronically catheterized at 128 ± 0.8 days of gestation (estimated by ultrasound). Under general anesthesia by endotracheal intubation with halothane (Fluothane) vaporized with 3 liters of O_2 and 1 liter of N_2O and under strict asceptic technique, polyvinyl catheters were placed in the femoral artery and vein of the dam and in the carotid artery and jugular vein of the fetus. The amniotic cavity was also catheterized with dual polyvinyl "birdcage" catheters. All catheters were exteriorized through a tether system (10) that allowed access to the catheters from the outside of the animals' cages and that permitted free movement of the animals within the cages. After a 1-week recovery period, dideoxyinosine was administered at a low infusion rate (approximately 42.5 μg/min/kg of body weight intravenously; see Table 1) to the dam (15 ml/h; via the femoral vein) or to the fetus (1.5 ml/h; via the carotid artery) in a randomized crossover manner. Dideoxyinosine was also administered to three dams at a 10-fold higher rate of infusion (approximately 425 μg/min/kg intravenously; see Table 1). Antipyrine (41.7 μg/min/kg intravenously) was coinfused in all experiments. Infusions were separated by 1 week. Infusate solutions were freshly prepared in sterile normal saline and were resterilized by filtration. Blood samples (2 ml; collected via the femoral artery) were collected from the dam before the start of the infusion and thereafter at 24, 25.5, 27, 28.5, and 30 h. Fetal blood samples (0.3 ml; collected via the jugular vein) were collected before the start of the infusion and thereafter at 27, 28.5, and 30 h. Additional maternal and fetal blood samples were collected from two animals during the low-rate dideoxyinosine infusions at 0.25, 0.5, 1, 3, and 6 h after the infusions were begun. Amniotic fluid samples (2 ml) were collected at times that coincided with the time that each blood sample was collected.

Analytical methods. The concentrations of dideoxyinosine and antipyrine in the blood and amniotic fluid samples were

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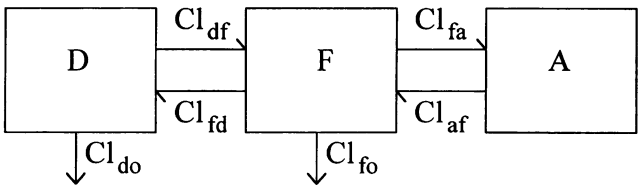

FIG. 1. Pharmacokinetic model used to describe dideoxyinosine plasma concentration-time profile in the maternal plasma (D), the fetal plasma (F), and the amniotic fluid (A).

simultaneously determined by a high-performance liquid chromatographic method developed in our laboratory. Briefly, 50-μl aliquots of plasma or amniotic fluid and 50 μl of internal standard solution (3-hydroxyacetamidophenol; 5 μg/ml in water) were loaded onto solid-phase extraction columns (Bond Elut C_{18}; 3 ml; Varian, Harbor City, Calif.), which were preconditioned with 2 ml of methanol and then 2 ml of water. The columns were washed twice with 2 ml of water; the analytes were eluted with 2 ml of methanol, dried under vacuum, and reconstituted with 100 μl of acetonitrile (6%). Then, 50 μl of this mixture was injected onto the high-performance liquid chromatographic system. This system included two programmable pumps (LC-6A; Shimadzu Corp., Kyoto, Japan), a C_{18} column (Ultrasphere ODS 5 μm; 4.6 mm by 25 cm; Beckman Instruments Inc., Fullerton, Calif.), a UV absorbance detector (SPD-6A; Shimadzu Corp., Kyoto, Japan) with the wavelength set at 254 nm, and an autoinjector (712 WISP; Waters Associates, Milford, Mass.). The analytes were eluted with a 35-min linear gradient with the following mobile phases (at 1 ml/min): acetonitrile-ammonium phosphate buffer (pH 4.0) at ratios of 6:94 (mobile phase A) and 25:75 (mobile phase B). At time zero, mobile phase A was 100%, at 20 min, mobile phase B was 100%, and at 25 min, mobile phase A was 100%. With this assay, the intraday coefficient of variation for dideoxyinosine was 7.5% at a sample concentration of 0.05 μg/ml and 3.6% at 5.0 μg/ml. For antipyrine, the coefficient of variation was 7.2% at 0.4 μg/ml and 11.2% at 40.0 μg/ml. The assay was found to be linear over these concentration ranges.

