Serum Fluvoxamine Levels in Breastfed Infants

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Background: Between 10% and 15% of new mothers will experience an episode of postpartum depression. Although antidepressants are effective agents for the treatment of postpartum depression, minimal data are available to support their safety in infants of breastfeeding mothers.

Method: In this article, we present 2 cases of nursing mother-infant pairs in which the mother was treated with fluvoxamine and in which infant serum fluvoxamine levels were obtained. Both mothers began the fluvoxamine treatment postpartum, and serum levels were obtained from mothers and infants after a minimum of 7 days on a stable maternal dose. One level was obtained from the infant in case 1, and 2 levels were obtained from the infant in case 2.

Results: Each of the infant serum fluvoxamine levels obtained was too low to quantify (at a limit of detection of 2.5 ng/mL). Neither of the infants experienced adverse events related to the mother's treatment with fluvoxamine. Each of the infants is reportedly healthy 2 to 3 years after the exposure.

Conclusion: While these results are encouraging, they are limited and cannot be generalized to all cases of infants exposed to fluvoxamine. Additional mother-infant serum fluvoxamine levels and infant behavioral observations will facilitate the risk-benefit decision-making process for women who choose to breast-feed while taking fluvoxamine.

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The incidence of postpartum depression is between 10% and 15%.[1] Because more than 50% of mothers will elect to breast-feed,[2] the use of antidepressant medication during lactation presents a common and challenging clinical concern. The benefits of breastfeeding for both mother and baby are well substantiated.[3] However, of paramount importance in the risk-benefit assessment is the risk to the infant from antidepressant exposure via the breast milk.

Data have been accumulating in the form of case reports. Llewellyn and Stowe[3] reviewed the literature regarding the use of psychotropic medications during lactation and suggested treatment guidelines. They advocated using an agent to which the patient has a known response or one for which data exist regarding use during lactation. As the selective serotonin reuptake inhibitors (SSRIs) become increasingly favored as the treatment of choice for depressive and anxiety disorders, more women will have documented responses to these agents. However, data about their use during lactation are minimal, and the majority of the reports involve sertraline. Llewellyn and Stowe[3] caution that the data on the use of one agent during lactation cannot necessarily be extrapolated to other agents in the same medication class. Likewise, clinical experience indicates that one SSRI cannot always be substituted effectively for another. Therefore, it is imperative that additional data be gathered on the safety of the many antidepressants currently in use.

Fluvoxamine is an SSRI that has been shown to be effective in the treatment of major depression and obsessive-compulsive disorder and is being studied for use in the treatment of other depressive and anxiety disorders. Because it does not have an active metabolite,[4] it may be particularly well suited for use during lactation. Only 2 case reports in the literature address the use of fluvoxamine during lactation.[4,5] In each case, milk and maternal serum levels of fluvoxamine were assessed, but infant serum fluvoxamine levels were not included. In this article, we present 2 cases of nursing mother-infant pairs in which the mother was treated with fluvoxamine and infant serum fluvoxamine levels were obtained.

METHOD

After a risk-benefit discussion, the mothers gave informed consent, including agreement to having the infant's serum sampled to assess the fluvoxamine level. The infants'

pediatricians were contacted, and each agreed to monitor the breastfed infant during maternal fluvoxamine treatment.

Sampling Technique

Samples were collected after a minimum of 7 days of consistent maternal dosing, assuring that the mothers' serum levels were at steady state. The samples were obtained approximately 12 hours after the mothers' last dose. Infant blood was obtained by antecubital venipuncture, performed by a skilled pediatric phlebotomist. The infant concentrations represented summary values that resulted from feedings throughout the day.

Sample Analyses

The serum levels of fluvoxamine were analyzed by high-performance liquid chromatography with ultraviolet detection. The quantitative limit of detection for a modified assay based on the original by Foglia et al.[6] was 2.5 ng/mL. Serum levels below 2.5 ng/mL may be detectable but are not reliably quantitated by analytical readouts. The previously stated limit of detection was adequate since levels of greater than 50 ng/mL were found in the adult patients studied during development of the assay. The coefficients of variation for high and low control samples were 0.4% and 3.4%, respectively.

