Breast milk distribution of theobromine from chocolate

Six nursing mothers ingested 113 gm of Hershey's milk chocolate containing 240 mg of theobromine. Samples of plasma, saliva, and breast milk were assayed for theobromine by high pressure liquid chromatography. Peak theobromine concentrations of 3.7 to 8.2 mg/l were found in all fluids at 2 to 3 hours after ingestion of chocolate. The disposition half-life of theobromine averaged 7.1 ± 2.1 hours, body clearance was 65 ± 20 ml/hour/kilogram, and the apparent volume of distribution was 0.62 ± 0.13 l/kg. Theobromine is only slightly bound to plasma and milk proteins and concentrations in milk and saliva matched plasma data closely. The mean concentration ratios were 0.82 ± 0.17 for milk/plasma and 0.92 ± 0.17 for saliva/plasma. If a mother ate a 4-ounce chocolate bar every 6 hours and the infant nursed when the theobromine concentration in milk was at its peak, the infant could ingest about 10 mg of theobromine per day.

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MUCH FOLKLORE concerns the ingestion of chocolate by nursing mothers. It has been said, "the food which produces the greatest trepidation [in mothers] is chocolate."1 Most common is the claim that chocolate consumed by the mother will cause diarrhea in the infant. Conversely, constipation in the infant has also been attributed to this food. In 1918, Talbot1 reported a case of eczema in a breast-fed infant after her mother ate a pound of chocolate. The eczema cleared when chocolate was omitted from the mother's diet, then reappeared when she drank cocoa.

No studies were found in the literature determining possible mechanisms by which chocolate ingested by a mother could adversely affect the nursing infant. Chocolate contains substantial amounts of theobromine and it is conceivable that this methylxanthine may be secreted in milk in sufficient quantities to affect breast-fed infants. This study assesses the absorption of theobromine from chocolate and the distribution of this xanthine into the milk of lactating women.

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Abbreviations used
Tv b: half-life
Cl b: body clearance
V b: volume of distribution

MATERIALS AND METHODS
Six Caucasian nursing women participated in the study. The subjects ranged in age from 21 to 36 years, weighed 55 to 70 kg, and had been nursing their infants for periods of three to 37 weeks. Only one woman smoked cigarettes. The purposes and procedures of the investigation were explained to the women and their informed consent was obtained.

The participants were asked not to consume any tea, coffee, cola drinks, or chocolate for 24 hours prior to the study. After an overnight fast, the women ate (within 10 minutes) 113 gm (4 ounces) of Hershey's milk chocolate.
Theobromine pharmacokinetics and distribution into breast milk of six nursing women following ingestion of 120 grams of chocolate.

Table I. Theobromine pharmacokinetics and distribution into breast milk of six nursing women following ingestion of 120 grams of chocolate

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (hr)</td>
<td>4.5-10.5</td>
<td>7.1 (2.1)</td>
</tr>
<tr>
<td>Volume of distribution (1/kg)*</td>
<td>0.44-0.82</td>
<td>0.62 (0.13)</td>
</tr>
<tr>
<td>Body clearance (ml/kg/hr)</td>
<td>37-89</td>
<td>65 (20)</td>
</tr>
<tr>
<td>Peak concentration (mg/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>4.5-7.8</td>
<td>5.7 (1.4)</td>
</tr>
<tr>
<td>Milk</td>
<td>3.7-7.5</td>
<td>5.3 (1.1)</td>
</tr>
<tr>
<td>Saliva</td>
<td>4.5-8.2</td>
<td>5.7 (1.3)</td>
</tr>
<tr>
<td>Time of peak concentration (hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>1.5-3.1</td>
<td>2.7 (0.6)</td>
</tr>
<tr>
<td>Milk</td>
<td>2.1-3.3</td>
<td>2.7 (0.5)</td>
</tr>
<tr>
<td>Saliva</td>
<td>2.0-3.2</td>
<td>2.8 (0.5)</td>
</tr>
<tr>
<td>Concentration ratio$\dagger$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk:plasma</td>
<td>0.60-1.06</td>
<td>0.82 (0.17)</td>
</tr>
<tr>
<td>Saliva:plasma</td>
<td>0.64-1.10</td>
<td>0.92 (0.17)</td>
</tr>
<tr>
<td>Percent protein binding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>15-25</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Milk</td>
<td>0-24</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>

*Calculated from: $V_d = \text{dose} \times t_{\chi}/(0.693 \times \text{area})$, where area is the total area under the plasma concentration versus time curve.
†Calculated from: $C_l = \text{dose}/\text{area}$.
‡Calculated from the ratio of areas under the respective concentration versus time curves.
§Concentrations in milk from left and right breasts are similar (Fig. 2).

RESULTS

The time course of theobromine concentrations in the plasma, milk, and saliva of one subject (K. L.) is shown in Fig. 1. The pattern is typical of that seen in the six women in this study. Theobromine was absorbed rapidly from chocolate with an average (± SD) absorption half-life of 0.5 ± 0.1 hours. A maximum theobromine concentration in the plasma of 4.5 to 7.8 mg/l was attained between 1.5 and 3.1 hours while milk yielded maximum concentrations of 3.3 to 7.5 mg/l at 2.1 to 3.2 hours, respectively, after administration.

