Antiepileptic Drugs During Breastfeeding

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Changes to LactMed: The National Library of Medicine has recently made some decisions that affect LactMed. First, all Toxnet databases are being either dropped, combined with other databases, or transitioned to a different platform. LactMed will now be available only at the NLM Bookshelf site: <https://www.ncbi.nlm.nih.gov/books/NBK501922/>. Information in the database is the same as on the former Toxnet site and it will continue to be updated monthly, around the third Tuesday of each month. Second, the LactMed® app will be dropped. This means that LactMed will only be available via a browser on the NLM Bookshelf as noted above. The app that you might have on your device at the current time is about 2 years out of date, so you are encouraged to use NLM Bookshelf to access LactMed.

WOMEN WITH EPILEPSY in the United States are less likely to breastfeed their infants, possibly because of concern that drugs in their milk might adversely affect their infants.¹ However, unlike many drugs, some antiepileptics have long-term follow-up data on their effects on breastfed infants. A multicenter study in the United States and the United Kingdom followed 181 infants born to mothers with epilepsy who were taking either carbamazepine, lamotrigine, phenytoin, or valproate as a single agent.² Infants were followed for 6 years. Of the infants, 78 were breastfed and 103 were not. After adjusting for maternal IQ, periconception folate use, and drug dosage, breastfed infants were found to have an average IQ that was 4 points higher than the nonbreastfed infants (108 versus 104 points). The difference was driven by the valproate group, which had an average 12-point difference between the breastfed and nonbreastfed groups (94 versus 106 points). The other drugs did not have statistically significant differences in IQ between the groups. Periconception folate use was also an important variable, with an average 5.7-point higher IQ among the infants of folate users.

Another prospective study in Norway followed infants of mothers who took antiepileptic drugs during pregnancy and lactation. These infants were compared with control groups of infants of mothers with untreated epilepsy and infants with fathers who took antiepileptics.³ Infants were assessed at 6, 18, and 36 months of age. Although some impairment in fine motor skills was found in infants exposed during pregnancy, continuous breastfeeding in children of women using antiepileptic drugs was associated with no greater impaired development than those with no breastfeeding or breastfeeding for <6 months. Of the 223 mothers studied, 71 were taking lamotrigine monotherapy, 48 were taking carbamazepine, and 27 were taking valproate.

These studies provide evidence that, at least for the drugs that were studied, breastfeeding by mothers taking an anti-

epileptic drug does not harm breastfed infants' intellectual development, and might improve it. Study results cannot necessarily be applied to mothers taking combinations of antiepileptic drugs.

The remainder of this column reviews individual drugs during breastfeeding. Additional references on specific drugs can be found in the corresponding LactMed records.

Carbamazepine

Carbamazepine has relatively high levels in breast milk and breastfed infants have serum levels that are measurable, but usually below the antiepileptic therapeutic range. Most infants have had no adverse reactions, but sedation, poor sucking, withdrawal reactions, and three cases of hepatic dysfunction have been reported. These have all been complicated by intrauterine exposure and, in some cases, concurrent drug therapy. Monitoring infant serum carbamazepine levels, liver enzymes, and a complete blood count during therapy might be useful if there are signs of toxicity. Carbamazepine can cause Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), which is not dose related.

Clobazam

Some information indicates that maternal doses of clobazam up to 30 mg/day produce low levels in milk. Clobazam has a half-life of 36–42 hours and is metabolized to N-desmethyloclobazam, which has ~20% the activity of clobazam and a half-life of 71–82 hours. Clobazam would not be expected to cause any adverse effects in breastfed infants, especially if the infant is >2 months.

Clonazepam

Maternal clonazepam occasionally causes sedation in the breastfed infants, especially when given with other central nervous system depressants. Monitoring of the infant's serum concentration may be indicated if excessive sedation occurs.

