Verapamil and Norverapamil in Plasma and Breast Milk During Breast Feeding

P. Anderson¹, U. Bondesson¹, I. Mattiasson², and B. W. Johansson²

¹ Department of Clinical Pharmacology, Karolinska Hospital, Stockholm and
² Heart Section, Department of Internal Medicine, Malmö Allmänna Sjukhus, Malmö, Sweden

Summary. The concentrations of verapamil and norverapamil have been measured in milk and plasma samples from a 32-year-old woman treated with verapamil 80 mg tds while breast-feeding her child.

The average steady-state concentrations of verapamil and norverapamil in milk were, respectively, 60% and 16% of the concentrations in plasma.

The breast-fed child received less than 0.01% of the dose of verapamil given to the mother. No verapamil or norverapamil (< 1 ng/ml) could be detected in the plasma from the child.

Key words: verapamil, breast milk; norverapamil, breast feeding, pharmacokinetics

Material and Methods

In order to study the pharmacokinetics of verapamil and norverapamil in the mother under steady-state conditions, venous blood samples were collected 4 weeks after the start of treatment, before the morning dose of verapamil 80 mg and after 0.5, 1, 2, 3, 4, 6, and 8.5 h. On the following day (Day 2) venous blood samples were again collected 0, 1 and 2 h after the morning dose. Breast feeding of the 3-month-old child was started 1 h after the morning dose of verapamil. Milk samples (10 ml) were taken from the breast with an electric breast pump. The first milk sample obtained (0.5 h) was discarded and samples were then collected 1, 2, 3, 4, 6, and 8 h after the morning dose of verapamil. The following day (Day 2) milk samples were taken after 0, 1, and 2 h.

Verapamil and norverapamil were analysed by gas chromatography-solid phase mass spectrometry, using a slight modification of the technique described by Anderson et al. [5].

The plasma concentration data were treated according to a linear one-compartment model. The areas under the plasma concentration-time curves (AUC) of verapamil and norverapamil, and the areas under the milk concentration-time curves of verapamil and norverapamil, were estimated by the trapezoidal method. The elimination rate constant (k) of the last terminal portion of the concentration-time curve was calculated by linear least-squares regression analysis. Plasma and milk half-time (t½) were calculated as ln 2/k. The plasma clearance of orally-administered verapamil at steady state was calculated according to the equation:

$$CL = \frac{Dose}{AUC (0-8)}$$
Table 1. Pharmacokinetics of verapamil and norverapamil in plasma and breast-milk in a lactating woman receiving oral verapamil 80 mg tds

<table>
<thead>
<tr>
<th></th>
<th>Verapamil plasma</th>
<th>Verapamil milk</th>
<th>Norverapamil plasma</th>
<th>Norverapamil milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>k (h⁻¹)</td>
<td>0.243</td>
<td>0.161</td>
<td>0.264</td>
<td>0.519</td>
</tr>
<tr>
<td>t₁/₂ (h)</td>
<td>2.86</td>
<td>4.29</td>
<td>2.63</td>
<td>1.34</td>
</tr>
<tr>
<td>CL (ml · min⁻¹)</td>
<td>3890</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vₚ (l · kg⁻¹)</td>
<td>16.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cₗ₀ (ng · ml⁻¹)</td>
<td>42.9</td>
<td>25.8</td>
<td>56.0</td>
<td>8.8</td>
</tr>
<tr>
<td>AUC (0–8) (h · ng · m1⁻¹)</td>
<td>342.8</td>
<td>206.4</td>
<td>447.6</td>
<td>70.1</td>
</tr>
<tr>
<td>Ratio AUCₘₕlilk/AUCₘₚₐₙ₃a</td>
<td>0.60</td>
<td>-</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

The apparent volume of distribution of the orally administered verapamil under steady-state conditions (Vₚₛₛ) was calculated as CL/k.

Results

The plasma and milk concentrations of verapamil and norverapamil in the mother are shown in Table 1. The corresponding concentration-time curves are shown in Fig. 1.

The plasma concentration of verapamil after the single dose ranged between 10.3 and 141.7 ng · ml⁻¹ at steady state on Day 1, i.e., there was an almost 14-fold variation in the plasma concentration of verapamil. The plasma levels of norverapamil during the same dosage intervals showed a similar variation between 14.0 and 182.0 ng · ml⁻¹.

The concentrations of verapamil in milk were lower than but paralleled by those in plasma. The maximum verapamil concentration in milk of 78.9 ng · ml⁻¹ was found 1 h after the dose of verapamil. In contrast, the concentration of norverapamil in milk was much lower, the maximum concentration of 22.0 ng · ml⁻¹ being reached at 2 h.

Plasma and milk samples taken during a similar dosage interval on the next day (Day 2) in general showed somewhat lower concentrations of verapamil and norverapamil (Fig. 1), as the morning dose of verapamil 80 mg was only given on Day 1.

In a venous blood sample taken from the child 1.5 h after the administration of verapamil, i.e. 0.5 h after the start of lactation (Day 1), neither verapamil nor norverapamil could be detected (<1 ng · ml⁻¹).

The pharmacokinetics of verapamil and norverapamil are presented in Table 1. The plasma half-time of verapamil was 2.86 h and the oral plasma clearance at steady state was 3890 ml · min⁻¹. The plasma half-time of norverapamil was 2.63 h. The steady-state concentrations AUCₜ₋ₕ of verapamil and norverapamil in plasma were estimated to be 42.9 and 56.0 ng · ml⁻¹, respectively. The steady-state concentrations of verapamil and norverapamil in milk were 25.8 and 8.8 ng · ml⁻¹, respectively. The ratios between the total concentrations in milk and in plasma (AUC (0–8) milk/AUC (0–8) plasma) were 0.60 for verapamil and 0.16 for norverapamil.