Pharmacokinetic analysis. A three-compartment pharmacokinetic model (Fig. 1), previously suggested by Szeto et al. (16) and Nanbo (11), was used to describe the dideoxyinosine and antipyrine concentration-versus-time data for maternal and fetal plasma and amniotic fluid. This model assumes that there is no irreversible clearance of the drug (e.g., by metabolism) by the placenta itself. Mean steady-state dideoxyinosine and antipyrine concentrations and equations 1 to 4 (integrated forms of equations 5, 6, 8, and 9, with the assumption that at steady state the net rate of drug transfer between the fetus and amniotic fluid is zero) were used to calculate the transplacental clearances and irreversible drug clearances from the dams and the fetuses.

$$CL_{df}=\frac{k_0{}^*C_{ssf}}{C_{ssf}{}^*C_{ssd}-C_{ssf}C_{ssd}{}^*} \quad (1)$$

$$CL_{do}=\frac{k_0C_{ssf}{}^*}{C_{ssf}{}^*C_{ssd}-C_{ssf}C_{ssd}{}^*}-CL_{df} \quad (2)$$

$$CL_{fd}=\frac{k_0C_{ssd}{}^*}{C_{ssf}{}^*C_{ssd}-C_{ssf}C_{ssd}{}^*} \quad (3)$$

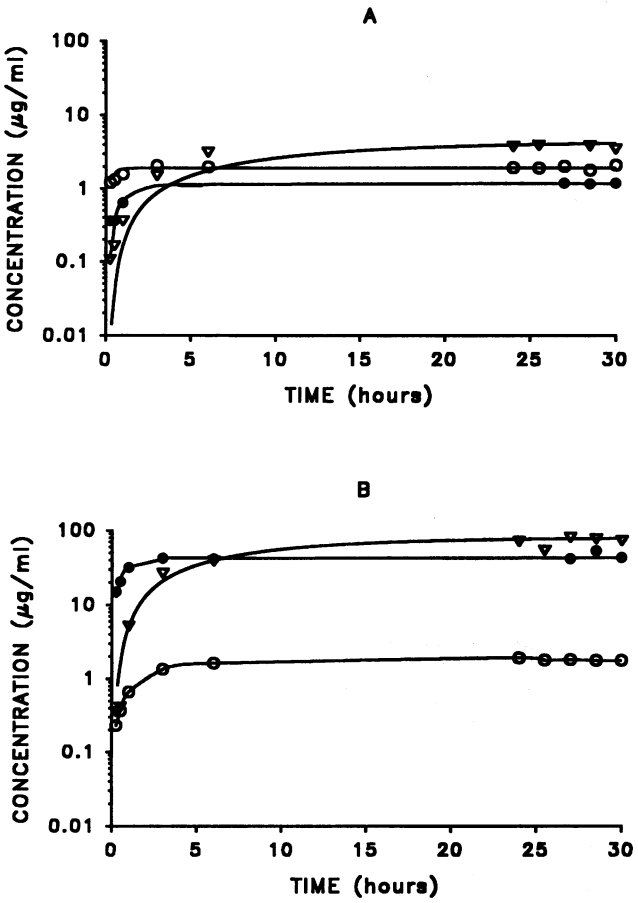

FIG. 2. Concentration of dideoxyinosine in maternal (○) and fetal (●) plasma and amniotic fluid (▽) after a low-rate dideoxyinosine infusion to a dam (A; T81511) and her fetus (B). Lines represent model fits.

$$CL_{fo}=\frac{k_0{}^*C_{ssd}}{C_{ssf}{}^*C_{ssd}-C_{ssf}C_{ssd}{}^*}-CL_{fd} \quad (4)$$

CL_{df} and CL_{fd} are transplacental drug clearances from the dam to the fetus and from the fetus to the dam, respectively; CL_{do} and CL_{fo} are irreversible drug clearances from the dam and the fetus, respectively; C_{ssd} and C_{ssf} are steady-state drug concentrations in the plasma of the dam and the fetus, respectively; k_0 is the drug infusion rate; the asterisk indicates variables after infusion of drug to the fetus.

