Serum Valproate Levels in 6 Breastfeeding Mother-Infant Pairs

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Background: Women with bipolar disorder are at high risk for recurrence of an affective episode in the postpartum period, and treatment with a mood stabilizer may be indicated. Few data are available to inform the risk-benefit decision regarding the use of valproate for women with bipolar disorder who elect to breast-feed.

Method: Serum valproate levels were obtained from 6 breastfeeding mother-infant pairs. All mothers had a diagnosis of bipolar disorder (Research Diagnostic Criteria) and were taking divalproex sodium as prophylaxis for or treatment of a recurrent affective episode. None of the mothers received valproate during pregnancy.

Results: The mothers had serum valproate levels near or within the therapeutic range (39.4 to 79.0 μg/mL). Infant serum levels were low, ranging from 0.7 to 1.5 μg/mL (0.9%–2.3% of maternal serum levels). No adverse clinical effects were observed in the infants.

Conclusion: Serum valproate levels were low in nurslings of mothers treated with valproate. These data can be used to inform clinical decisions regarding the use of valproate during breastfeeding.

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In women with bipolar disorder, the risk for recurrence of an affective episode in the postpartum period is 40% to 70%.[1–3] Because of this high risk, it has been recommended that lithium therapy be initiated immediately postpartum.[4,5] However, breastfeeding is contraindicated during maternal lithium therapy, according to the American Academy of Pediatrics.[6] As an electrolyte, lithium passes readily into the breast milk. Breast milk lithium levels average one third to one half of maternal serum lithium levels, and infant serum levels are approximately equivalent to milk levels.[7,8] Neonatal toxicity, including symptoms of cyanosis, hypothermia, and hypotonia, has been reported.[9]

Although the American Academy of Pediatrics Committee on Drugs considers maternal valproate treatment to be compatible with breastfeeding,[6] there are limited data concerning valproate levels in nurslings from 9 published cases of mother-infant pairs.[10–13] Eight of the mothers were treated with valproate during gestation and continued the medication while breastfeeding. Wisner and Perel[12] reported the only case in which a nursing mother began valproate in the immediate postpartum period. The serum valproate levels of these 9 infants were variable, ranging from less than 1.0 to 13.4 μg/mL (1.5% to 40% of maternal serum levels, respectively). Stahl et al.[13] reported the only adverse event concurrent with breastfeeding, a case of thrombocytopenic purpura and anemia in a 3-month-old breastfed infant whose mother was treated with valproic acid during and after pregnancy.

In this article, we present 6 cases of mother-infant valproate levels. All of the mothers began valproate therapy postpartum. The infants in this series were 4 to 19 weeks of age at the time of sampling.

METHOD

All subjects gave written informed consent following a risk-benefit discussion. The consent included the mother's agreement to having her infant's serum sampled to assess the valproate level. The infants' pediatricians were contacted, and each agreed to monitor the breastfed infant during maternal valproate treatment. All patients took valproate as divalproex sodium.

Subjects

All subjects were enrolled in an ongoing investigation, Prevention of Postpartum Episodes in Women with Bipolar Disorder. Mothers were included if they met Research Diagnostic Criteria for bipolar disorder and had not taken valproate during pregnancy. All mothers (except the one in case 2) initiated valproate treatment within 24 hours of giving birth. The mother in case 2 began valproate treatment at 13 weeks postpartum. In each instance, valproate was titrated, as tolerated, to achieve a maternal serum level in the therapeutic range (defined as 50–100 μg/mL). Four

Table 1. Serum Concentrations of Valproate in Mothers and Nursing Infants

Case	Infant Age (wk)	Maternal Dose (mg/d)	Maternal Serum Level (μg/mL)	Infant Serum Level (μg/mL)	% of Maternal Serum Level	% Breast-fed
1	4	750	39.4	0.9	2.3	100
2	4	1000	68.4	0.7	1.0	80
3	19	750	73.5	1.5	2.0	100
4	4	750	79.0	0.7	0.9	100
5	4	1000	56.2	0.7	1.2	50
6	7	1000	56.3	1.0	1.9	100

of the mothers took the entire valproate dose at bedtime. The mothers in cases 1 and 5 took valproate in divided doses (250 mg q.a.m./500 q.h.s. and 250 mg q.a.m./750 mg q.h.s., respectively). Most infants were fully breast-fed, although the infants in cases 2 and 5 were breast-fed for 80% and 50% of feedings, respectively. The mother-infant pairs were followed through the 20th postpartum week.

