Q&A 409.2

Lamotrigine – is it safe to take while breastfeeding?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Date prepared: February 2016

Background

Lamotrigine is an anti-epileptic drug (AED) used as adjunctive or monotherapy of partial seizures and generalised seizures, including tonic-clonic seizures, and for seizures associated with Lennox-Gastaut syndrome. It is also used in the treatment of bipolar disorder (1).

The National Institute for Health & Care Excellence (NICE) guidance on epilepsy states that all women and girls with epilepsy should be encouraged to breastfeed, except in very rare circumstances (2). For most women taking AEDs, breastfeeding is generally safe and should be encouraged. The decision regarding the use of AEDs whilst breastfeeding should be made between the mother and the prescriber based on the balance of risks and benefits (2).

Lamotrigine is rapidly absorbed from the gastrointestinal tract, with a bioavailability of 98%. Protein binding is about 55% and it is extensively metabolised in the liver and excreted principally as an inactive glucuronide conjugate. Mean elimination half-life, in adults, is 24 to 35 hours (3). During pregnancy, lamotrigine clearance progressively increases and may lead to an increase in symptoms if doses are not altered. Maternal lamotrigine-induced toxicity may occur in the first few weeks postpartum if doses that were increased during pregnancy are not adjusted (4,5).

Answer

Passage into breast milk

Considerable published evidence shows that lamotrigine passes into breast milk in significant amounts and has been detected in the serum of breastfed infants.

Infant intake of lamotrigine via breast milk has been estimated at between 2 and 20% of the weight adjusted maternal dose, with reported infant serum levels of up to 50% of maternal plasma levels (6-10).

Large inter-individual variation in breast milk concentrations of lamotrigine have been noted (4). In one study of 30 breastfeeding women receiving lamotrigine for epilepsy or bipolar disorder, serial breast milk samples were collected over 24 hours to determine the time course of excretion. The mean milk/plasma ratio was 0.41 but the value was highly variable ranging from 0.06 to 1.47. The mean relative infant dose was 9.2% (range 3.1% - 21.1%). The authors noted that whilst the time course of excretion showed considerable intra-individual variability, there was even greater between subject variations which may be due to pharmacogenetic factors (4,8).

Also, due to the potential for drug interactions resulting in altered lamotrigine levels, the relationship of maternal dosage to the concentration in breast milk can be quite variable (11).

Where maternal therapy has been used in pregnancy, neonatal serum levels are approximately equivalent to maternal concentrations at birth and gradually decrease over time, irrespective of whether or not the infant is breastfed (5,10). Neonates are particularly at risk for high plasma levels because ability to metabolise the drug by glucuronidation is reduced, plasma protein binding is relatively low, and maternal plasma and milk levels can rise dramatically in the immediate postpartum period if the dosage is not reduced to the pre-pregnancy dosage (11). Results from one case report indicate that the neonatal lamotrigine elimination half-life was approximately twice that seen in adults (9).

Adverse effects in breast fed infants

An apparent withdrawal syndrome developed in a 6-week old infant after abrupt weaning in a mother taking lamotrigine 200 mg daily in late pregnancy and postpartum (12). Symptoms included loss of

appetite, neuromotor hyperexcitability and irritability and occurred 2 weeks after cessation of breastfeeding. Symptoms resolved within 48 hours of treatment of the infant with lamotrigine 1 mg/kg daily. Neuromotor development was normal 1 month after discontinuation of therapy (12).

A 16 day old, fully breastfed infant developed several mild episodes of apnoea that culminated in a severe cyanotic episode requiring resuscitation. The mother had been taking increasing doses of lamotrigine throughout pregnancy, which was reduced slowly after delivery, and at the time of the apnoeic episodes was taking 850 mg daily. A high lamotrigine concentration was detected in breastmilk and the neonatal lamotrigine serum concentration was in the upper therapeutic range. Symptoms resolved after breastfeeding was stopped and the infant made a full recovery (9).

Elevated platelet counts were observed in 7 of 8 infants (average age 3.8 weeks, range 2 to 10 weeks) whose mothers were taking lamotrigine whilst breastfeeding. These were not associated with any adverse clinical effects (8). Secondary thrombocytoses are commonly seen in up to 36% of neonates in association with prematurity, infection and drug exposure (13,14).

The majority of rashes associated with lamotrigine are mild and self-limiting; however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life-threatening rashes such as Stevens–Johnson syndrome, toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (1). If an infant rash occurs, breastfeeding should be discontinued until the cause can be established (11). No serious cases of rash have been reported in breastfed infants. Transient elevation of liver enzymes occurred in premature breastfed twins whose mother was taking lamotrigine with other unspecified medications for bipolar disorder (15).

In a large study of early child development and exposure to AEDs prenatally and through breastfeeding, prenatal exposure to AEDs was associated with a higher risk of impaired fine motor skills at age 6 months, especially in children exposed to multiple AEDs. Breastfeeding in women using AEDs was not associated with any harmful effects on child development at 6 to 36 months of age. The authors concluded that women with epilepsy should be encouraged to breastfeed their children irrespective of AED used (16)

In a long-term study of AED exposure during breastfeeding and cognitive outcomes, no differences in average IQ scores, at age 3 years or age 6 years, were found between those infants who were exposed to lamotrigine via breastmilk (n = 30) and those who were not (n = 36). However, the authors state that due to study limitations caution is needed, and further study is required. (17,18).

