Estimates of Nursing Infant Daily Dose of Fluoxetine through Breast Milk

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Background: This study compared three methods of estimating the daily dose of fluoxetine to nursing infants and the relationship between these estimates and infant serum concentrations.

Methods: Breast milk and infant serum concentrations of fluoxetine and norfluoxetine were obtained from 10 nursing mother–infant pairs. Quantification of daily infant dose was determined by three methods: 1) collection of the total volume of breast milk over 24 hours and determination of the average breast milk concentration (Baby's Total Daily Dose); 2) determination of the maximum and minimum breast milk concentrations during 24 hours and an estimated milk consumption of 150 mL/kg/day (Atkinson Model); and 3) determination of the gradient of excretion of medication into breast milk at a specified time after the maternal dose, applying this gradient to each nursing collection and summing the values for 24 hours (Mathematical Model). The relationship between the 24-hour medication dose, obtained from each method, and the infant serum concentrations was examined.

Results: A total of 177 breast milk and 10 infant serum samples were collected. An estimate of the infant daily medication dose obtained by the Mathematical Model was the best predictor of total infant serum concentration.

Conclusions: Breast milk analysis may allow one to determine whether medication concentrations will be detectable in an infant, eliminating the need for an infant serum concentration. Although the Mathematical Model seems to reflect infant serum concentration most accurately, all three methods suggest that the maximum dose that a nursing child receives over the course of a year equals as much as 120 mg, or 160 ± 47% of the maternal daily dose. Biol Psychiatry 2002;52:446–451 © 2002 Society of Biological Psychiatry

Key Words: Breastfeeding, postpartum, depression, fluoxetine, collection, infant

Introduction

The postpartum period represents a time of increased vulnerability for the onset or recurrence of major depression (O’Hara 1986). The impact of postpartum depression can be significant, affecting maternal–child bonding (Murray et al 1996; Stein et al 1991) and infant development (Campbell and Cohyn 1991; Murray 1997). In addition, untreated maternal depression can progress to include symptoms of suicidality. Although treatment options include psychotherapeutic interventions (Appleby et al 1997), in many cases, symptom severity may warrant the use of psychotropic medications. Postpartum women who require pharmacologic intervention for a psychiatric condition who desire to continue breastfeeding are faced with a difficult dilemma. The documented health benefits of breast milk and support by the American Academy of Pediatrics places these women, infants, and their treating clinicians in a precarious situation.

After a review by Wisner and colleagues (1996), the data on antidepressant use in postpartum breastfeeding women rapidly expanded. Nevertheless, data regarding the extent of medication exposure in the nursing infant, as well as any subsequent effects on infant growth and development, are limited. Although infant serum concentrations can be obtained, many women feel averse to subjecting an infant to a potentially unnecessary venipuncture. If further information about the relationship between breast milk and infant serum concentrations were available, women may have a desired alternative.

Although numerous case reports, case series, and small studies have examined breast milk and infant serum concentrations, a disparity has emerged in the method of estimating infant daily dose. Several groups utilize the concentration of medication in breast milk relative to that in maternal serum to provide the milk-to-plasma (M/P) ratio. Estimates of the infant’s daily dose of medication have frequently used such measures and an estimated daily infant milk consumption of 150 mL/kg/day to provide the total infant daily dose (Ilett et al 1998; Kristensen et al 1999; Ohman et al 1999; Schmidt et al 2000; Spigset et al 1997).
The limitations of single-point breast milk measures were underscored by detailed breast milk excretion studies of sertraline (Stowe et al 1997), paroxetine (Stowe et al 2000), and fluoxetine (Kristensen et al 1999). Kristensen et al (1999) found greater variability and higher M/P ratios with single breast milk measurements when compared with average milk concentrations and suggest that calculations based on frequent sampling more accurately represent infant dose. In an earlier study of sertraline (Kristensen et al 1998), the infant daily dose calculated using the average milk concentration (AUCmilk/dose interval time) and an estimated milk volume of 150 mL/kg/day was four times greater than that calculated from measured cumulative drug excretion and breast milk volume over 24 hours.

More extensive investigations have identified that sertraline (Stowe et al 1997) and paroxetine (Stowe et al 2000) demonstrate a concentration gradient from fore milk to hind milk, with sertraline demonstrating a time course effect and maximum concentrations at 7–10 hours after dose. Frequent sampling across time and intensive sampling across a single feed may more accurately represent an infant’s dose of medication.

