Effect of Zidovudine on Transplacental Pharmacokinetics of ddI in the Pigtailed Macaque (Macaca nemestrina)

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Since zidovudine and ddI may be used in combination in the future to treat pregnant women who are human immunodeficiency virus positive, we conducted a study to determine whether zidovudine affects the transfer of ddI across the placenta. Zidovudine and ddI were infused simultaneously to three near-term pregnant macaques (Macaca nemestrina) at 156 ± 1.5 days of gestation. Samples of maternal and fetal blood and amniotic fluid were drawn at intervals for 30 h. The steady-state dideoxynosine concentrations in the plasma of the dam (Cssd), the fetus (Cssf), and the amniotic fluid (Cssa) and the ratios Cssd/Cssf and Cssd/Cssf were found to be not significantly different from the values previously determined after the administration of ddI alone during the same pregnancy. We conclude that concurrent zidovudine administration does not affect the transfer of ddI across the placenta in near-term Macaca nemestrina.

Clinical trials are being conducted to study the use of combination therapy with ddI (2',3'-dideoxyinosine, didanosine) and zidovudine (3'-azido-3'-deoxythymidine) in the treatment of patients infected with the human immunodeficiency virus (4, 13). The simultaneous or alternate use of these drugs, which have different dose-limiting toxicities, should reduce drug toxicity (13). However, as with any combination therapy, potential drug interactions must also be considered. For example, ddI and zidovudine could conceivably compete at transport sites. Also, since both of these dideoxynucleosides are renally secreted and metabolized (7, 8), each could potentially affect the clearance of the other when they are administered in combination. Information on these potential pharmacokinetic interactions is limited. No pharmacokinetic interaction between ddI and zidovudine was found when the drugs were administered in combination intravenously to either rats (21) or pigtailed macaques (Macaca nemestrina) (20). However, Gallo et al. (6) reported a trend (not statistically significant) toward a reduction in both the volume of distribution at steady state and the total clearance of zidovudine when ddI and zidovudine were coadministered to healthy monkeys (Macaca fascicularis). The potential effects of zidovudine on the pharmacokinetics of ddI were not taken into account in the latter study. Since combination therapy with ddI and zidovudine may be offered in the future to pregnant women who are human immunodeficiency virus positive, we investigated as part of an ongoing series of studies on dideoxynucleosides the possibility of a pharmacokinetic interaction between these two drugs, particularly as it may apply to maternal-fetal transfer. The nonhuman primate model was chosen because its placenta is anatomically and physiologically similar to those of humans. The pigtailed macaque is particularly suitable since not only is it susceptible to the simian immunodeficiency virus (14), which produces an AIDS-like syndrome, but it also has been shown to be susceptible to infection with human immunodeficiency virus (1). In addition, the pharmacokinetics of zidovudine (11) and ddI (17) in M. nemestrina have previously been shown by our laboratory to be similar to those in humans.

MATERIALS AND METHODS

ddI was supplied by the National Institute of Allergy and Infectious Diseases (Developmental Therapeutics Branch, Division of AIDS). Zidovudine (lot 80/0557-130-B) was donated by Burroughs Wellcome Co. (Research Triangle Park, N.C.). All other chemicals used were of reagent grade.

Animals. Three near-term pregnant macaques were studied at 156 ± 1.5 days of gestation (as estimated by ultrasound). Approximately 4 weeks prior to the studies, chronic catheters were placed (under general anesthesia) in the femoral artery and jugular vein in the fetus, in the amniotic cavity as described before (15), ddI (42.5 µg/min/kg of body weight given intravenously i.v.) and zidovudine (46 µg/min/kg i.v.) were simultaneously infused (at 15 ml/h via the femoral vein) to the dams for 30 h. Blood samples were drawn from the dam (2 ml, via the femoral artery) at 0, 24, 25.5, 27, 28.5, and 30 h and from the fetus (0.5 ml, via the jugular vein) at 0, 27, 28.5, and 30 h. Amniotic fluid samples (2 ml) were drawn to coincide with the time that each blood sample was drawn.

Analytical methods. ddI and zidovudine concentrations in plasma and amniotic fluid were determined simultaneously by a high-performance liquid chromatographic method (15) developed in our laboratory. Simultaneous determination of zidovudine concentrations did not require any adjustment to the previously described method. The intraday coefficients of variation for zidovudine by this method were 12.5% at a sample concentration of 0.4 µg/ml and 3.7% at 4.0 µg/ml. The accuracies (mean ± standard deviation of percent deviations from expected concentrations) were −1.7% ± 4.7% at 0.4 µg/ml and 4.4% ± 3.7% at 4.0 µg/ml.

Data analysis. The Mann-Whitney U test was used to compare the steady-state concentrations of ddI in maternal plasma (Cssm), fetal plasma (Cssf), and amniotic fluid (Cssa), their ratios, and systemic clearance (CL) with the corresponding values previously determined during the same pregnancy (138 days) after administration of ddI without zidovudine (15).