Ethosuximide

Ethosuximide has relatively high levels in breast milk. Dosages of 50–60% of the maternal weight-adjusted dosage are excreted into human milk and infant plasma levels of 25–30% of maternal plasma levels are common. Consequently, some sources consider ethosuximide to be a risky drug to use during breastfeeding. Although no adverse effects attributable solely to ethosuximide in breast milk have been reported, measurement of an infant serum level might help rule out toxicity if there is a concern.

Gabapentin

Maternal doses of gabapentin up to 2.1 g/day produce relatively low levels in infant serum. A single oral dose of either 300 or 600 mg given to the mother before cesarean section appeared to have no effect on breastfeeding initiation.

Lacosamide

Lacosamide has not been well studied in breastfeeding. Available information indicates that a maternal dose of 200 mg/day produces low levels in milk. Dosages up to 400 mg/day appeared to not adversely affect development in three infants who were breastfed for 7–9 months.

Lamotrigine

With lamotrigine, it is important to distinguish between short-term and long-term adverse effects, because lamotrigine passes into milk in relatively high concentrations. Breastfed infants have serum lamotrigine concentrations highly correlated with maternal serum and milk concentrations. Because lamotrigine's metabolism is often more rapid during pregnancy than at other times, dosages often must be increased during pregnancy. Maternal serum and milk levels can rise considerably in as little as a few days postpartum if dosages are not reduced after delivery.

Although most infants breastfed during maternal lamotrigine display no adverse reactions, occasional adverse reactions have been reported in infants who receive lamotrigine in milk. Twenty-six years of adverse reaction reports were compiled by a French pharmacovigilance center. Of 174 reports in breastfed infants, lamotrigine was reported to cause adverse reactions in six infants and to be one of the drugs most often suspected in serious adverse reactions, such as sedation, hypotonia, weight loss, and liver damage.

Another possible consequence of the high infant serum levels is neonatal abstinence syndrome with weaning. A 6-week-old infant developed apparent withdrawal symptoms after abrupt weaning by a mother who was taking lamotrigine 200 mg/day during late pregnancy and postpartum. Symptoms included loss of appetite, neuromotor hyperexcitability, and irritability. Symptoms occurred 2 weeks after weaning and were completely alleviated within 48 hours after instituting lamotrigine 1 mg/kg daily in the infant. Neuromotor

development of the infant normalized 1 month after discontinuing therapy.

Other adverse reactions in the literature attributed to lamotrigine include anemia, elevated platelet counts, elevated liver enzymes, and apnea with a high maternal dosage. If an infant rash occurs, breastfeeding should be discontinued until the cause can be established, because serious rashes requiring hospitalization have been reported in ~0.3–0.8% of patients aged 2–17 years. The rashes have included SJS/TEN and fatalities have been reported. Fortunately, no serious rashes have been reported yet as a result of breastfeeding, but they cannot be ruled out.

Levetiracetam

Maternal doses of levetiracetam up to 3,500 mg/day produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants. Some evidence suggests that levetiracetam might reduce the maternal breast milk supply occasionally.

Oxcarbazepine and Eslicarbazepine

Seventeen infants have been reported to have been exposed to oxcarbazepine during breastfeeding. The only adverse effect reported has been a withdrawal reaction, probably related to the decreased postpartum exposure to the drug in breast milk. Breastfeeding seemed to ameliorate the symptoms. Eslicarbazepine is a relatively new drug that is the active metabolite of oxcarbazepine. No specific information is available during breastfeeding, but it would be expected to be similar to oxcarbazepine.

Phenobarbital and Primidone

Excretion of phenobarbital into breast milk is unpredictable, but can be quite extensive. Primidone is active, but also metabolized to phenobarbital. In one study of nine mothers taking primidone, their infants' phenobarbital plasma levels were 37% of their mothers' plasma levels. Both of these drugs have caused sedation and poor nursing in breastfed infants. Neonatal withdrawal syndromes including convulsions have also been reported after abrupt discontinuation of breastfeeding. Fortunately, these drugs are not often used because of their sedating side effects.