Given the variability in the methods of the studies to date, our group compared three different methods of estimating a nursing infant’s daily dose of fluoxetine. These methods included 1) collection of the total volume (mL) of breast milk from a single breast for 24 hours and determination of the average breast milk concentration (ng/mL), followed by a multiplication by two to account for both breasts (Baby’s Total Daily Dose); 2) determination of the maximum and minimum breast milk concentration during 24 hours and application of an estimated milk consumption of 150 mL/kg/day (Atkinson Model) (Atkinson et al 1988); and 3) determination of the gradient of excretion at a specified time after maternal dose, applying this gradient calculation to each breastfeeding time/collection and summing the values for 24 hours (Mathematical Model). The relationship between the infants’ estimated 24-hour medication dose, obtained from each method, and the infant serum concentrations of medication obtained (1–5 hours after nursing) was examined.

Methods and Materials

Subjects

Ten postpartum women who were treated with fluoxetine for major depressive disorder during breastfeeding were recruited for participation in the current study. Subjects were informed of the unknown risks associated with the use of fluoxetine during nursing and of other available treatment options. Written informed consent, in a manner approved by the UCCA IRB, was obtained from all subjects for participation in the study.

Sample Collection

For seven subjects, breast milk samples were collected on 2 separate days. All breast milk samples were taken from the same breast and collected in sterile polypropylene tubes with the use of electric or manual breast pumps. On the first day of collection, subjects collected samples from the initial feed in 10-mL aliquots from fore milk to hind milk. For the remainder of feedings that day, subjects collected the first 10 mL of breast milk at 3–5 hour intervals. On the second day of collection, subjects pooled breast milk collected from a single breast for each feed. Infants were fed from the opposite breast. For six of these subjects, breast milk concentrations of fluoxetine and norfluoxetine obtained on the first day of collection have been reported previously (Hendrick et al 2001).

For three subjects, breast milk samples were collected from the same breast over the course of a single day. This change in milk collection was implemented for subject convenience. For the first feed of the day, the women collected breast milk in 10-mL aliquots from fore milk to hind milk. For the remainder of feedings that day, the subjects collected the first 10 mL of breast milk separately, and the remaining breast milk was pooled as one collection.

Breast milk samples were labeled and stored in the subjects’ home freezer until brought to the UCLA laboratory, where they were kept frozen. Once samples from at least two subjects were received, they were packed in dry ice and shipped to the Emory University School of Medicine for assay.

Maternal and infant serum samples were obtained following a minimum of 6 weeks of maternal treatment with a fixed dose of fluoxetine. Maternal and infant serum samples were collected in Vacutainer tubes (American Scientific, Las Vegas, Nevada) without additives. Blood was centrifuged at 950 g for 10 min, with serum removed and transferred in 1-mL aliquots to sterile polypropylene tubes. Tubes were coded and stored at −20°C until assay. Maternal and infant serum concentrations have been previously reported by our group (Hendrick et al 2001).

Determination of Breast Milk and Serum Concentrations of Fluoxetine

Breast milk analysis of fluoxetine and norfluoxetine was performed at the Emory University School of Medicine and consisted of a liquid/liquid and solid phase extraction (100 mg EXTRASEP C18, Nalge Nune International, Rochester, New York) followed by high-performance liquid chromatography (HPLC) separation and ultraviolet detection, as described by Stowe et al (2000). Serum analysis of fluoxetine and norfluoxetine was performed via an isocratic HPLC separation as described by Hendrick et al (2001).

Quantification of Fluoxetine and Norfluoxetine

Quantification of the 24-hour infant dose of fluoxetine and norfluoxetine was determined in three ways.

1. Baby’s Total Daily Dose. The concentration and volume of each collection were used to determine a 24-hour infant dose.
2. Atkinson Model. An estimate of the 24-hour dose from maximum to minimum was calculated using the following equation:

\[
\frac{[\text{Fluoxetine}/\text{Norfluoxetine}]_{\text{BM}}}{\text{Volume of Breast Milk (150 ml/kg)}} \times \text{Infant Weight}
\]

The maximum dose was determined using the highest measured concentrations of fluoxetine and norfluoxetine. The minimum dose was determined using the lowest measured concentrations of fluoxetine and norfluoxetine. The volume of milk ingested was calculated as 150 mL/kg/day. Maximum and minimum breast milk concentrations were divided by the maternal serum concentration to provide a range of M/P ratios.