This model was also fit by using nonlinear least-squares regression (PCNONLIN) to the pre-steady-state and steady-state data available for two animals. The differential equations used to describe the model (11) are listed as equations 5 to 10.

$$\frac{dC_d}{dt}=\frac{k_0}{V_d}+\frac{k_{21}V_fC_f}{V_d}-(k_{12}+k_{10})C_d \quad (5)$$

$$\frac{dC_f}{dt}=\frac{k_{12}V_dC_d}{V_f}+\frac{k_{32}V_aC_a}{V_f}-(k_{21}+k_{20}+k_{23})C_f \quad (6)$$

$$\frac{dC_a}{dt}=\frac{k_{23}V_fC_f}{V_a}-k_{32}C_a \quad (7)$$

TABLE 1. Fetal-maternal clearance and concentration ratios for dideoxyinosine at steady state[a]

Dideoxyinosine infusion rate and parameter	Animal				Mean ± SD
	T86169	T81511	F84292	89127	
Low-rate infusion					
k_0 (μg/min/kg)	42.50	42.48	42.33	42.28	42.40 ± 0.11
k_0* (μg/min/kg)	41.67	47.03	41.50	41.36	42.89 ± 2.76
C_{ssd} (μg/ml)	1.77	1.95	1.55	2.33	1.90 ± 0.33
C_{ssd}* (μg/ml)	0.94	1.80	1.20	1.79	1.43 ± 0.43
C_{ssf} (μg/ml)	0.70	1.19	0.83	0.98	0.93 ± 0.21
C_{ssf}* (μg/ml)	72.90	45.52	48.87	90.58	64.47 ± 21.25
CL_{df} (ml/min/kg)	0.23	0.65	0.46	0.19	0.38 ± 0.21
CL_{do} (ml/min/kg)	23.91	21.68	27.21	18.10	22.73 ± 3.83
CL_{fd} (ml/min/kg)	0.31	0.88	0.68	0.36	0.56 ± 0.27
CL_{fo} (ml/min/kg)	0.26	0.18	0.18	0.10	0.18 ± 0.07
C_{ssf}/C_{ssd}	0.40	0.61	0.54	0.42	0.49 ± 0.10
CL_{df}(norm)	0.12	0.09	0.06	0.02	0.07 ± 0.04
CL_{fd}(norm)	0.12	0.13	0.08	0.03	0.09 ± 0.04
C_{ssa}/C_{ssf}	4.38	3.25	2.79	3.45	3.47 ± 0.67
C_{ssa}*/C_{ssf}*	1.50	1.63	1.08	0.90	1.28 ± 0.34
High-rate infusion					
k_0H (μg/min/kg)	425.00	424.26	423.65	NA	424.30 ± 0.68
C_{ssd}H (μg/ml)	15.13	22.25	15.58	NA	17.65 ± 3.99
C_{ssf}H (μg/ml)	7.69	11.09	7.92	NA	8.90 ± 1.90
C_{ssf}H/C_{ssd}H	0.51	0.50	0.51	NA	0.51 ± 0.00
C_{ssa}H/C_{ssf}H	2.96	2.32	2.40	NA	2.56 ± 0.35

[a] SD, standard deviation; k_0, rate of infusion; C_{ss}, concentration at steady state; d, dam; *, variables after infusion of the drug to the fetus; f, fetus; CL, clearance; o, irreversible removal; norm, normalized to antipyrine clearance; a, amniotic fluid; H, after high-rate dideoxyinosine infusion; NA, not available.

$$\frac{dC_d^*}{dt}=\frac{k_{21}V_fC_f^*}{V_d}-(k_{12}+k_{10})C_d^* \quad (8)$$

$$\frac{dC_f^*}{dt}=\frac{k_0^*}{V_f}+\frac{k_{12}V_dC_d^*}{V_f}+\frac{k_{32}V_aC_a^*}{V_f}-(k_{21}+k_{20}+k_{23}^*)C_f^* \quad (9)$$

$$\frac{dC_a^*}{dt}=\frac{k_{23}^*V_fC_f^*}{V_a}-k_{32}C_a^* \quad (10)$$

Equations 5 to 7 describe the drug concentrations in the dam, fetus, and amniotic fluid, respectively, after infusion to the dam. Equations 8 to 10 describe these respective concentrations after infusion of drug to the fetus. C_d, C_f, and C_a are drug concentrations in the dam, the fetus, and the amniotic fluid, respectively; k_0 is the infusion rate; V_d, V_f, and V_a are the volumes of distribution of the dam, fetus, and amniotic fluid, respectively; the asterisk indicates variables after infusion of drug to the fetus; k_{12}, k_{21}, k_{10}, k_{20}, k_{23}, and k_{32} represent intercompartmental rate constants. Different weighting schemes were investigated to arrive at the best fit of the model to the data. Of these, except for one data set, weights equal to the reciprocal concentration squared yielded the best fit of the model to the data.