RESULTS AND DISCUSSION

We deliberately determined the fetal-maternal drug exposure ratio (Cssf/Cssf) at steady state because under non-steady-state conditions this ratio would change constantly with time because of the nonparallel change in drug concentrations in fetal and maternal plasma. Accurate determination of the area under the plasma concentration-time curve after administration of a single dose would provide information on exposure of the fetus to the drug relative to maternal exposure. However, since only a limited volume of blood may be obtained from the fetus, complete characterization of the area under the plasma...
alone. The pharmacokinetics of ddI, which they do, the provided that ddI and zidovudine follow linear pharmacokinetics (0.83 mg/min/kg i.v.). Interestingly, this ratio is with ddI (0.78 ± 0.06) was not significantly different (P > 0.05; Mann-Whitney U test) from the corresponding ratio when zidovudine was administered alone (0.83 ± 0.07) (Table 2) (11). This suggests that the transplacental transfer of zidovudine is unaffected by the coadministration of ddI. The mean ratio of the zidovudine concentration in amniotic fluid to that in fetal plasma (3.14 ± 0.31) after coinfusion with ddI was higher than the corresponding ratio reported for zidovudine alone (0.93 ± 0.27) (11) after 14.4 to 17.4 h of infusion. This discrepancy may be explained by one or more of the following reasons. A difference in experimental design could contribute to the discrepancy. In our study on zidovudine alone (11) ketamine and halothane were used prior to and during sampling. The presence of these drugs may have affected this ratio. Alternatively, since Boudinot et al. (3) have suggested that a saturable absorption mechanism may be involved in the absorption of zidovudine, it is possible that the presence of ddI in the amniotic fluid may interfere with the reabsorption of zidovudine from the amniotic fluid by the fetus. Zidovudine would therefore tend to accumulate in the amniotic fluid, giving rise to a higher ratio of the concentration in amniotic fluid to that in fetal plasma than that when zidovudine is administered alone. Even under these circumstances, such an interaction would not be clinically significant since the ratio of the concentration in fetal plasma to that in maternal plasma (unpublished data) after single- or multiple-dose administration. Thus, if the ddI/Css ratio in pregnant women (in our AIDS Clinical Trials Group Protocol 249) is also found to be approximately 50%, the dose administered to a pregnant woman will need to be doubled if the goal is to achieve ddI concentrations in the fetus comparable to those achieved in adults in the clinic. This difference in ratio between zidovudine and ddI most probably results from the magnitude of the transplacental CLs relative to the irreversible loss of the drug by the fetus. As indicated in our previous report (15), Csf/Css is not only a function of the CLs of the drug across the placenta from the fetus to the dam (CLsd) and vice versa (CLsd) but is also a function of the irreversible loss of the drug (by metabolism) from the fetus (CLfo): (Csf/Css = [CLsf/(CLsd + CLfo)]). When a drug crosses the placenta by passive diffusion, like ddI (15) and zidovudine (11) do, the magnitude of CLfo with respect to CLsf and CLsd will determine the Csf/Css ratio. On the basis of our data on the Csf/Css ratio for ddI and zidovudine, we propose that the CLfo for ddI relative to its CLsf and CLsd is greater than that for zidovudine. This is probably because ddI is less lipophilic (octanol/water partition coefficient [p] = 0.07) (2) than zidovudine (p = 1.26) (22), and therefore, the values of its transplacental clearances (CLsf and CLsd) are likely to be lower than those of zidovudine. Coadministration of zidovudine did not produce any significant change in the Csf/Css for ddI, Csf, Css, Csd, and Csf/Css for ddI were also not significantly changed (Table 1), indicating that the transplacental pharmacokinetics of ddI are unaffected by coadministration of zidovudine. Therefore, it is not necessary to adjust the dosage of ddI when it is given in combination with zidovudine.

Our interpretation of Csf/Css is based on total rather than unbound drug because the binding of both zidovudine and ddI to plasma proteins in M. nemestrina is negligible (11, 17). In addition, we assumed that the 2- to 3-week period between the times that experiments were conducted with ddI alone and ddI in combination with zidovudine did not produce significant changes in the transplacental pharmacokinetics of either ddI or zidovudine. This is a reasonable assumption because at near term, the structure and physiology of the placenta are unlikely to undergo significant changes over a 2- to 3-week period.

The Csf/Css for zidovudine when it was coadministered with ddI (0.78 ± 0.06) was not significantly different (P > 0.05; Mann-Whitney U test) from the corresponding ratio when zidovudine was administered alone (0.83 ± 0.07) (Table 2) (11). This suggests that the transplacental transfer of zidovudine is unaffected by the coadministration of ddI. The mean ratio of the zidovudine concentration in amniotic fluid to that in fetal plasma (3.14 ± 0.31) after coinfusion with ddI was higher than the corresponding ratio reported for zidovudine alone (0.93 ± 0.27) (11) after 14.4 to 17.4 h of infusion. This discrepancy may be explained by one or more of the following reasons. A difference in experimental design could contribute to the discrepancy. In our study on zidovudine alone (11) ketamine and halothane were used prior to and during sampling. The presence of these drugs may have affected this ratio. Alternatively, since Boudinot et al. (3) have suggested that a saturable absorption mechanism may be involved in the absorption of zidovudine, it is possible that the presence of ddI in the amniotic fluid may interfere with the reabsorption of zidovudine from the amniotic fluid by the fetus. Zidovudine would therefore tend to accumulate in the amniotic fluid, giving rise to a higher ratio of the concentration in amniotic fluid to that in fetal plasma than that when zidovudine is administered alone. Even under these circumstances, such an interaction would not be clinically significant since the ratio of the concentration in fetal plasma to that in maternal plasma, a measure of fetal exposure to the drug (relative to maternal exposure), would not be affected.

