Drowsiness and Poor Feeding in a Breast-Fed Infant: Association with Nefazodone and Its Metabolites

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OBJECTIVE: To investigate whether adverse effects in a premature neonate could be attributed to nefazodone exposure via breast milk.

CASE SUMMARY: The breast-fed white infant (female, 2.1 kg, 36 weeks corrected gestational age) of a 35-year-old woman (60 kg) taking nefazodone 300 mg/d was admitted to the hospital because she was drowsy, lethargic, unable to maintain normal body temperature, and was feeding poorly. A diagnosis of exposure to nefazodone via breast milk was considered only after other more likely diagnoses had been excluded. After breast feeding was discontinued, the infant's symptoms resolved slowly over a period of 72 hours. The maternal plasma and milk concentration–time profiles for nefazodone and its metabolites, triazoledione, HO-nefazodone, and *m*-chlorphenylpiperazine, were quantified by HPLC. The calculated infant dose for nefazodone and its active metabolites (as nefazodone equivalents) via the milk was only 0.45% of the weight-adjusted maternal nefazodone daily dose.

DISCUSSION: Our data suggest a putative association between maternal nefazodone ingestion and adverse effects in a premature breast-fed neonate. The measured amount of drug exposure would normally be considered safe in a full-term infant. However, there was a temporal relationship between resolution of adverse effects in the infant and cessation of breastfeeding.

CONCLUSIONS: This case highlights the importance of individualizing the risk–benefit analysis for exposure to antidepressants in breast milk, especially when dealing with premature neonates.

KEY WORDS: nefazodone, breast milk, adverse effects, premature infant, antidepressants.

Ann Pharmacother 2000;34:1269-72.

Approximately 10–15% of mothers experience depression following the birth of their infant,[1] while a smaller percentage of women in the general population[2] also experience depression throughout pregnancy. In both cases, use of an antidepressant drug is often a mainstay of therapy. However, there is increasing awareness that there may be significant transfer of maternal medications to the fetus in utero and also to the neonate via breast milk. In the case of neonatal exposure by breast feeding, the use of new antidepressants requires a considered risk–benefit analysis for the individual mother–baby pair.[3] However, such an evaluation can be difficult, as information on the distribution of these molecules into milk and their effects on the neonate often is sparse.

The novel antidepressant nefazodone inhibits reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine, and at the same time blocks 5-$HT2_A$ receptors.[4] The parent drug has a short half-life of two to four hours[5] and is metabolized to a number of metabolites, three of which (triazoledione, hydroxynefazodone [HO-nefazodone], *m*-chlorophenylpiperazine) have some pharmacologic activity.[4] We report a case in which adverse effects were apparent in a breast-fed infant following the mother's use of nefazodone for postnatal depression. The distribution of nefazodone and its metabolites into human milk is documented, and predictions regarding infant exposure are made.

CASE REPORT

A 35-year-old white woman (60 kg) delivered a premature female infant at 27 weeks' gestation. The mother was well following delivery and was able to lactate and collect milk that was bottle-fed to her infant, who was in the Special Care Nursery. The mother became depressed and started treatment with nefazodone 200 mg in the morning and 100 mg at night when her infant was seven weeks old. One week later, the infant was discharged from the hospital and was breast-fed at home. At nine weeks of age (2.1 kg), the infant was readmitted to the hospital because she had become drowsy, lethargic, unable to maintain normal body temperature, and was not feeding well. Extensive investigations, including a cranial ultrasound and detailed microbiologic investigations, failed to identify a cause for the symptoms; at this point (age 10 wk), exposure to nefazodone via breast milk was considered in the differential diagnosis. Breast feeding was ceased, and the symptoms resolved gradually over a period of 72 hours. Serial milk and plasma samples were collected from the mother when the infant was aged 10.5 weeks to assess the extent of transfer of nefazodone and its active metabolites from plasma into milk and also to estimate infant dose. At this stage, the moth-

Author information provided at the end of the text.

Funding provided from the Women's & Infants Research Foundation, Western Australia; Bristol-Myers Squibb Pharmaceuticals Australia supplied analytical standards.

er was still expressing and discarding her breast milk to maintain her milk supply.