Statistical analysis. The paired Student's t test was used to compare the transplacental maternal-fetal dideoxyinosine clearances, normalized to the corresponding antipyrine clearance. The test was also used to compare the fetal-maternal drug concentration ratios after low and high-rate dideoxyinosine infusions and the amniotic fluid-fetal plasma drug concentration ratios after low-rate dideoxyinosine infusions to the dam and fetus and the high-rate dideoxyinosine infusion to the dam.

RESULTS

Representative concentration-versus-time profiles for dideoxyinosine in maternal and fetal plasma and in amniotic fluid are shown in Fig. 2. The exact infusion rates used in each animal, mean steady-state drug concentration data, and clearances calculated from these data are shown in Table 1 for dideoxyinosine and in Table 2 for antipyrine.

Steady-state dideoxyinosine concentrations in maternal plasma after infusion to the dam (C_{ssd}) were similar to those achieved after infusion to the fetus (C_{ssd}*) (1.90 ± 0.33 versus 1.43 ± 0.43 μg/ml). Concentrations in fetal plasma after infusion to the dam (C_{ssf}), however, differed considerably from those seen after infusion to the fetus (C_{ssf}*) (0.93 ± 0.21 versus 64.47 ± 21.25 μg/ml). After the high-rate dideoxyinosine infusion, steady-state dideoxyinosine concentrations in the dam (C_{ssd}H) and in the fetus (C_{ssf}H) were approximately 10 times higher than C_{ssd} and C_{ssf}, respectively. However, the fetal-maternal concentration ratio, C_{ssf}/C_{ssd} (0.49 ± 0.10), was not significantly different from the ratio C_{ssf}H/C_{ssd}H (0.51 ± 0.00), as determined in three animals by the paired Student's t test ($P > 0.05$). The steady-state amniotic fluid-fetal plasma dideoxyinosine concentration ratio after low-rate dideoxyinosine infusion to the dam (C_{ssa}/C_{ssf}) was significantly higher than the corresponding ratio (C_{ssa}*/C_{ssf}*) after infusion to the fetus (3.47 ± 0.67 versus 1.28 ± 0.34; $P < 0.05$) but was not significantly different from the corresponding ratio (C_{ssa}H/C_{ssf}H) (2.56 ± 0.35; $P > 0.05$) after high-rate dideoxyinosine infusion to the dam. C_{ssa}H/C_{ssf}H was also significantly higher than C_{ssa}*/C_{ssf}* ($P < 0.05$).

The maternal-fetal clearance of dideoxyinosine (CL_{df}) was not significantly different from the fetal-maternal clearance (CL_{fd}) (0.38 ± 0.21 versus 0.56 ± 0.27 ml/min/kg; $P > 0.05$). There was no significant difference between these clearances even when they were normalized to the corresponding anti-

TABLE 2. Fetal-maternal clearance and concentration ratios for antipyrine at steady state[a]

Dideoxyinosine infusion rate and parameter	Animal				Mean ± SD
	T86169	T81511	F84292	89127	
Low-rate infusion					
k_0 (μg/min/kg)	41.67	42.12	41.76	41.68	41.81 ± 0.21
k_0* (μg/min/kg)	41.67	47.28	41.74	41.67	43.09 ± 2.79
C_{ssd} (μg/ml)	6.99	6.44	4.81	6.85	6.27 ± 1.00
C_{ssd}* (μg/ml)	7.22	6.33	4.53	9.66	6.94 ± 2.13
C_{ssf} (μg/ml)	4.90	5.95	3.96	5.93	5.19 ± 0.95
C_{ssf}* (μg/ml)	21.00	11.76	8.19	12.68	13.41 ± 5.42
CL_{df} (ml/min/kg)	1.83	7.39	7.70	8.36	6.32 ± 3.02
CL_{do} (ml/min/kg)	6.02	5.62	8.24	9.52	7.35 ± 1.85
CL_{fd} (ml/min/kg)	2.70	7.00	8.82	13.61	8.03 ± 4.52
CL_{fo} (ml/min/kg)	0.00	0.99	0.54	0.00	0.38 ± 0.48
C_{ssf}/C_{ssd}	0.70	0.92	0.82	0.87	0.83 ± 0.09
C_{ssa}/C_{ssf}	1.31	1.24	1.26	1.05	1.21 ± 0.12
C_{ssa}*/C_{ssf}*	0.40	0.80	0.73	0.97	0.73 ± 0.24
High-rate infusion					
k_0H (μg/min/kg)	41.67	41.63	41.72	NA	41.67 ± 0.05
C_{ssd}H (μg/ml)	6.36	6.28	5.53	NA	6.06 ± 0.37
C_{ssf}H (μg/ml)	6.25	5.83	5.39	NA	5.82 ± 0.35
C_{ssf}H/C_{ssd}H	0.98	0.93	0.97	NA	0.96 ± 0.02
C_{ssa}H/C_{ssf}H	0.78	0.73	0.72	NA	0.74 ± 0.03