The pharmacokinetic data obtained for the six subjects are summarized in Table I. In analyzing the time course of theobromine concentrations, a one-compartment open model and first-order kinetics were assumed. The elimination half-life in the six subjects varied from 4.5 to 10.5 hours. Assuming complete bioavailability of theobromine, the body clearance ranged from 37 to 89 ml/kg/h and apparent volume of distribution was 0.44 to 0.82 l/kg.

Table I. Theobromine pharmacokinetics and distribution into breast milk of six nursing women following ingestion of 120 grams of chocolate

If theobromine was not completely absorbed, the actual values for $C_l$ and $V_d$ would be less than those calculated.

The concentration of theobromine in the plasma, milk, and saliva generally declined in parallel. One exception was a woman who exhibited a theobromine $t_{\chi}$ of 7.1 hours in plasma while milk and saliva yielded a $t_{\chi}$ of 3.7 to 4.4 hours. All except one woman breast-fed her infant during the course of the study. No change in milk:plasma ratio occurred upon breast feeding and essentially identical theobromine concentrations were found in breast milk at the beginning and at the completion of nursing by the infants.
Theobromine appears to equilibrate rapidly between plasma and the other fluids analyzed, as indicated by the parallel rise and fall of the respective concentrations shown in Fig. 1. The mean milk-to-plasma ratio was 0.82. The range of values and similarity in distribution ratios for milk from the left and right breasts are shown in Fig. 2. The mean saliva to plasma ratio was 0.92 ± 0.17. Protein binding is sometimes a factor determining drug distribution from plasma into other biologic fluids. The extent of binding of theobromine to plasma proteins averaged 21% while the range of binding to macromolecules in milk was 0 to 24%.

**DISCUSSION**

The pharmacokinetics of theobromine determined in this study are similar to those observed previously with theophylline in nursing women. Theophylline is eliminated slightly faster with a mean t½ of 5.6 hours compared to 7.1 hours for theobromine while average CL values were 3.23 and 3.80 l/hour, respectively. The mean VD for theophylline was 24.5 liters versus 36.4 liters for theobromine. This difference may be related to plasma protein binding because theophylline is 42 to 69% bound while theobromine is only 15 to 25% bound in plasma. Binding in milk is slight (less than 24%) for both xanthines. The range of the milk to plasma ratios was 0.61 to 0.87 for theophylline and 0.59 to 1.09 for theobromine.

Yurchak and Jusko recently reported a case of a breast-fed infant exhibiting irritability and fretful sleeping on days the mother took theophylline. In a subsequent study of four nursing women given this drug, it was found that sufficient theophylline distributed into milk to yield a pharmacologic dose to a nursing infant. Theobromine shares the pharmacologic effects of the other methylxanthines, theophylline and caffeine. These effects include central nervous system stimulation, production of diuresis, stimulation of cardiac muscle, and relaxation of smooth muscle. Theobromine is present in all cacao products. The amount of theobromine contained in four ounces of Hershey's milk chocolate is similar to the amount (240 mg) used as a single pharmacologic dose.

This study shows that theobromine passes freely into human milk following ingestion of chocolate. The mean milk to plasma ratio was 0.82 and the peak concentration in the milk occurred at 2.1 to 3.3 hours after ingestion of chocolate. Based on our average data, if a woman ate a four-ounce chocolate bar every six hours and her infant ingested a liter of milk daily, nursing when the concentration of theobromine in milk was at a peak, the infant could be exposed to about 10 mg theobromine or approximately 1 to 2 mg/kg/day. This dosage would probably not be pharmacologically significant for most infants. This amount could be sufficient, however, to produce effects in some sensitive individuals. Recent studies with theophylline and caffeine in newborn infants have revealed extremely slow metabolism of these drugs. For example, while adolescents exhibit an average t½ for theophylline of 3.7 hours, premature infants show t½ values ranging from 13 to 58 hours. Similarly, caffeine has a t½ of three to five hours in adults and 32 to 149 hours in newborn infants. It is probable that the half-life of theobromine is increased in newborn infants as it is for theophylline and caffeine. If this were the case and if the mother frequently ate chocolate, the breast-fed infant could accumulate substantial amounts of theobromine. This may be responsible for some of the purported effects of the drug.

No adverse effects were seen in the infants during the present study. The only adverse effect noted was slight nausea in three of the women immediately after ingestion of the chocolate. Babka and Castell found that chocolate syrup (containing 101 to 405 mg theobromine and 8 to 31 mg caffeine) administered to normal adult volunteers caused an immediate and sustained decrease in lower esophageal sphincter pressure. In some subjects this was associated with symptomatic reflux. These effects were attributed to the methylxanthines in the chocolate which also may relate to the veracity of the folklore associated with this candy.
We appreciate the technical assistance of Mrs. Anna Poliszczuk and the referral of volunteers by Drs. Jacob Steinhart and Theodore Putnam.

REFERENCES

3. Zoomas BL: Personal communication, Hershey Food Corporation, Hershey, PA.