Sertraline and Norsertraline Levels in Three Breastfed Infants

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Background: In assessing the safety of medication use in breastfeeding, it is important to know whether the drug used by the mother will be present in the breastfed infant. Compared with data for tricyclic antidepressants (TCAs), which have generally not been found in the plasma of breastfed infants, there are few data on the use of serotonin selective reuptake inhibitors (SSRIs) in breastfeeding. This poses a dilemma for breastfeeding women and their treating clinicians, because of the enhanced tolerability of SSRIs compared with TCAs, and because some patients do not respond well to TCAs.

Method: Sertraline and norsertraline plasma concentrations were measured in three breastfeeding mother-infant pairs. Maternal and infant plasma samples were drawn a few minutes apart. Two of the infants had an additional sample assayed without contemporaneous maternal samples examined. Drug assay was by high-performance liquid chromatography. Limit of reproducible quantifiability was 2 ng/mL, and limit of detectability was 1 ng/mL.

Results: Maternal sertraline dose ranged from 50 to 100 mg/day. All infant plasma samples showed low levels (< 2 ng/mL) of either sertraline and norsertraline or norsertraline alone. Breastfeeding was continued, and the infants have shown no adverse effects on short-term follow-up.

Conclusion: These data suggest that sertraline and/or its almost inactive metabolite may be present at very low concentrations in the plasma of breastfed infants. No adverse effects were noted in the infants. Limitations of the findings and possible implications for the use of sertraline during breastfeeding are discussed.

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During the postpartum period, women are at risk for exacerbation, recurrence, and onset of depressive and anxiety disorders.[1,2] These disorders are generally responsive to pharmacotherapy.

For breastfeeding women considering pharmacotherapy, the following three questions need to be addressed: (1) Will the medication be transferred to the baby? (2) Are there any short-term adverse consequences for the baby during the period of breastfeeding? (3) Are there any long-term adverse consequences from exposure to medication?

With regard to antidepressant use in breastfeeding, there is one case report of a possible adverse effect with fluoxetine[3] and another with doxepin.[4] The limited published data on short-term adverse effects of antidepressant use in breastfeeding appear to be consistent with the findings of Ito et al.,[5] who studied 838 infants exposed to a variety of medications during breastfeeding and concluded that "short-term effects, if any, are mild and pose little risk to the infant."(p1393) There are limited data on long-term follow-up of infants exposed to antidepressants in breastfeeding.[6]

Because antidepressants are lipophilic, they pass into the breast milk[6] but are not necessarily detectable in the infant's plasma.[7] Drugs are well absorbed by the infant's gastrointestinal tract, and clearance is mostly through hepatic metabolism.[8] Therefore, concentration of drug in the infant's plasma, rather than milk concentration, is the best indicator of exposure to medication,[9] but there are limited data available in this area for most psychotropic medications.

Most of the data on antidepressant use in breastfeeding were obtained from women treated with the tricyclic antidepressant nortriptyline. Nortriptyline has not been detected in breastfed infants[7,10]; 10 of the 12 infants described by Wisner and Perel[7,10] had no detectable hydroxynortriptyline either, but 2 infants less than 10 weeks old had low levels of this metabolite.

Published data on the use of serotonin selective reuptake inhibitors (SSRIs), including infant plasma drug concentrations, are limited to three reports. Lester et al.[3] described a baby with high plasma levels of fluoxetine and norfluoxetine who experienced colic that may have been drug-related. Subsequently, Taddio et al.[11] reported

Table 1. Plasma Concentrations of Sertraline (SER) and Norsertraline (NSER) in Mothers and Infants

Case	Maternal SER Dose (mg/d)	Infant's Age (Wk)		Infant's Plasma Concentration (ng/mL)		Maternal Plasma Concentration (ng/mL)	
		Maternal SER Began	Plasma Sampling	SER	NSER	SER	NSER
Case 1							
Time 1[a]	50	4	6	< 2[b]	< 2	…	…
Time 2	75	8[c]	15	0[d]	< 2	38.5	95.8
Case 2							
Time 1[a]	75	6	16	0	< 2	…	…
Time 2	100	20[c]	26	0	< 2	18.4	48.5
Case 3							
Time 1	75	Birth	8	< 2	< 2	51.9	82.9

[a]Maternal serum not examined at Time 1 for Cases 1 and 2.
[b]< 2 ng/mL = detectable but not reliably quantifiable.
[c]Time from initial sampling to dose increase: 2 weeks for Case 1, 4 weeks for Case 2.
[d]0 ng/mL = not detected by assay with limit of detectability 1 ng/mL.

on 11 infants partially or exclusively breastfed while their mothers used fluoxetine. None of the infants showed any adverse effects. Neither fluoxetine nor norfluoxetine was found in the 1 infant in whom it was measured (assay sensitivity 1 ng/mL). In another report, Altshuler et al.[12] did not find sertraline in one breastfed baby whose mother used sertraline and nortriptyline.