Summary

- Lamotrigine passes into breast milk in significant amounts and infant plasma levels of up to 50% of maternal levels have been reported. Infant intake of lamotrigine via breast milk has been estimated at between 2 and 20% of the weight adjusted maternal dose.
- The risk to the breastfed infant is highest in the neonatal period because of reduced capacity for glucuronidation, relatively low plasma protein binding and altered maternal pharmacokinetic parameters in the postpartum period when the drug has been used in pregnancy.
- There is considerable inter- and intra-individual variation in the passage of lamotrigine into breast milk. Pharmacogenetic factors may be involved.
- Few adverse reactions have been reported in breastfed infants exposed to lamotrigine via breast milk. There are single case reports of withdrawal syndrome when breastfeeding was stopped suddenly and of severe apnoea.
- If an infant rash occurs, breastfeeding should be discontinued until the cause can be established.
- If lamotrigine is used by a breastfeeding mother, monitor the infant for sedation, poor feeding, adequate weight gain, and developmental milestones. Combination therapy may pose an increased risk to the infant, especially when adverse effects, such as drowsiness, are additive. Premature infants should not be exposed to lamotrigine via breast milk.

Limitations

The above outline is provided for general guidance. Many decisions as to the safety of lamotrigine in breastfeeding mothers will need to be taken on a case-by-case basis, particularly if there are unusual circumstances e.g. infant morbidity, requirement for high doses, concurrent medication etc. In these instances, further advice can be sought from the UK Drugs in Lactation Advisory Service provided by the Trent Medicines Information Service or the West Midlands Medicines Information Service.

References

1. Summary of Product Characteristics - Lamictal . GlaxoSmithKline UK. Accessed on-line at www.emc.medicines.org.uk on 11/01/2016 (date of text revision 03/07/2015).
2. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management (Clinical guideline CG 137. Published Jan 2012) Accessed via http://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-35109515407813 on 11/01/2016.
3. Brayfield A (ed), Martindale: The Complete Drug Reference. [online] London: Pharmaceutical Press Accessed via http://www.medicinescomplete.com/ on 13/01/2016
4. Madadi P, Ito S. Perinatal exposure to maternal lamotrigine. Clinical considerations for the mother & child. Can Fam Phys 2010;56:1132-1134
5. Clark CT, Klein AM, Perel JM et al. Lamotrigine dosing for pregnant patients with bipolar disorder. Am J Psychiatry 2013;170:1240-1247.
6. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsia 2000; 41:709-13.
7. Page-Sharp M, Kristensen JH, Hackett LP et al. Transfer of lamotrigine into breast milk. Ann Pharmacother 2006; 40:1470-1.
8. Newport DJ, Pennell PB, Calamaras MR et al. Lamotrigine in breast milk and nursing infants: determination of exposure. Pediatrics. 2008;122:e223-231
9. Nordmo E, Aronsen L, Wasland K et al. Severe apnea in an infant exposed to lamotrigine in breast milk. Ann Pharmacother. 2009;43:1893-7
10. Fotopoulou C, Kretz R, Bauer S, Schefold JC et al. Prospectively assessed changes in lamotrigine concentration in women with epilepsy during pregnancy, lactation and the neonatal period. Epilepsy Res 2009;85;60-64
11. National Library of Medicine. “LactMed Database”. Available at <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm> [accessed on-line 21/1/16]
12. Popescu L, Marceanu M, Moleavin I. Withdrawal of lamotrigine caused by sudden weaning of a newborn: a case report. Epilepsia 2005;46 (Suppl 6):407.Poster 1351.
13. Dame C, Sator AH. Primary and secondary thrombocytosis in childhood. Br J Haematol 2005;129:165-177
14. McPherson RJ, Juul S. Patterns of thrombocytosis and thrombocytopenia in hospitalised neonates. J Perinatol 2005;25:166–172
15. Precourt A, Morin C. Use of lamotrigine during breastfeeding – descriptive analysis of our population and report of five cases of premature neonates Breastfeed Med 2011;6 (Suppl 1):S-17. Abstract 35
16. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding. JAMA Neurol 2013;70:1367-74
17. Meador KJ, Baker GA, Browning N et al. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology 2010; 75:1954-60.
18. Meador KJ, Baker GA, Browning N et al. Antiepileptic drug exposure during breastfeeding and cognitive outcomes at age 6 years. Epilepsy Curr 2014;14 (Suppl 1):249-50

Quality Assurance

Prepared by
Sarah Fenner
West Midlands Medicines Information Service

Date Prepared
8 February 2016

Checked by
Peter Golightly, West Midlands Medicines Information Service

Date of check
19 February 2016

Search strategy

- Embase: [LAMOTRIGINE] AND [BREAST MILK OR LACTATION OR LACTATION INHIBITION OR MILK PRODUCTION OR BREAST FEEDING]. Limit to Humans and English Language
- Medline: [LAMOTRIGINE] AND [MILK,HUMAN OR LACTATION OR BREAST FEEDING]. Limit to Humans and English Language
- UKDILAS in-house database (Trent & West Midlands Medicines Information Services)
- US National Library of Medicine. Drugs & Lactation database – Lactmed http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
- Hale TW. Medications & Mother's Milk Online. http://www.medsmilk.com/
- National Institute for Clinical Excellence (NICE) Clinical Guidelines. http://www.nice.org.uk/
- Infant Risk Center http://www.infantrisk.com/