[a] SD, standard deviation; k_0, rate of infusion; *, variables after infusion of the drug to the fetus; C_{ss}, concentration at steady state; d, dam; f, fetus; CL, clearance; o, irreversible removal; a, amniotic fluid; H, after high-rate dideoxyinosine infusion; NA, not available.

pyrine clearance (0.07 ± 0.04 versus 0.09 ± 0.04; $P > 0.05$). Irreversible clearance of dideoxyinosine by the dam (CL_{do}) was 22.73 ± 3.83 ml/min/kg; such clearance by the fetus (CL_{fo}) was 0.18 ± 0.07 ml/min/kg.

For antipyrine (Table 2), C_{ssd} (6.27 ± 1.00 μg/ml) and C_{ssf} (5.19 ± 0.95 μg/ml) were not significantly different ($P > 0.05$) from C_{ssd}* (6.94 ± 2.13 μg/ml) and C_{ssf}* (13.41 ± 5.42 μg/ml), respectively. CL_{df} (6.32 ± 3.02 ml/min/kg) was not significantly different ($P > 0.05$) from CL_{fd} (8.03 ± 4.52 ml/min/kg). C_{ssf}/C_{ssd} (0.83 ± 0.09) and C_{ssf}H/C_{ssd}H (0.96 ± 0.02) were close to unity. C_{ssa}*/C_{ssf}* (0.73 ± 0.24) was not significantly different ($P > 0.05$) from C_{ssa}/C_{ssf} (1.21 ± 0.12) or from C_{ssa}H/C_{ssf}H (0.74 ± 0.03).

The pharmacokinetic parameter estimates (CL_{df}, CL_{fd}, CL_{do}, CL_{fo}) obtained by fitting the model in Fig. 1 to dideoxyinosine concentration-versus-time data from two animals agree closely with the values calculated by using the steady-state data for those animals (Tables 1 and 3). These estimates were obtained by simultaneously fitting the model to six sets of data for each animal (i.e., maternal and fetal plasma and amniotic fluid data after maternal and fetal infusions).

DISCUSSION

We deliberately chose the steady-state experimental design to study the transplacental transfer of dideoxyinosine in order to avoid having distributional disequilibrium confound the interpretation of our data. Under a non-steady-state design, drug concentrations in the dam and her fetus are constantly changing; therefore, the maternal-fetal plasma concentration ratio is not constant but varies with time. Even with a steady-state design, caution should be used in interpreting the fetal-maternal plasma drug concentration ratio since this value is dependent not only on the transplacental clearances (CL_{df} and CL_{fd}) but also on the irreversible loss of the drug by the fetus (CL_{fo}) (equation 11).

$$\frac{C_{ssf}}{C_{ssd}} = \frac{CL_{df}}{CL_{fd} + CL_{fo}} \quad (11)$$

Thus, a fetal-maternal concentration ratio of less than unity should not necessarily be interpreted as evidence of active fetal-maternal drug transport, since, despite passive placental transfer of the drug, a ratio of less than unity may be completely explained by the irreversible loss of the drug by the fetus. To determine whether dideoxyinosine is actively or

TABLE 3. Estimates of pharmacokinetic parameters for dideoxyinosine in two animals[a]