CLINICAL STUDY

The study of nefazodone and its metabolites was conducted under a protocol approved by the Ethics Committee of the King Edward Memorial Hospital; the patient gave written informed consent. The study commenced at 0800 when the morning dose of nefazodone 200 mg was given. Blood samples (heparinized) were taken from an indwelling venous catheter before administration and at approximately one, two, three, four, five, six, and 12 hours after administration. All available milk was collected using an electric breast pump before nefazodone administration and at approximately one, two, three, four, five, and six hours after administration.

HPLC ESTIMATION OF NEFAZODONE AND ITS METABOLITES IN PLASMA AND MILK

The analytes of interest were extracted from plasma and milk samples using chlorobutane. Subsequently, HPLC analysis was carried out using a system comprising a Waters µBondapak Phenyl column (3.9 mm i.d. × 30 cm) and a solvent of 0.05 M $(NH_4)_2HPO_4$ (pH 3):methanol:acetonitrile:water (1:10:41:80) pumped at a flow rate of 1.3 mL/min. Peaks were detected by their ultraviolet absorbance at 254 nm. Under these conditions, approximate retention times were: *m*-chlorophenylpiperazine, 3.9 minutes; trazodone, 5.6 minutes; triazoledione, 9.9 minutes; HO-nefazodone, 10.6 minutes; aprindone, 16.1 minutes; and nefazodone, 18 minutes. Correlation coefficients for the standard curves were typically >0.998, and the within-day coefficients of variation were as follows: 7.4% and 5% for nefazodone at 98 and 1950 µg/L, respectively; 8.3% and 3.4% for HO-nefazodone at 107 and 642 µg/L, respectively; 5.5% and 1.7% for triazoledione at 104 and 2084 µg/L, respectively; and 12.2% and 2.2% for *m*-chlorophenylpiperazine at 9 and 522 µg/L, respectively.

PHARMACOKINETIC ANALYSIS

Plasma and milk AUCs were calculated by the log trapezoidal rule and used to estimate milk/plasma (M/P) ratio. Since the patient was unable to produce a milk sample at 12 hours after the dose, concentrations of the four analytes at this time were assumed to be the same as those measured immediately before the dose was administered, so that a milk AUC at 12 hours could be estimated. The likely infant dose was calculated as the concentration of nefazodone or its active metabolites (as nefazodone equivalents) multiplied by an average milk intake of 0.15 L/kg/d[6] and expressed relative to the weight-adjusted maternal dose rate. Maximum plasma and milk concentrations (C_{max}) and their respective times (t_{max}) for nefazodone and its metabolites were interpolated directly from the data.

Results

The plasma and milk concentration–time profiles for nefazodone, triazoledione, HO-nefazodone, and *m*-chlorophenylpiperazine are shown in Figure 1. Pharmacokinetic descriptors, M/P ratios, and estimated infant doses for nefazodone and its metabolites are summarized in Table 1. In general for both plasma and milk, t_{max} occurred between one and three hours for all analytes, while corresponding C_{max} values were significantly (4- to 18-fold) lower in milk than in plasma. M/P ratios based on AUC were correspondingly small and ranged from 0.02 to 0.27. In the case of nefazodone, the low M/P ratio correlates well with its extensive plasma protein binding (>99%). The total infant dose exposure (as nefazodone equivalents) was 0.45% of the weight-adjusted maternal dose, with the major contribution coming from nefazodone (0.3%).