SSRIs are increasingly replacing tricyclic antidepressants as a preferred first-line treatment for depression and anxiety because of their tolerability and safety profile.[13] It is, therefore, important to collect information about any adverse effects of these drugs in breastfeeding. In this report, we describe three cases of women who used sertraline while breastfeeding.

METHOD

Maternal and infant plasma were sampled simultaneously 12 to 15 hours after the mothers' last dose of sertraline and 2 to 3 hours after the infants' last feeding. Sampling was conducted 2 to 10 weeks after the mothers were on a stable dose of medication. Infant plasma drug concentration was examined to see if drug was present in the infant. Maternal drug concentration was examined to check compliance: If drug was not detected in the infant, was the mother taking medication?

Assay Technique

A minimum of 2 mL of blood (to provide 1 mL of plasma) was collected in Vacutainer tubes with powdered EDTA as an anticoagulant. Samples were spun for 10 minutes in a refrigerated centrifuge to separate plasma. Plasma was frozen at –20°C until the assay was conducted. The analytes in the plasma were extracted into an organic solvent and then into a low volume of acidic phosphate. Drug assay was conducted by high-performance liquid chromatography using a C-18 column and ultraviolet absorbance detection. The lower limit for quantifiable and reliable linear detectability is 2 ng/mL for sertraline and norsertraline. For the low control, the mean within-day coefficient of variation was 4.8% for sertraline and 1.7% for norsertraline. The mean between-day coefficient of variation was 4.0% for sertraline and 3.1% for norsertraline. The lower limit for qualitative detectability (i.e., drug detectable but not quantifiable) is 1 ng/mL.

CASE REPORTS

Table 1 shows infant age at the time of the plasma sampling, maternal and infant plasma concentrations of sertraline and norsertraline, and dose of sertraline used by the mother. Plasma concentrations < 2 ng/mL but above 1 ng/mL are detectable but not reliably quantifiable. Patients made informed treatment choices after a detailed discussion of available information and consultation with the babies' pediatricians. Two of the babies (Cases 1 and 2) were exclusively breastfed and the third had two supplemental 12-ounce bottles of formula daily. According to their mothers and pediatricians, all three infants are doing well and have shown no adverse effects at last follow-up (age 12 months for Case 1, 19 months for Case 2, and 11 months for Case 3).

Case 1

Ms. A, a 38-year-old white woman, came to the clinic 3 weeks before her due date. She was medication-free during the pregnancy and had a recurrence of panic disorder and major depression. Treatment with nortriptyline and cognitive-behavior therapy began before delivery. Nortriptyline was discontinued at 4 weeks postpartum because improvement was only partial. A trial of sertraline was initiated and associated with rapid improvement. After Ms. A was on sertraline 50 mg/day for 15 days, the infant plasma showed both sertraline and norsertraline (both < 2 ng/mL, below the level of reliable quantifiability). Because of continuing symptoms, Ms. A's dose was increased to 75 mg/day, 2 weeks after the first plasma sampling. After 7 weeks on 75 mg/day, the infant plasma showed < 2 ng/mL of norsertraline and no sertraline. The

baby developed benign neonatal sleep[14] at age 4 months, which spontaneously resolved at age 6 months.

Case 2

Ms. B, a 38-year-old white woman, was seen at 6 weeks postpartum while breastfeeding her second baby. She had a history of recurrent major depression, anxiety, alcohol abuse, bulimia nervosa, borderline personality disorder, and multiple serious suicide attempts. She had been taking no medication during the pregnancy. She developed postpartum exacerbation of depression and was worried that this would cause a relapse of drinking, bingeing, and self-mutilation. Because of the risk of an impulsive suicide attempt, she decided on a trial of sertraline rather than a tricyclic antidepressant. After 8 weeks on sertraline 75 mg/day, the infant's plasma showed norsertraline (< 2 ng/mL) but no sertraline. The maternal dose was increased to 100 mg/day after the initial plasma sampling. A second assay of infant plasma 6 weeks after the dose increase continued to show the presence of low levels of norsertraline (< 2 ng/mL) and absence of sertraline.

Case 3

Ms. C, a 34-year-old white woman, came to the clinic 2 weeks before her due date because of concern about postpartum exacerbation of panic disorder and major depression. She chose to start sertraline in the immediate postpartum period because of her prior unsatisfactory experiences with tricyclic antidepressants and a family history of good response to sertraline. Clinical response on sertraline 75 mg/day was excellent. When the infant was 8 weeks old, the infant plasma showed < 2 ng/mL for both sertraline and norsertraline. Although there was no evidence of adverse effects of medication on the baby, Ms. C gradually weaned her infant over the next 2 months, because she wanted to limit exposure to medication.