Parameter	Animal	
	T81511	F84292
k_{12} (min^{-1})	0.00168 ± 0.00081	0.00089 ± 0.00024
k_{21} (min^{-1})	0.01794 ± 0.00332	0.01330 ± 0.00195
k_{10} (min^{-1})	0.05094 ± 0.02185	0.05244 ± 0.00938
k_{20} (min^{-1})	0.00662 ± 0.00313	0.00430 ± 0.00189
k_{23} (min^{-1})	0.00130 ± 0.00214	0.00080 ± 0.00373
k_{23}* (min^{-1})	0.00068 ± 0.00109	0.00028 ± 0.00133
k_{32} (min^{-1})	0.00227 ± 0.00019	0.00153 ± 0.00044
V_d (ml/kg)	417 ± 167	534 ± 87
V_f (ml/kg)	47 ± 2	49 ± 2
V_a (ml/kg)	7 ± 12	7 ± 35
CL_{df} (ml/min/kg)	0.699 ± 0.210	0.474 ± 0.104
CL_{fd} (ml/min/kg)	0.838 ± 0.151	0.652 ± 0.092
CL_{do} (ml/min/kg)	21.248 ± 2.133	28.016 ± 1.349
CL_{fo} (ml/min/kg)	0.309 ± 0.146	0.211 ± 0.092
CL_{af} (ml/min/kg)	0.017 ± 0.027	0.011 ± 0.053
CL_{fa} (ml/min/kg)	0.061 ± 0.099	0.039 ± 0.182
CL_{fa}* (ml/min/kg)	0.032 ± 0.050	0.0138 ± 0.065

[a] SE, standard error; k, intercompartmental rate constant; 1, maternal compartment; 2, fetal compartment; 3, amniotic fluid compartment; *, variables after infusion of the drug to the fetus; V, volume of distribution; d, dam; f, fetus; a, amniotic fluid; CL, clearance; o, irreversible removal.

passively transferred across the placenta, we deliberately adopted an experimental design in which the drug is administered to both the dam and the fetus, allowing unique estimation of the transplacental clearances, CL_{df} and CL_{fd}. In addition, to allow for comparison with a passive diffusion marker, antipyrine was always included in our infusions. Ideally, CL_{df} and CL_{fd} should be estimated after simultaneous administration of the drug to the dam and her fetus. This is only possible, however, if labeled drug (radiolabeled or a stable labeled isotope) is administered to either the fetus or the dam while the other of the pair receives the unlabeled drug. We decided not to use this approach primarily because our experimental design involved long-term infusions, a prohibitively expensive method when using labeled drug. Our approach does make the assumption that all clearance parameters remain invariant in the period (approximately 1 week) between fetal and maternal drug administrations.

CL_{df} and CL_{fd} for dideoxyinosine were found not to be significantly different from each other, indicating passive diffusion of the drug across the placenta. This conclusion is supported by our observation that the dideoxyinosine fetal-maternal plasma drug concentration ratio is invariant over a 10-fold range change in the rate of dideoxyinosine infusion. These observations are consistent with the finding of passive passage of dideoxyinosine across other biological barriers, such as the membranes of T lymphocytes (2) and canine mononuclear cells (4). This finding is in contrast to those for many other dideoxynucleosides, which are normally found to be at least partially actively transported across cell membranes by carrier-mediated processes. The transplacental clearances of antipyrine were also found to be not significantly different from each other, indicating, as expected, passive diffusion of the drug across the placenta. However, the magnitudes of these clearances, as a result of the higher lipophilicity of antipyrine (octanol/water partition coefficient [P] = 1.77) (14), were greater than those estimated for dideoxyinosine ($P = 0.07$) (2).

Normalization of dideoxyinosine clearance with respect to antipyrine clearance allows one to make more meaningful comparisons of clearances obtained from in vivo and in vitro studies. For example, in the case of experiments with isolated perfused placental lobes, normalization of clearance to that of a flow-limited reference molecule (such as antipyrine) with negligible metabolism and protein binding corrects for experimental variables such as the extent of the perfused area and flow rates. Other investigators (3, 6), using isolated perfused human placentas, have also concluded that the transfer of dideoxyinosine across the placenta is passive and not saturable. The normalized CL_{df} calculated in our study (0.09 ± 0.04) was similar to the clearance index (clearance of dideoxyinosine/clearance of antipyrine) (0.14 ± 0.05) calculated by Bawdon et al. (3). Dancis et al. (6) concluded that 50% of the dideoxyinosine crossing the placenta from the maternal to the fetal side was degraded by the placenta. However, others have disputed this finding (5). We do not have data from which to draw conclusions regarding the metabolism of dideoxyinosine by the placenta. However, our results are adequately described by the model in Fig. 1, which attributes the C_{ssf}/C_{ssd} ratio of 0.5 to elimination of the drug by the fetus. In this model, the placenta may be considered part of the fetal compartment, and thus, irreversible elimination of dideoxyinosine other than by the dam may be either by the placenta or by the fetus.