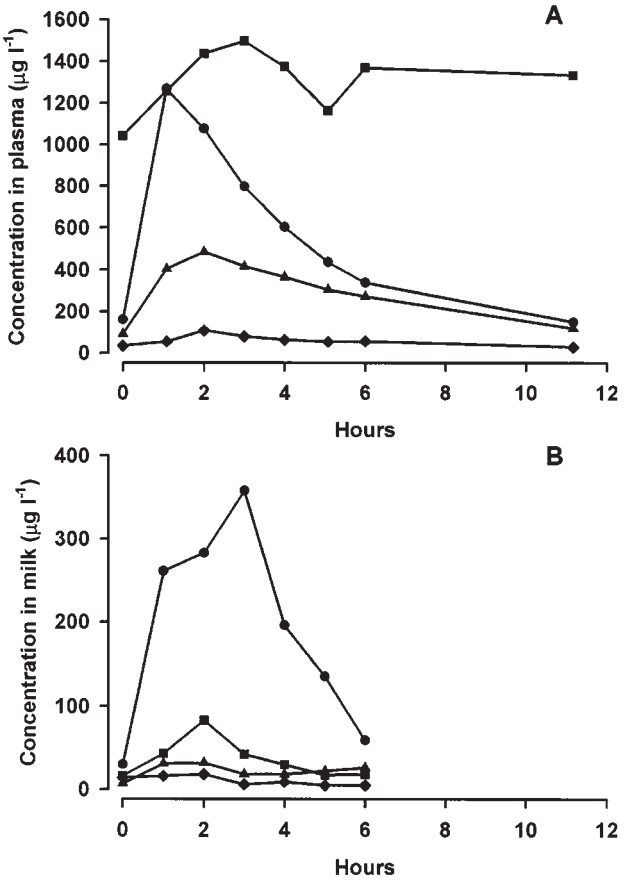

Figure 1. Plasma (A) and milk (B) concentration–time profiles for nefazodone (●), triazoledione (■), HO-nefazodone (▲), and *m*-chlorophenylpiperazine (◆) for the patient following a morning dose of nefazodone 200 mg.

Table 1. Pharmacokinetic Descriptors for Nefazodone and Its Metabolites in Milk and Plasma and Estimated Infant Dose Following the Morning Oral Dose of Nefazodone 200 mg

Parameter	Nefazodone	Triazoledione	HO-Nefazodone	*m*-Chlorophenylpiperazine
$M/P_{AUC\ 0-12\ h}$	0.27	0.02	0.07	0.19
Milk C_{max} (µg/L)	358	83	32	18
Milk t_{max} (h)	3	3	2	2
Plasma C_{max} (µg/L)	1270	1500	484	109
Plasma t_{max} (h)	1.08	3	2	2
Infant dose (%)[a]	0.3	0.06	0.04	0.05

C_{max} = maximum concentration; M/P = milk/plasma ratio; t_{max} = time to reach C_{max}.
[a]Expressed as nefazodone equivalents and adjusted proportionally to the total daily dose of 300 mg.

Discussion

This study shows a clear temporal relationship between the cessation of exposure to nefazodone through breast milk in a premature infant and the resolution of adverse clinical symptoms. Oversedation and failure to thrive in the neonate resolved after discontinuation of breast feeding. Previous medical interventions had been ineffective. A Naranjo probability scale[7] assessment indicated that it was probable that the adverse reaction was drug related. In hindsight, it is regrettable that no infant blood sample was taken for drug analysis.

Nefazodone is known to have a sedative effect[8]; this can be beneficial in the hyperarousal and sleep disturbance experienced by many women with postnatal depression. However, our detailed study of the distribution of nefazodone and its active metabolites in human milk showed that the infant would be expected to receive an average dose of only 0.45% of the maternal weight-adjusted nefazodone dose. A recent article by Dodd et al.[9] reported an M/P ratio of 0.1 for nefazodone in a patient taking nefazodone 200 mg twice daily. This is about one-third of the M/P ratio (0.27) found in our study. The difference may be attributed to the use of a single pair of milk and plasma concentrations rather than using AUC data, as we did in our study, for the calculation of the M/P ratio.

However, our case highlights the importance of individualizing both the calculation and impact of drug exposure on the neonate. In our case, the infant was born 13 weeks preterm and was still only at a corrected gestational age of 36 weeks and weighed only 2.1 kg when the drowsiness and poor feeding were noted. Infant exposure to antidepressants and other drugs is generally considered safe when the relative infant dose is <10% of the maternal dose.[6] However, plasma concentrations in the infant are not only dependent on intake, but also on hepatic and renal clearance mechanisms.[10] In our case, we suggest that clearance likely was low, considering the infant's gestational age and body weight. The adult elimination half-lives for nefazodone (2–4 h), HO-nefazodone (1.5–4 h), *m*-chlorophenylpiperazine (4–8 h), and triazoledione (18 h) are likely to be longer in the neonate. The case therefore illustrates the importance of low neonatal clearance capacity in preterm infants. Nefazodone was the preferred antidepressant drug in this patient. For this reason, rechallenge by reintroducing breast feeding was not an option.

Summary

While this report suggests a putative association between nefazodone and adverse effects in a breast-fed baby, the calculated infant dose was very low, and the association should be interpreted with caution. Our findings do not necessarily mean that breast feeding should be avoided in full-term or older infants whose mothers are taking nefazodone. Finally, when maternal use of novel antidepressants is necessary, decisions on breast feeding should be made following an individual risk–benefit analysis and should be accompanied by careful observation of the infant. In the medium to long term, due consideration must also be given to the possible effects of these drugs on the infant during a period where there is significant brain growth and neurodevelopment.

