

Perinatal exposure to maternal lamotrigine

Clinical considerations for the mother and child

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ABSTRACT

QUESTION The question of neonatal safety during breastfeeding when mothers are taking lamotrigine (LTG) has become more prevalent in my practice. There are some theoretical concerns about breastfeeding while taking LTG, which have been compounded by a published case report of toxicity in the breastfed neonate of a mother taking LTG. How should I advise my patients who wish to breastfeed while taking LTG?

ANSWER Most neonates born to mothers taking LTG have already been exposed to the drug for 9 months in utero, given the chronic indications for which the drug is intended. Lamotrigine exposure via breast milk is considerably less than placental transfer, with serum LTG concentrations in neonates higher at birth than during lactation. While a single case of toxicity has been reported in a neonate exposed to LTG via breast milk, in most circumstances, breastfeeding can be initiated and maintained given the tremendous benefits of mothers' milk. On the other hand, toxicity during breastfeeding might occur more commonly in the mother, if sufficient and gradual dose readjustments are not undertaken in the weeks following delivery.

RÉSUMÉ

QUESTION Dans ma pratique, la question de l'innocuité pour le nouveau-né de l'allaitement par une mère qui prend de la lamotrigine (LTG) se pose de plus en plus souvent. L'allaitement pendant que la mère prend de la LTG soulève des préoccupations théoriques, qui ont été exacerbées par la publication d'un rapport de cas de toxicité chez un nouveau-né allaité par une mère prenant de la LTG. Quels conseils devrais-je donner à mes patientes qui souhaitent allaiter alors qu'elles prennent de la LTG?

RÉPONSE La plupart des nouveau-nés dont la mère prend de la LTG ont déjà été exposés au médicament in utero pendant 9 mois, étant donné la nature chronique de la maladie pour laquelle le médicament est administré. L'exposition à la lamotrigine par le lait maternel est considérablement moins grande que par le transfert placentaire, et les concentrations sériques de LTG chez les nouveau-nés sont plus élevées à la naissance que durant l'allaitement. Même si on a rapporté un cas unique de toxicité chez un nouveau-né exposé à la LTG par le lait maternel, dans la plupart des circonstances, on peut amorcer et continuer l'allaitement étant donné les bienfaits importants du lait maternel. D'autre part, la toxicité durant l'allaitement peut se produire plus fréquemment chez la mère si l'on n'a pas entrepris de rajuster suffisamment et graduellement la dose durant les semaines suivant l'accouchement.

Lamotrigine (LTG) continues to increase in popularity¹ for the treatment of epilepsy and bipolar disorder in the perinatal period. The safety data pertaining to fetal exposure to LTG during pregnancy are largely reassuring,^{2,3} but there are relatively few mother-infant pairs who have been studied systematically in the postpartum period. Concerns have been raised about the slow elimination half-life of LTG in newborns and the extent to which LTG that is excreted into breast milk⁴; this concern, as well as a recent case report of toxicity in a breastfed neonate of a mother taking LTG,⁵ has made the question of safety for the exposed child during breastfeeding more prevalent.

Given the risks of untreated maternal disease for both the mother and the infant, any discussion of safety should also consider the marked interindividual variability in LTG metabolism and clearance in women

of childbearing age.⁶⁻⁸ In the following sections we will consider these issues, with an emphasis on clinical considerations for the management of mothers and their neonates exposed to LTG.

Excretion into human milk

In contrast to studies in thousands of pregnant women taking LTG, the largest study of its use during breastfeeding consists of 25 mothers and their nursing infants,⁹ bringing the collective number of studied cases to 51 mother-infant pairs.^{4,5,9-11} Within this collective group of studies, large interindividual variability in breast milk concentrations of LTG exists.