3. Mathematical Model. To determine the excretion gradient of fluoxetine and norfluoxetine into breast milk, the concentration for each 10-mL fraction of the first feed was divided by that of the minimum observed concentration and presented as a ratio from fore milk to hind milk. This excretion gradient was extrapolated to each subsequent feed and used to calculate a 24-hour infant dose for fluoxetine and norfluoxetine and to estimate a 24-hour volume of milk ingested.

The total amounts obtained from methods 1 and 3 were doubled to approximate exposure from both breasts. Each model provided an estimate of infant daily medication dose.

Statistical Analysis

Three multiple linear regression analyses were used to investigate the relationship between the infant medication dose and the total infant serum concentration (the sum of the infant serum fluoxetine concentration and the infant serum norfluoxetine concentration). The independent variables included the infant dose of fluoxetine and the infant dose of norfluoxetine. The total infant serum concentration served as the outcome variable. The infant medication dose and the total infant serum concentration were continuous variables.

Paired t tests comparing calculated values of the infant medication dose were used to determine which model gave the most conservative estimate.

Results

Ten postpartum women who were being treated with fluoxetine at a mean dose of 34 ± 12.8 mg/day were included in our study. The 10 infants ranged in age from 5 weeks to 5 months. A total of 177 breast milk samples and 10 infant serum samples were obtained. Eight women collected 90–100% of breast milk over the course of the day. Two women (patients 3 and 7) collected 50–70% of breast milk and did not collect enough samples from the first feed to determine a gradient; therefore, multiple linear regression analyses to determine the relationship between estimates of daily fluoxetine dose and infant serum concentrations included only the eight subjects who collected 90–100% of breast milk.

Detectable concentrations of fluoxetine (3–242 ng/mL) and norfluoxetine (18–314 ng/mL) were present in all breast milk samples. Information regarding the maternal fluoxetine dose, the maternal serum concentration, infant weight, the infant daily dose for each model, and the infant serum concentration for each subject are presented in Table 1.

Results of the linear regression analyses are presented in Table 2. Estimates of the infant 24-hour medication dose obtained by the Mathematical Model were the best predictors of total infant serum concentration (\(r^2 = .93, p = .0014\)). In comparison, the Atkinson Model (\(r^2 = .56, p = .13\)) and Baby’s Total Daily Dose (\(r^2 = .44, p = .24\)) seemed less able to predict the total infant serum concentra-
Estimating Infant Daily Dose of Fluoxetine and Norfluoxetine

Table 2. Linear Regression Analyses for Three Methods of Estimating Infant Daily Dose of Fluoxetine and Norfluoxetine

<table>
<thead>
<tr>
<th>Infant dose F (mg/day)</th>
<th>Infant dose NF (mg/day)</th>
<th>Estimated volume (mL)</th>
<th>Infant dose F (mg/day)</th>
<th>Infant dose NF (mg/day)</th>
<th>Measured volume (mL)</th>
<th>Mean infant dose (± SD) F (mg/day)</th>
<th>Mean infant dose (± SD) NF (mg/day)</th>
<th>Mean volume (± SD) (mL)</th>
<th>Infant’s Serum level</th>
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<td>.11 ± .074</td>
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<td>.065 ± .027</td>
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<td>776 ± 75</td>
<td>ND</td>
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*Atkinson Model: Using maximum and minimum measured breast milk concentrations of fluoxetine and norfluoxetine to give “Hi” and “Lo” values.

F, fluoxetine; NF, norfluoxetine; M/P, milk-to-plasma ratio; ND, Non-detectable; NC, Not calculated; NM, Not measured.

Discussion

This study compared three different methods of estimating the 24-hour infant medication dose of fluoxetine. Estimates based on the Mathematical Model, utilizing gradient effects, were the best predictors of total infant serum concentration. Separate linear regressions were used to examine the relationship between infant medication dose and infant serum concentration for each model. The results show that breast milk analysis may allow one to predict whether an infant will have a detectable concentration of medication and potentially minimize the need for infant blood draws.

The literature on antidepressants and nursing demonstrates a lack of consensus regarding what determines actual infant exposure. Case reports, case series, and small studies have relied on various methods of quantifying this exposure, utilizing M/P ratios, single breast milk concentrations, average milk concentrations, gradient and time course effects, and assumed volumes of milk consumption. Our findings suggest that the results obtained utilizing different methods of estimation may not be consistent, and that meta-analyses based on combined data may not be useful. Furthermore, the determination of infant dose as a percentage of maternal dose assumes that the infant would have similar volumes of distribution for a given weight relative to adults, a data set that is lacking. A conservative approach underscores that the clinician would be prudent to err on the side of caution and overestimate rather than underestimate exposure.