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EXTRACTO

OBJETIVO: Investigar si los efectos adversos presentados por un neonato prematuro pudieran ser atribuídos a la nefazodona ingerida a través de la lecha materna.

RESUMEN DEL CASO: Una infante alimentada con leche materna (2.1 kg, 36 semanas de edad gestacional), cuya madre de 36 años de edad (60 kg) estaba tomando nefazodona (300 mg/d), fue admitida al hospital en estado de adormecimiento, letargo, falta de control de su temperatura corporal, y pobremente alimentada. Después de excluir otros posibles

diagnósticos, se determinó que la infante había estado expuesta a la nefazodona a través de la leche materna. Después de cesar su alimentación materna, los síntomas de la infante se resolvieron lentamente sobre un período de 72 horas. Los perfiles de concentración plasmáticos y en la leche materna contra el tiempo para la nefazodona y sus metabolitos, triazolediona, HO-nefazodona, y m-chlorphenyl-piperazina, fueron cuantificados mediante cromatografía líquida de alta resolución. La dosis de nefazodona y sus metabolitos (como equivalentes de nefazodona) que se calcula que la infante recibió a través de la lecha materna fue solamente un 0.45% de la dosis diaria de nefazodona cuando se ajusta al peso.

DISCUSIÓN: Mientras esta información recogida sugiere una asociación putativa entre la ingestión de la nefazodona vía leche materna y los efectos adversos presentados por la infante, la dosis que se calcula que la infante haya recibido fue muy baja para llegar a conclusiones definitivas sobre esta asociación. Estos hallazgos no necesariamente indican que la alimentación con leche materna debe ser excluída en niños de nacidos a término completo y cuyas madres están tomando nefazodona. Finalmente, cuando el uso maternal de este antidepresor novedoso es necesario, el riesgo/beneficio de recibirlo debe ser pesado contra los posibles efectos que el medicamento pueda tener en el infante.

CONCLUSIONES: Este caso señala la importancia de individualizar el riesgo/beneficio de exponer a infantes, sobretodo neonatos prematuros, a los efectos potenciales que los antidepresores pueden tener cuando son ingeridos a través de la leche materna.

Encarnación C Suárez

RÉSUMÉ

OBJETIVO: Déterminer si les effets indésirables présents chez un prématuré peuvent être attribués à une exposition à la néfazodone par le lait maternel.

RÉSUMÉ DU CAS: Il s'agit d'une petite fille de 36 semaines d'âge gestationnel corrigé pesant 2.1 kg et d'une mère de 36 ans pesant 60 kg qui prend 300 mg de néfazodone par jour. L'enfant a été admise à l'hôpital pour somnolence, léthargie, incapacité à maintenir une température corporelle adéquate, et difficulté à s'alimenter. Un diagnostic d'exposition à la néfazodone par le lait maternel a été considéré après que les autres diagnostics aient été exclus. Suivant la cessation de l'allaitement, les symptômes du bébé se sont résolus sur une période de 72 heures. Les courbes de concentration en fonction du temps de la néfazodone et ses métabolites (triazoledione, hydroxynéfazodone, m-chlorphenylpipérazine) dans le plasma et le lait maternel ont été déterminées par HPLC (chromatographie liquide haute performance). La dose de néfazodone et de ses métabolites actifs (en équivalents de néfazodone) qu'a reçue le bébé par le lait maternel a été calculée. Elle correspondait à seulement 0.45% de la dose quotidienne de néfazodone que prenait la mère ajustée selon son poids.

DISCUSSION: Les données suggèrent une association entre l'ingestion maternelle de néfazodone et les effets indésirables observés chez un prématuré allaité. La concentration mesurée du médicament serait normalement considérée sécuritaire chez un enfant né à terme. Toutefois, il y a eu une relation temporelle entre la résolution des symptômes chez l'enfant et la cessation de l'allaitement. Ce cas illustre l'importance d'individualiser l'analyse risques-bénéfices pour l'exposition aux antidépresseurs dans le lait maternel, particulièrement lorsqu'il s'agit de prématurés.

Esthel Rochefort