Lidocaine, Quinidine, and Theophylline Binding to Human Milk*

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ABSTRACT

Lidocaine, quinidine, and theophylline binding to normal pooled mature human milk was determined using equilibrium dialysis at 4°C. Binding to milk was compared with binding to pooled human serum. The observed binding was related to the relative lipid solubility of each drug in milk. The potential for the excretion of each drug into milk was also evaluated.

Introduction

Knowledge of drug excretion into human milk is important to women requiring pharmacotherapy during breast-feeding of their infants. Although the excretion of lidocaine and quinidine into human milk has been demonstrated in single case reports, the percent binding of these drugs to human milk has not been reported. While the excretion of theophylline into human milk has been documented and its binding to milk has been investigated, the report was a single study in which the results were widely discrepant, ranging from 0 percent to 24 percent binding.

The present study determines the percent binding of lidocaine, quinidine, and theophylline to human milk using equilibrium dialysis and compares it to their binding to human serum based upon the physicochemical characteristics of each drug.

Materials and Methods

NORMAL MILK POOL

Residual mature human milk samples were obtained from 11 normal, non-drug using women who were breast-feeding their infants. The samples were pooled in volumes ranging from 15 mL to 95 mL per individual. These specimens had been frozen after use in another research project. To this pooled mixture was added saturated sodium fluoride, 25 mL/L, as a preservative. This protocol had been approved by the Human Subjects Committee of the University of California, San Diego School of Medicine. The pH of the pooled milk, as determined by pH meter, was 6.9. Its total protein concentration was 12 g/L, measured by an automated timed-endpoint biuret method.*
Drug Solutions

Lidocaine hydrochloride monohydrate,* quinidine sulfate dihydrate,† and theophylline free acid‡ were each prepared at concentrations of both 5 and 10 mmol/L in the pooled human milk and in phosphate buffer, pH 7.4, 0.1 mmol/L. To each solution was added saturated sodium fluoride, 25 mL/L, as a preservative.4

Equilibrium Dialysis

Equilibrium dialysis was performed with dialysis cells of volume 5 mL on each side of the membrane; and dialysis membranes of molecular-weight cutoff 6,000, 0.073 mm thickness.§ To facilitate the establishment of equilibrium, each drug concentration in milk was dialyzed against the same concentration in buffer on a platform rocker in a walk-in refrigerator at 4°C for 18 hours. Each drug concentration was studied in duplicate. These same conditions have been previously used by this laboratory for study of drug binding to various human tissues.4

Drug Analyses

Post dialysis milk and buffer solutions were diluted in drugfree pooled human serum¶ to achieve concentrations within the range of linearity of the assays used. Dilutions ranged from 50 to 1,000-fold. Lidocaine and quinidine were measured by automated homogeneous enzyme immunoassays§ while theophylline was measured by an automated particle-enhanced turbidimetric immunoassay.**

Calculation of Binding

Since the drug concentrations in post-dialysis milk samples (C_milk) represented total (bound plus free, B + F) drug while those in the post-dialysis buffer samples (C_buffer) represented free (F) drug, the concentration of bound (B) drug was given by (C_milk - C_buffer). The percent binding was then calculated as follows:

\[ %B = 100\% \times \frac{(B)}{(B + F)} = 100\% \times \frac{C_{\text{milk}} - C_{\text{buffer}}}{C_{\text{milk}}} \]

The average values from the duplicate experiments for each drug were used for each calculation.

Results

The percent binding of lidocaine, quinidine, and theophylline to human milk is shown in table I. Quinidine demonstrated a relatively high percent binding at 5 (74 percent) and 10 mmol/L (44 percent); lidocaine showed lower binding (28 percent and 23 percent, respectively); and theophylline showed only minimal binding (4 percent and 5 percent, respectively.)