Newport et al demonstrated this variability in a recent investigation of more than 210 breast milk samples that were collected from 25 mothers for various analyses, including foremilk-to-hindmilk analysis, 24-hour

sampling, and one-time spot sampling.⁹ The authors confirmed the imprecision in using milk-plasma ratios derived from spot analysis to estimate infant exposure levels during lactation: milk-plasma ratios ranged from 0.06 to as high as 1.47.⁹ Using the mean breast milk concentration from each individual, the daily theoretical infant dose via milk (daily breast milk intake multiplied by mean breast milk concentration of medication) was calculated at 0.51 mg/kg per day. Compared with the LTG dose typically administered to neonates therapeutically (2 mg/kg daily), the relative infant dose (RID) was calculated to be 25%. The percentage of the weight-adjusted maternal dose (ie, RID derived from maternal dose instead of infant therapeutic dose) was 9.2% (range 7.4% to 10.9%),⁹ which was lower than previously reported values.^{12,13}

While the RID provides a clinically useful estimation of neonatal exposure to medication in breast milk in the absence of neonatal plasma concentrations, several studies have found that the plasma concentration of LTG in the breastfed neonate ranges from 18% to 43% of the maternal plasma LTG concentration,^{4,6,10,14} with neonatal serum LTG concentrations sometimes reaching therapeutic levels.^{4,5,10} Drug exposure from pregnancy might have contributed to infant plasma concentrations in these cases. The clinical significance of these findings depends in part on the toxicity profile of LTG. Notably, in all the published studies thus far, one case report of a serious neonatal adverse event has been reported.⁵

A 16-day-old, full-term infant experienced several mild apneic episodes that culminated in cyanosis requiring resuscitation. The mother had been using LTG monotherapy for the duration of the pregnancy, with LTG doses escalating to 875 mg daily near the end of pregnancy. The mother herself experienced LTG-induced toxicity (ie, diplopia, blurred vision, dizziness, nausea, twitching in hips and elbows, and one episode of dyspnea) in the postpartum period, about 1 week before the neonate's adverse events. At the time of the apneic episodes, the infant's serum LTG concentration was 4.87 µg/L, approximately 35% lower than LTG concentrations at birth via in utero exposure.⁵ The question remains as to why the apnea occurred at 16 days of life, given the higher drug concentration measured at birth. Furthermore, serious clinical effects from LTG-toxicity (eg, respiratory depression, coma) are extremely rare according to toxicity data from overdose cases from the American Association of Poison Control Centers.¹⁵ Given these ambiguities, it is debatable whether the events in this case report were triggered by LTG, or by some other factors. Nonetheless, there is some evidence that the free fraction of LTG is higher in neonatal plasma than in maternal plasma, which can have implications for drug concentrations at sites of action in the central nervous system.⁹ Whether there are differences in the sensitivity of neonates to LTG (pharmacodynamics) as compared with older children and adults remains to be determined.