Phenytoin

Because of the low levels of phenytoin in breast milk, amounts ingested by the infant are small and usually cause no difficulties in breastfed infants when used alone, but rare idiosyncratic reactions are possible. Two breastfed infants (one full, one partial) whose mothers took phenytoin during pregnancy and postpartum became hyperexcitable when their serum phenytoin dropped to unmeasurable levels at 3–6 weeks of age. This probably represents an abstinence syndrome rather than direct toxicity of the drug in breast milk. Phenytoin can also cause SJS/TEN.

Pregabalin

Very little information is available on pregabalin during breastfeeding. In 10 women who were studied, the average daily infant dosage was 0.31 mg/kg, or ~7% of the maternal

weight-adjusted dosage. This would indicate that breastfeeding is acceptable, but more data are needed.

Topiramate

Doses of topiramate up to 200 mg/day produce relatively low levels in infant serum. Most infants have had no adverse effects, but one peculiar side effect has been reported. The breastfed infant of a mother who was taking 100 mg/day of topiramate developed watery foamy stools with 8–10 bowel movements daily at 40 days of age. The infant's rate of weight gain also declined. Topiramate was detected in breast milk at a relatively high concentration. Two weeks later, breastfeeding was discontinued. Within 24 hours, the stool frequency declined to two to three times daily, was more solid, and the color and odor normalized.

Valproate and Divalproex

Valproic acid levels in breast milk are low and infant serum levels range from undetectable to low. Divalproex is quickly converted to the active drug valproic acid in the body. Although these drugs are used extensively in epilepsy and mood disorders, no definite adverse reactions to valproic acid in breastfed infants have been reported. Theoretically, breastfed infants are at risk for valproic acid-induced hepatotoxicity, so infants should be monitored for jaundice and other signs of liver damage during maternal therapy. A questionable case of thrombocytopenia has been reported, so to monitor the infant for unusual bruising or bleeding.

Zonisamide

Maternal doses of zonisamide up to 400 mg/day produce high levels in milk and infant serum. Three reports of infants being breastfed have been found. An infant whose mother was taking an unspecified dose of zonisamide during pregnancy and breastfeeding had a serum zonisamide concentration that was 3.6 mg/L or 17% of the maternal serum concentration at 9 days postpartum. The half-life of zonisamide in this infant and one other was estimated to be ~100 hours, but infant serum levels in neonates decrease during the first month of life despite breastfeeding. Some clinicians recommend that mothers taking zonisamide only partially breastfeed to reduce the exposure of the infant to the drug and to consider monitoring infants' serum zonisamide concentrations. Although no adverse reactions have been reported in breastfed infants, zonisamide may have the highest risk of SJS/TEN of all antiepileptics.⁴

Summary

Most antiepileptic drugs that have breastfeeding information reported appear to be acceptable to use during breastfeeding as single agents. Long-term follow-up data indicate that maternal carbamazepine, lamotrigine, phenytoin, and

valproate cause no long-term developmental problems in breastfed infants. Long-term outcomes with other drugs and the many possible drug combinations have not been well studied. Use of periconception folic acid also improves intellectual outcome in the infants of women taking antiepileptic drugs.

Acute adverse reactions have been reported with some drugs, such as lamotrigine. All infants whose mothers take antiepileptic drugs should be monitored for side effects such as apnea, drowsiness, adequate weight gain, and developmental milestones, especially in younger exclusively breastfed infants and when using combinations of antiepileptics. As a class, antiepileptics have a greater risk of hypersensitivity reactions, including SJS/TEN, than other drug classes, especially in children.^{4,5} Breastfed infants should be watched carefully for rashes. Routine measurement of infant serum levels is generally not necessary except to rule out toxicity if there is a concern.

Disclosure Statement

No competing financial interests exist.

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