Disposition of Zidovudine in Obese Pregnant Women with Human Immunodeficiency Virus Type 1 Infection

To the Editor—A recently published retrospective analysis by Matheson et al. [1] of zidovudine use during pregnancy suggests that antenatal zidovudine therapy may be responsible for a considerable amount of zidovudine’s protective effect in preventing vertical transmission of human immunodeficiency virus type 1 (HIV). Current Centers for Disease Control and Prevention guidelines suggest administering oral zidovudine (500 mg/day) to the mother beginning at 14–34 weeks of gestation, followed by intravenous zidovudine therapy during labor, and then oral therapy for the newborn [2]. These recommendations are based on a study that demonstrated zidovudine therapy reduces vertical transmission by about two-thirds when administered in this manner [3].

Administration of the same standard dose of oral zidovudine, however, does not result in the same plasma concentrations among adults [4, 5]. The variability in plasma concentrations is a consequence of between-patient differences in the absorption, distribution, metabolism, and excretion of zidovudine.

As determined on the basis of population pharmacokinetic information, the current dosage of zidovudine (100 mg five times daily) in a 70-kg person produces an average plasma concentration (Css) of ~0.7 μM; however, this Css can range from 0.18 to 2.8 μM [5]. While the effects of achieving and maintaining this average plasma concentration are unknown, suboptimal virologic results have been observed in patients receiving a 150-mg/day regimen of zidovudine [6]. Pregnancy introduces additional sources of variability in the disposition of zidovudine [7], likely as a result of an additional compartment (the fetus) and physiologic changes, such as increased hepatic blood flow and body weight.

We studied the plasma concentrations of zidovudine in 2 obese pregnant women with HIV. Zidovudine concentrations measured by RIA and pharmacokinetic parameters were determined with a Bayesian estimation strategy. Results are presented in table 1. The first woman weighed 142.5 kg and was in her eighth month of pregnancy when zidovudine concentrations were obtained. Her peak zidovudine concentration (1 h after a dose) was 1.7 μM after receiving 200 mg of the drug. This is about half of the expected concentration, on the basis of the linear nature of zidovudine’s disposition. The dosage required for this woman to achieve the average population Css (0.7 μM) would have been 1800 mg/day.

The second woman weighed 128 kg and was in her ninth month of pregnancy. Her peak concentration of zidovudine was 0.87 μM after receiving a 100-mg dose, and she would have required 1000 mg/day to reach the average Css. After these plasma concentrations were obtained, the first woman’s baby was stillborn, and the mother was lost to follow-up. The second woman gave birth to a healthy child, but whether or not the baby acquired HIV is not known at this time.

We found extreme variability in the pharmacokinetic disposition of zidovudine in these 2 obese pregnant women with HIV-infection. These data suggest that while there will be differences in the plasma concentrations of zidovudine among all pregnant women receiving the standard recommended dosage of 500 mg/day, there are certain groups in which this variability is more profound. Preliminary data suggest a relationship between maternal virus burden and the likelihood of transmission [8]; monitoring zidovudine disposition in the mother to achieve and maintain a targeted Css with a therapeutic goal of decreasing virus load may be an important strategy to help prevent more children from becoming infected.

Reference Table:

Table 1. Disposition of zidovudine in 2 obese pregnant women and the average population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Obese patient 1</th>
<th>Obese patient 2</th>
<th>Population average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily dosage (mg)</td>
<td>600</td>
<td>300</td>
<td>500</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Peak concentration (μM)</td>
<td>1.7</td>
<td>0.87</td>
<td>2.0</td>
</tr>
<tr>
<td>Total body clearance (L/h)</td>
<td>413</td>
<td>217</td>
<td>126</td>
</tr>
<tr>
<td>Daily dosage required to maintain average plasma concentration (mg)</td>
<td>1800</td>
<td>1000</td>
<td>500–600</td>
</tr>
</tbody>
</table>

References