Sampling Technique

Steady-state blood samples were collected from the mothers after a minimum of 7 days of consistent maternal dosing. The samples were obtained approximately 12 hours after the mothers' evening dose. None of the mothers took any additional prescribed or over-the-counter medications. Sampled infants were at least 4 weeks of age. By that time, it is likely that the mother would have achieved steady state at her therapeutic dose. In addition, infant samples are somewhat easier to obtain at this age than they would be in the newborn period. Infant blood was obtained by antecubital venipuncture, performed by a skilled pediatric phlebotomist. The infant concentrations represent summary values that resulted from feedings throughout the day. Although the infant samples were random, it is likely that the infant blood levels represented a steady state and would not have varied significantly relative to the time of sampling. None of the nurslings experienced adverse events.

Sample Analyses

The serum levels of valproate were analyzed by a fluorescence polarization immunoassay (Medtox Laboratories, Saint Paul, Minn.). The sensitivity was 0.7 μg/mL. Interday coefficients of variation for high and low control samples were 2.9% and 3.8%, respectively.

RESULTS

The results are summarized in Table 1. Adult valproate levels between 50 and 100 μg/mL have been associated with clinical response. With the exception of case 1 (maternal valproate level = 39.4 μg/mL), all of the mothers had serum valproate levels within the therapeutic range (56.2–79.0 μg/mL) taking doses of 750 or 1000 mg/day. Infant blood levels ranged from 0.7 to 1.5 μg/mL and were 0.9% to 2.3% of maternal serum levels. Four of the 6 infants were sampled within the first month after birth. The remaining 2 were sampled at 7 and 19 weeks of age.

DISCUSSION

Our series is unique because in every case the infant exposure to valproate was exclusively during breastfeeding. Infant serum valproate levels in this series were generally lower than those previously reported.[10–13] It is noteworthy that 4 of the infants were very young (4 weeks old) at the time of sampling. In reviewing the literature regarding antidepressant use during breastfeeding, Wisner et al.[14] concluded that infants less than 10 weeks of age may be at greater risk for toxicity associated with maternal antidepressant treatment during breastfeeding, since the only adverse events were reported in young infants. In this series, however, none of the infants, including the very young, experienced adverse events.

While these data are very encouraging, they are limited. An unanswered question is whether chronic exposure to valproate, even at very low levels, might have adverse consequences for the infant. Given the low serum levels of valproate in the breastfed infants reported here, the likelihood of adverse consequences from chronic exposure to valproate via breast milk alone appears small. However, since there are only 7 reported cases of infants with exposure exclusively during breastfeeding (6 in this report and 1 from reference 12), more data are needed.

Stahl et al.[13] reported a case of thrombocytopenic purpura and anemia in the breastfed infant of a woman with epilepsy treated with valproic acid. However, the facts of the case do not support causality. The mother had taken valproic acid during her pregnancy; therefore, the cumulative exposure of the infant was much greater than would be the case if the infant's exposure had begun in the postpartum period. Omtzigt et al.[15] demonstrated that the pharmacokinetics of valproate during pregnancy can best be explained by a fetal deep compartment model. Their data indicate that there is a decreased clearance of valproate and its metabolites from the fetal compartment relative to the maternal compartment, resulting in fetal accumulation after chronic exposure. Consequently, one would expect that serum valproate levels in exposed fetuses would far exceed those found in nurslings. The infant reported by Stahl et al.[13] was 3 months old when signs of thrombocytopenic purpura developed at a serum valproate level of 6.6 μg/mL. Despite the fact that it is likely that this infant had substantially greater valproate exposure in utero and immediately after birth, the authors concluded that "it seems unlikely that transplacental transfer of valproic acid contributed to any greater extent to the thrombocytopenia in our case because there were no petechiae immediately after birth."[13(p1002)] It is curious, then, that when the signs of thrombocytopenic purpura devel-

oped at age 3 months, they readily attributed the disease to the valproate exposure via breast milk. The infant's signs and symptoms were similar to those of idiopathic thrombocytopenic purpura (ITP), and, at the time of diagnosis, the infant was noted to have "a slight cold." Therefore, an alternative explanation might be that the infant had ITP with a viral etiology. Stahl et al.[13] argued against a diagnosis of ITP on the basis of the apparent anemia detected in the infant (82 g/L of hemoglobin); however, this is based on reference values (131–163 g/L) that do not reflect the transient decrease in newborn hemoglobin levels in the first 3 months of life (95–145 g/L at 3 months of age[16]). Breastfeeding was discontinued 1 month after the infant was diagnosed, and the infant was completely recovered within 4 months of diagnosis, a time course also consistent with ITP.

The prescribing of any medication for a breastfeeding woman must always include a thorough risk-benefit assessment. The benefits of nursing have been established,[17] but must be weighed against the possible effects of even small amounts of valproate detected in the newborn. Similarly, the very substantial risk of a recurrent bipolar episode in an untreated woman must be weighed against the risk to the infant of exposure to medication through breastfeeding.

Drug names: divalproex sodium (Depakote), valproic acid (Depakene).

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