A lack of interaction between ddI and zidovudine with respect to the maternal-fetal transfer of the drugs is in agreement with the finding that the transplacental transfer of ddI is passive both in vivo (15) and in vitro (5). Zidovudine, too, is passively transferred across the placenta (10, 11, 18). Consistent with this is the observation that the overall clearance of ddI from plasma when ddI is administered alone (24.37 ± 2.78 ml/min/kg) (15) was not significantly different from that ob-

### Table 1. Steady-state ddI concentrations after infusion of ddI alone and in combination with zidovudine

<table>
<thead>
<tr>
<th>Therapy and animal</th>
<th>ddI concn (µg/ml) in the following macaques:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T81511</td>
</tr>
<tr>
<td>ddI alone</td>
<td></td>
</tr>
<tr>
<td>Dam</td>
<td>1.95</td>
</tr>
<tr>
<td>Fetus</td>
<td>1.19</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>3.86</td>
</tr>
<tr>
<td>Fetus/dam</td>
<td>0.61</td>
</tr>
<tr>
<td>Amniotic fluid/fetus</td>
<td>3.25</td>
</tr>
</tbody>
</table>

| ddI + ZDV |        |        |        |           |
| Dam          | 1.94   | 1.65   | 2.00   | 1.86 ± 0.19 |
| Fetus        | 0.92   | 0.73   | 0.84   | 0.83 ± 0.10 |
| Amniotic fluid | 3.65  | 3.24   | 4.49   | 3.79 ± 0.64 |
| Fetus/dam    | 0.48   | 0.44   | 0.42   | 0.45 ± 0.03 |
| Amniotic fluid/fetus | 3.96  | 4.44   | 5.37   | 4.59 ± 0.72 |

### Table 2. Steady-state zidovudine concentrations after coinfusion of ddI and zidovudine

<table>
<thead>
<tr>
<th>Animal</th>
<th>Zidovudine concn (µg/ml) in the following macaques:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T81511</td>
</tr>
<tr>
<td>Dam</td>
<td>1.35</td>
</tr>
<tr>
<td>Fetus</td>
<td>1.15</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>3.20</td>
</tr>
<tr>
<td>Fetus/dam</td>
<td>0.85</td>
</tr>
<tr>
<td>Amniotic fluid/fetus</td>
<td>2.79</td>
</tr>
</tbody>
</table>

* Data for ddI given alone are from reference 15.
* ddI was given at 42.5 µg/min/kg i.v., and zidovudine was given at 46.0 µg/min/kg i.v.
* The zidovudine dose was 23.0 µg/min/kg i.v.

P > 0.05 when compared with data obtained after administration of ddI alone.

[^1]: Data for ddI given alone are from reference 15.
[^2]: ddI was given at 42.5 µg/min/kg i.v., and zidovudine was given at 46.0 µg/min/kg i.v.
[^3]: The zidovudine dose was 23.0 µg/min/kg i.v.
[^4]: P > 0.05 when compared with data obtained after administration of ddI alone.
served (22.91 ± 2.39 ml/min/kg) when ddI was coadministered with zidovudine. Similarly, the clearance of zidovudine from plasma when zidovudine was coadministered with ddI (32.99 ± 1.66 ml/min/kg) was not different from that when zidovudine was previously infused alone to nonpregnant macaques in our laboratory (33.4 ± 7.9 ml/min/kg) (20).

A lack of interaction between zidovudine and ddI at a metabolic level could have been predicted, since ddI and zidovudine are metabolized by different metabolic pathways in macaques (12, 17) and ddI does not inhibit zidovudine glucuronidation in human liver microsomes (19). However, both drugs are secreted by the kidneys, possibly via the same pathway. Probencid, an organic anion transport inhibitor, decreased the renal CL of zidovudine (16) in monkeys, indicating active secretion of zidovudine. ddI is also renally secreted in an active manner (9). Therefore, the possibility of an interaction at a renal CL level (in both the dam and the fetus), which would manifest itself in the form of changes in systemic CL, could not have been precluded. Such an interaction would affect fetal exposure to one or both drugs. However, our data indicate that the total CL of ddI and zidovudine are not affected in the presence of the other drug, a finding that is in agreement with previous data obtained in our laboratory (20).

We conclude that the concurrent administration of zidovudine and ddI does not affect the transfer across the placenta or the CL of either drug in near-term M. nemestrina.

ACKNOWLEDGMENT

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REFERENCES