The steady-state concentrations of dideoxyinosine achieved in the maternal plasma are within the range observed in the clinic (7) and close to the in vitro 50% inhibitory concentration for the human immunodeficiency virus (9). After maternal infusion, the steady-state concentrations of dideoxyinosine in the fetal plasma were approximately half those in the maternal plasma. This ratio (C_{ssf}/C_{ssd}) was lower than the corresponding ratio after antipyrine (0.83 ± 0.09) and zidovudine (0.85 ± 0.08) administration (8). These differences are explained by irreversible clearance of dideoxyinosine from the fetus, which is significant when compared with its transplacental clearances (Table 1). In contrast, because the irreversible clearance of antipyrine (Table 2) is marginal when compared with its transplacental clearances, the fetal-maternal plasma concentration ratio is close to unity. Since the lipophilicity of zidovudine (P = 0.86 to 1.26) (17, 18) is similar to that of antipyrine, a similar argument can be made to explain its fetal-maternal plasma drug concentration ratio.

When dideoxyinosine was infused into the fetuses, 25- to 77-fold higher concentrations (relative to the maternal plasma dideoxyinosine concentrations) were achieved in the fetal plasma. As seen in equation 12 (16),

$$\frac{C_{ssf}^*}{C_{ssd}^*} = \frac{CL_{do} + CL_{df}}{CL_{fd}} \quad (12)$$

the fetal-maternal concentration ratio, when drug is infused to the fetus, is dependent on the transplacental clearance of the drug as well as on the irreversible clearance from the dam. Since CL_{do} is much larger than CL_{fd}, the ratio is very large. In humans (7), renal clearance values for dideoxyinosine have been shown to exceed the glomerular filtration rate, indicating that dideoxyinosine undergoes active tubular secretion. The concentrations of dideoxyinosine achieved in fetal plasma during infusion of the drug to the fetus may have been sufficiently high to saturate a component of fetal renal excretion. This would result in a lower amniotic fluid/fetal plasma dideoxyinosine concentration ratio when the drug is administered to the fetus than when it is administered to the dam. This was observed in all four animals. Thus, in the three-compartment pharmacokinetic model (Fig. 1) used to describe the concentration of dideoxyinosine in maternal and fetal plasma and in amniotic fluid versus time, the renal clearance of dideoxyinosine was allowed to change with the route of administration (fetal versus maternal). With this approach, estimates of CL_{df}, CL_{fd}, CL_{do}, and CL_{fo} were similar to those calculated from the steady-state data. The model therefore appears to describe the data adequately. However, the pharmacokinetic parameters associated with amniotic fluid were estimated with poor confidence, in part because of the inherent variability in the concentration of dideoxyinosine in amniotic fluid-versus-time data. Amniotic fluid is accumulated fetal urine, and the amniotic fluid is swallowed by the fetus, resulting in some reabsorption of dideoxyinosine through the gastrointestinal tract and perhaps the lungs of the fetus. Both micturition and swallowing by the fetus may be erratic. These phenomena contribute to the variability in the dideoxyinosine concentration-versus-time profile in amniotic fluid. On the basis of the estimated intercompartmental rate constants (Table 3), the fetal compartment reached equilibrium with the maternal compartment with a half-life of 29 min for animal T81511 and 40 min for animal F84292.

We conclude that in *M. nemestrina*, the transplacental transfer of dideoxyinosine is passive and constant over the dosage range studied. Fetal exposure to dideoxyinosine is 50% the maternal exposure. When a constant infusion of dideoxyinosine is administered to the dam, drug does not accumulate in the fetus. We predict that when dideoxyinosine is administered to pregnant women in a chronic oral dosing regimen, the average area under the fetal plasma dideoxyinosine concentration-time curve will be half that of the maternal plasma

dideoxyinosine concentration-time curve during a single dosing interval.

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