DISCUSSION

We report three infants, breast-fed while their mothers used sertraline, who showed low plasma concentrations of sertraline and norsertraline or norsertraline alone. None of the babies showed any obvious adverse effects according to their mothers and pediatricians. One of the infants developed benign neonatal sleep myoclonus, a short-lived benign condition of uncertain etiology.[15] To our knowledge, this is the first report on plasma concentrations of both sertraline and norsertraline in breastfed infants. The assay used was capable of detecting drug concentrations down to 1 ng/mL.

Norsertraline was more consistently found in the infants compared with sertraline. This may be related to higher maternal plasma norsertraline concentrations, compared with sertraline concentrations, possibly resulting in the infants' ingesting more norsertraline in the milk. However, because drug concentrations in the milk were not measured, we do not know whether the usual finding of higher plasma concentrations of norsertraline compared with sertraline[16] is also associated with higher norsertraline concentrations in the milk. The younger infants (Case 3 and first sampling for Case 1) showed both sertraline and norsertraline, whereas the older infants (Case 2 and second sampling for Case 1) showed only norsertraline. These age-associated differences are possibly consistent with increasing drug clearance consequent to maturation of the infant hepatic enzyme systems.[8] Relatedly, Wisner and colleagues[17] suggested that enhanced maturation of hepatic enzyme systems may be responsible for the fact that metabolites of tricyclic antidepressants have been detected only in infants younger than 3 months of age and not in older infants.

Our findings are similar to those of Altshuler et al.[12] who did not detect sertraline at ages 3 weeks and 7 weeks in one breastfed baby. Norsertraline was not measured in this baby. However, norsertraline has an intrinsic serotonergic activity of only about 10% compared with sertraline.[18] Also, a recent report using an in vivo model suggests that norsertraline does not contribute to central serotonin reuptake inhibition.[19]

Knowledge of how exposure to low levels of psychoactive medications can affect development is an important component of assessing the safety of treatment. However, as yet, no long-term follow-up studies have examined this issue. Reports of infants breastfeeding while their mothers were taking antidepressant medication are based on short-term follow-up. Recently, Buist and Janson[20] reported on 15 children breastfeeding while their mothers were taking the tricyclic antidepressant dothiepin and found no adverse effects 3 to 5 years later. In fact, compared with the children of depressed mothers who were not treated with antidepressant postpartum, these children performed better on some subscales of cognitive development on the McCarthy Scales of Children's Abilities.[21] Relatedly, 55 children exposed in utero to the SSRI fluoxetine showed no difference on cognitive testing compared with children exposed to known nonteratogens.[22] This may be noteworthy because the transfer of medication across the placenta in pregnancy is much more extensive than transfer to the infant in breast milk.[9]

We report here results of plasma drug concentrations in three infants breastfed while their mothers were taking sertraline in doses from 50 to 100 mg/day. It is questionable whether drugs or their metabolites have any adverse effects at the trace concentrations we found. When trace concentrations of drug or drug metabolite are found in thriving infants showing no adverse effects, one must weigh the demonstrated benefits of breastfeeding[23] against the unknown risk of exposure to antidepressant medication.[17] Mothers and their treating clinicians must

then decide whether to continue medication and breastfeeding.[17] Although long-term follow-up studies have not yet been conducted, preliminary evidence currently shows no adverse outcome in infants exposed to antidepressants. It is also important to bear in mind that untreated maternal psychiatric illness may have adverse effects on several aspects of child development, including intelligence.[24,25] Consequently, antidepressant treatment of breastfeeding mothers with depression or anxiety disorders may have benefits for the child.[20]

Although the assay detected sertraline or its metabolite in the three infants we described, it is not possible to know if the drug was continuously present in the infant, because infant plasma was examined at only one timepoint. We did not assess antidepressant concentrations in milk, because we did not expect the results of this assessment to change treatment: being lipophilic, sertraline was expected to be present in the milk, and we therefore considered infant plasma concentration to be more clinically informative.[9] The relationship between the concentrations of drug in maternal plasma and milk and infant plasma is clearly of interest for future studies.

A practical consideration for clinicians is that the sensitive assays used in this report are not available in commercial laboratories. This report would suggest that the use of sertraline in low doses (75–100 mg/day) in nursing mothers is quite likely associated with minimal exposure of the infant to active medication. One option is for clinicians to send plasma samples to research laboratories in medical schools or to seek out commercial laboratories that conduct highly sensitive drug assays.[17] Considering the low drug concentrations detected in this study and the lack of demonstrable adverse effects to date, it is questionable whether these latter approaches are indicated for routine use.

Further data are needed to replicate this report of very low plasma concentrations of sertraline and/or norsertraline in breastfed infants. We encourage clinicians to collect and report such information. In addition, long-term follow-up studies of infants breastfed while their mothers use psychotropic medication are needed.

Drug names: doxepin (Sinequan and others), fluoxetine (Prozac), nortriptyline (Pamelor and others), sertraline (Zoloft).

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