The Mathematical Model proposed in our previous studies on sertraline (Stowe et al 1997) and paroxetine (Stowe et al 2000) provided an apparent overestimation of infant exposure when compared with the other methods of calculation. Such a conservative approach may also have partially accounted for the immature metabolic status of nursing infants and the greater efficiency of the infant to obtain breast milk over a breast pump. A recent study of sertraline (Stowe et al 2001) demonstrated similar predictability for infant desmethylsertraline concentrations as found in the present study.
Depending on when breast milk is sampled, the Atkinson Model demonstrates tremendous variability in its estimates and may not accurately reflect 24-hour medication exposure. The lack of predictability of the Total Daily Dose Model is surprising but may be accounted for in part by the lack of efficiency of breast pumps, which varies from woman to woman and pump to pump. In addition, women collected milk at different times, and the intervals when infants nursed may have influenced the results of the Total Daily Dose Model.

In our analysis, the lack of significance of the Mathematical Model estimates over the Total Daily Dose Model estimates may have been due to greater variability in the values for the Mathematical Model. Although the overall mean was higher for the Mathematical Model than for the Total Daily Dose Model, when the paired differences for each subject were examined, greater variability was present for the former model than for the latter model.

Much of the recent literature regarding antidepressants and nursing has focused on infant serum concentrations. Without data on the dose of medication that an infant receives through breastfeeding, serum concentrations alone provide little information about infant metabolic capacity, making their significance difficult to interpret. Increased data that accurately models breast milk can provide a basis for interpreting such infant serum measures and perhaps even be used to estimate medication exposure without the need to perform an infant blood draw, an alternative that would be desirable to many parents.

Our study found that, for the Mathematical Model, the breast milk norfluoxetine dose was a significant negative predictor of the total infant serum concentration. A higher breast milk norfluoxetine concentration may reflect greater maternal metabolic capacity and less infant exposure. In addition, infant metabolic patterns may be inherited from the mother. Although the relative lower weight of infant 5 would have led us to anticipate higher serum concentrations, this infant may have had a greater metabolic capacity that contributed to lower serum measures. Infant 5 was also the youngest and, due to a prolonged gastric emptying time, may have had incomplete fluoxetine/norfluoxetine absorption. Subject 1, on the other hand, had the second highest breast milk norfluoxetine concentration, as determined by the Mathematical Model, and the highest total infant serum concentration. This infant’s pattern of a high serum fluoxetine concentration as compared with norfluoxetine was similar to the mother’s pattern and suggests a poor metabolizer. Age-related and metabolic factors seem to have a significant role in the relationship between breast milk and infant serum concentrations.

Although minimizing the degree of infant exposure to antidepressants through breast milk is important, one must also put the degree of exposure in perspective with the need to treat major maternal psychiatric illnesses. Using the largest estimate of the infant dose of fluoxetine (0.33 mg/day), an infant who is fully breastfed for 1 year would receive a total of 120 mg of fluoxetine. Although milk consumption varies as infant weight and feeding patterns change over the course of a year, these figures provide some perspective of the infant’s antidepressant dose relative to the maternal daily dose, which averaged 34 ± 12.8 mg/day of fluoxetine for our sample. Assuming consistent milk consumption, the maximum exposure that an infant would receive over the course of a year equals 160 ± 47% of the maternal daily dose (range 43%–584%). The clinical relevance of such a dose when weighed against the effects of untreated major maternal psychiatric illness or the foregone benefits from breast milk is unclear. Further long-term studies should focus on the neurodevelopmental outcome of children exposed to antidepressants through nursing.

Our study was limited by sample size and by the individual’s efficiency using the method of breast milk collection (e.g., mechanical vs. electric). Although our sample size achieved statistical power, a future study with a larger sample size would be important to provide greater confidence in the Mathematical Model. Our calculations assumed equal exposure from both breasts and infant consumption of all milk from each breast. Because nursing infants of varying ages and weights feed at different intervals, the times of serum sampling were not standardized relative to maternal or infant ingestion of medication and breast milk, respectively. In addition, a single infant serum medication concentration may not be representative of total infant exposure, although, given the long half-life of parent drug and metabolite, this concern may be less significant for fluoxetine. Despite these limitations, our data suggest that the use of breast milk concentrations and the refinement of mathematical modeling for each medication will provide a basis for interpreting infant serum concentrations and negate the need to obtain infant blood.

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References