CASE REPORTS

Case 1

This mother delivered a healthy baby girl at term. By 8 weeks postpartum, the mother experienced severe symptoms of bulimia nervosa and major depression (DSM-IV criteria), despite an adequate trial of sertraline that had begun immediately postpartum. She agreed to a trial of fluvoxamine, but elected to decrease breastfeeding from 100% to 50% in an effort to minimize her infant's exposure to the medication. Fluvoxamine was titrated to 300 mg q.a.m. and trazodone, 50 mg q.h.s., was added for sleep dysregulation. After 7 days on a stable dose, mother and infant blood levels of fluvoxamine were obtained. The assay for an infant serum level requires 1 mL of blood (the maximum amount of blood drawn from an infant at one time), and therefore the fluvoxamine level was prioritized over the trazodone level in this infant. The serum fluvoxamine level in the mother was 62 ng/mL, and in the infant, it was too low to quantify (i.e., < 2.5 ng/mL). At the time of sampling, the infant was described as active and alert and was reported by her pediatrician to be thriving. The mother continued to breast-feed while taking fluvoxamine until the infant was 7 months old. The mother reports that at 2 years of age her daughter is well.

Case 2

This mother had a history of recurrent major depressive disorder and obsessive-compulsive disorder (DSM-IV criteria) with incomplete remissions after trials of fluoxetine, sertraline, paroxetine, and clomipramine. She delivered a healthy baby girl at term, whom she chose to breast-feed. She agreed to treatment with fluvoxamine, and she began taking 50 mg q.h.s. immediately postpartum. Two weeks after birth, the infant was noted to have neonatal jaundice, with a total serum bilirubin level of 13.6 mg/dL. A serum fluvoxamine level obtained from the infant was too low to quantify (i.e., < 2.5 ng/mL). The mother refused to submit to a maternal blood draw because of a needle phobia. Breastfeeding continued, and the infant's jaundice resolved. The mother's fluvoxamine dose was titrated to 300 mg q.h.s. At 8 weeks, a second infant serum level was obtained, and again, the level was not quantifiable. The mother reports that at 3 years of age her daughter is healthy.

DISCUSSION

Each of the infant serum levels of fluvoxamine reported in this series was not quantifiable. The mother in case 1 decided to decrease the frequency of breastfeeding in an attempt to decrease infant exposure to the medication. This is not a strategy that we generally recommend. The majority of reported infant serum levels of antidepressants are from fully nursing mother-infant pairs, and the data from those reports indicate a low risk for toxicity. It is noteworthy that in case 2, the infant was fully breastfed and was 8 weeks old at the time of the second sampling. In reviewing the literature regarding antidepressant use during breastfeeding, Wisner et al.[2] concluded that infants less than 10 weeks of age may be at greater risk for toxicity associated with maternal antidepressant treatment during breastfeeding because the only adverse events were reported in very young infants. Neither of the infants in this series experienced adverse events related to the fluvoxamine exposure.

Wright et al.[4] and Yoshida et al.[5] have published case reports of infants exposed to fluvoxamine via breast milk. In each of these reports, the exposure is an estimate based on a calculation using the maternal milk-to-plasma ratio obtained from a one-time sampling. Stowe et al.[7] have demonstrated the limited accuracy in utilizing such a calculation by collecting time course data on sertraline and desmethylsertraline levels in human breast milk. They observed a gradient in the concentration of drug from the foremilk to the hindmilk as well as a variation in concentration relative to the time from a given dose. They suggest that utilizing a time course equation might be the most accurate assessment of an infant's daily dose. Additionally, they demonstrated that those infants who received higher daily doses based on this calculation were the same infants that had detectable serum levels of both sertraline and desmethylsertraline.

Our maternal and infant serum data are encouraging because in each instance the infant serum level was not

quantifiable. However, these are the first published infant serum fluvoxamine levels, and therefore, the results cannot be generalized to all cases of infant exposure to the medication. The physiology of the newborn is distinct from that of older infants and adults, particularly with respect to hepatic function, glomerular filtration and tubular secretion, and gastrointestinal absorption.[3] These differences may contribute significantly to differences in the physiologic disposition of drugs, even in small quantities. Furthermore, the question remains as to whether chronic exposure to fluvoxamine, even at very low levels, might have adverse consequences for the infant, including neurobehavioral effects. Additional mother-infant serum fluvoxamine levels and infant behavioral observations will help to answer these questions and will facilitate the risk-benefit decision-making process for women choosing to breast-feed while taking fluvoxamine.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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