Discussion

Lidocaine, quinidine, and theophylline were studied at high concentrations (5 and 10 mmol/L) in order to permit relatively extensive dilution (50- to 1,000-fold) of the milk and buffer samples, thereby minimizing matrix effects in the serum-based drug immunoassays utilized. The temperature of 4°C and addition of sodium fluoride have previously been used to preserve these drugs during prolonged dialysis.4

The percent binding of quinidine to human milk (5 mmol/L, 74 percent; 10 mmol/L, 44 percent) was greater than its binding to pooled human serum previously studied under identical conditions by this laboratory (5 mmol/L, 36 percent; 10 mmol/L, 29 percent).4 This may be explained by the fact that quinidine is relatively lipophilic, as reflected by its much greater solubility in chloroform than in water.5

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† Matheson Coleman & Bell, East Rutherford, NJ 07073.
‡ Bel-art #D–1600–5, Fisher Scientific, Pittsburgh, PA 15205.
¶ Product #7023, Sigma Chemical Company, St. Louis, MO 63178.
¶¶ EMIT, Syva Company, San Jose, CA 95130.
** Beckman Instruments, Inc., Fullerton, CA 92634.
LIDOCAINE, QUINIDINE, AND THE THEOPHYLLINE BINDING TO HUMAN MILK

TABLE I

<table>
<thead>
<tr>
<th>Drug Concentration Studied</th>
<th>Measured Concentrations (mmol/L)</th>
<th>Calculated Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milk (B+F)</td>
<td>Buffer (F)</td>
</tr>
<tr>
<td>5 mmol/L:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine (1,172 mg/L)</td>
<td>6.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Quinidine (1,954 mg/L)</td>
<td>5.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Theophylline (901 mg/L)</td>
<td>5.5</td>
<td>5.3</td>
</tr>
<tr>
<td>10 mmol/L:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine (2,343 mg/L)</td>
<td>12.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Quinidine (3,914 mg/L)</td>
<td>7.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Theophylline (1,802 mg/L)</td>
<td>11.1</td>
<td>10.5</td>
</tr>
</tbody>
</table>

B = Bound drug.
F = Free drug.
Each value is the average of two duplicates.

Consequently, the high lipid content of human milk should enhance its binding in this fluid relative to serum. The difference between the pKb of quinidine (8.3), a weak base, and the pH of the milk studied (6.9) is greater than that between the pKb of quinidine (8.3) and the pH of human serum (7.4) so that there is relatively more ionization of quinidine in milk than in serum. In vivo, this would lead to "ion-trapping" and would further enhance the excretion of quinidine into milk.

Lidocaine, also a weak base, has a pKb (7.9) lower than that of quinidine so that the difference between its pKb and serum pH is less than that of quinidine, thereby leading to relatively less "ion-trapping" of lidocaine than quinidine in milk in vivo. The percent binding of lidocaine to milk observed here in vitro (5 mmol/L, 28 percent; 10 mmol/L, 23 percent) is lower than that for quinidine. Furthermore, it is greater than the binding of lidocaine to human serum previously studied under identical conditions by this laboratory (5 mmol/L, 4 percent; 10 mmol/L, 5 percent). This may be due to the fact that, like quinidine, lidocaine is relatively lipophilic as reflected by its good solubility in chloroform and relative insolubility in water. Thus, the high lipid content of human milk should facilitate its binding in this matrix.

In contrast, theophylline is a weak acid of pKa 8.6. Consequently, it is relatively less ionized in milk (pH 6.9) than in serum (pH 7.4) so that, in vivo, there would be minimal "ion-trapping" observed in milk. Its low binding to milk found here in vitro (5 mmol/L, 4 percent; 10 mmol/L, 5 percent) relative to human serum previously studied by this laboratory under identical conditions (5 mmol/L, 29 percent; 10 mmol/L, 19 percent) may be due to the fact that theophylline is much less lipophilic than either quinidine or lidocaine. This is demonstrated by its relatively modest solubility in chloroform.

The importance of the effects of ionization and lipophilicity of drugs on their excretion into milk has been suggested by others as well. Knowledge of the percent binding of lidocaine, quinidine, and theophylline to human milk should further the understanding of their relative excretion into this matrix. It should also be important to mothers who breast-feed their infants while receiving one or more of these medications.
Acknowledgments

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References