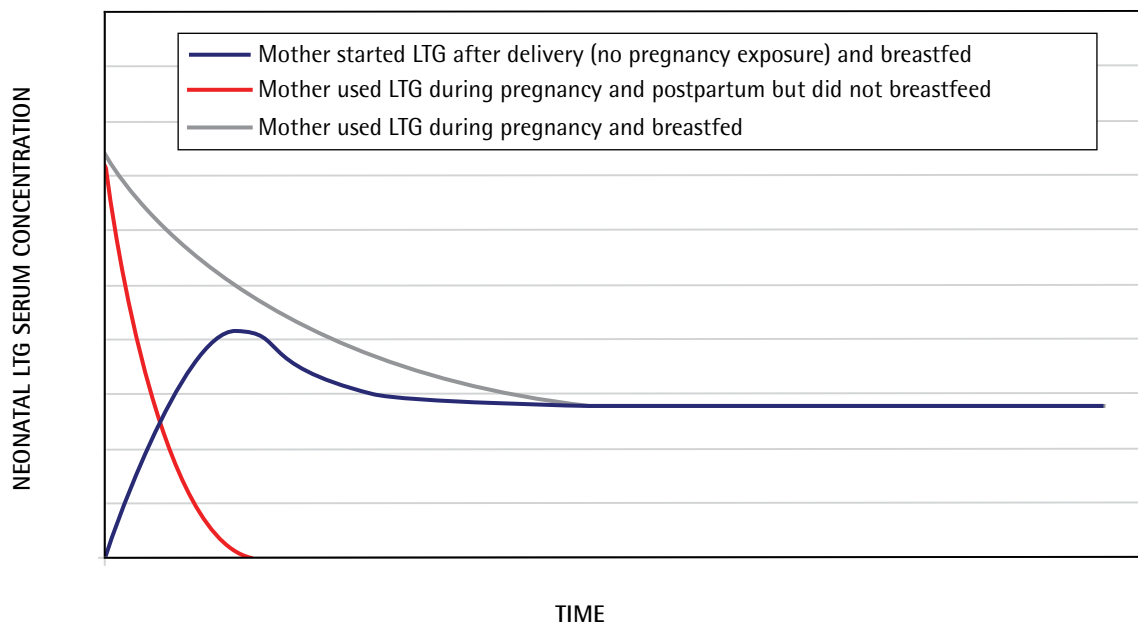
Concerns about breastfeeding while taking LTG also stem from the slow glucuronidation capacity of neonates (generally reaching adult levels by around 2 to 6 months of age),¹⁶ potentially leading to LTG accumulation due to continuous and prolonged medication exposure via breast milk.⁴ However, neonatal LTG serum concentrations are approximately equivalent to maternal LTG concentrations at delivery owing to gestational exposure in most cases.^{6,8} Breastfed infants exposed to LTG in utero and via breast milk actually have up to 12 times lower LTG serum concentrations in the weeks following birth as compared with LTG concentrations at delivery.^{6,8} Therefore, in infants exposed to LTG in utero, LTG concentrations are highest at birth and gradually decrease over time—this is irrespective of whether or not the infant is breastfed (**Figure 1**).

Maternal LTG disposition during pregnancy and lactation

One of the most important clinical considerations in pregnancy and the postpartum period is the maintenance of therapeutic maternal LTG concentrations among largely variable and fluctuating pharmacokinetic alterations. In nonpregnant volunteers, LTG is 55% protein bound and metabolized primarily in the liver by glucuronidation.¹⁷ It is rapidly absorbed with a mean steady-state elimination half-life of 24.1 (SD 5.7) hours in adults.¹⁷ During pregnancy, LTG clearance has been shown to progressively increase to a peak of greater than 300% at 32 weeks of gestational age compared with that of baseline, prepregnancy levels.^{5,6,8,10,18} This corresponds with an increase in seizure frequency during the seventh month of gestation.⁶⁻⁸ After 32 weeks, clearance values steadily decrease and reach prepregnancy levels as rapidly as 1 month after birth.⁶⁻⁸ As a result, maternal LTG-induced toxicity is prevalent in the first several weeks postpartum, probably because LTG doses that were increased during pregnancy are not tapered accordingly.^{5,6} However, gradual dose reduction is complicated if the patient develops seizures after delivery. These pregnancy-related changes in LTG pharmacokinetics might not be remarkable in certain individuals. For example, subjects with initially low clearance values tend to have lower clearances throughout pregnancy.⁷ This variability might be pharmacogenetically controlled, as dysfunctional genotypes have been described for the uridine diphosphate glucuronosyltransferase 1A4 (UGT 1A4) enzyme responsible for about 90% of total LTG clearance.^{6,19,20} Polymorphisms in UGT 2B7, a minor contributor to LTG glucuronidation, have also been suggested to affect LTG clearance.²¹


The clinical consequences of the dramatic pregnancy-induced changes in LTG clearance require close observation of maternal levels; the highest risk for seizure

Figure 1. Predicted LTG neonatal serum concentration versus time profiles for 3 hypothetical scenarios



LTG –lamotrigine.

onset appears to be in the seventh month of gestation.⁷ A prophylactic increase in LTG dosage throughout pregnancy has been recommended,⁶ although it is difficult to predict how much each patient's dose will need to be increased. Pharmacogenetic analysis and the development of clinical models might be useful in these circumstances.

Close maternal and infant therapeutic drug monitoring is recommended in the postpartum period. 

Competing interests

None declared

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Drs Madadi and Ito are members of the Motherisk Program.

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