Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: October 19, 2010  Date Consulted: September 23, 2010

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To: Division of Neurology Products (DNP)

Drug: Lamictal XR Tablets, NDA 22-115

Subject: Breastfeeding

Materials Reviewed:
- OSE PREA: Pediatric Postmarketing Adverse Event Review for lamictal XR Tablets, September 14, 2010
- Lamotrigine lactation literature review

Consult Question: Provide input on the current state of knowledge from literature or other sources concerning maternal-child transfer of lamotrigine through human milk and consequent adverse events.
INTRODUCTION
Lamictal XR Tablets (NDAs 22-115 and 22-509) were approved on May 29, 2009, as adjunctive therapy for primary generalized tonic-clonic seizures and partial seizures with or without secondary generalization in patients $\geq 13$ years of age. The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) require referral of all adverse event reports to the Office of Pediatric Therapeutics (OPT) for the first year after an approved labeling change as a result of a PREA or BPCA study. OPT must present reports to the Pediatric Advisory Committee (PAC). Lamictal XR Tablets is scheduled to be presented at the December 2010 PAC Meeting.

In preparation for the December 10, 2010 PAC Meeting, the Office of Surveillance and Epidemiology (OSE)” provided a lamotrigine adverse event review and reported on an unlabeled and serious adverse event of “cyanosis neonatal”. A 16 day old nursing infant whose mother was taking Lamictal 850 mg/day for seizures, experienced several apnea episodes, one of which required basic cardiac life support. The infant had a serum lamotrigine level of 4.87 $\mu$g/mL upon hospital admission.

The Division of Neurology Products consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) on September 23, 2010, to provide information on the current state of knowledge from literature or other sources concerning maternal-child transfer of lamotrigine through human milk and consequent adverse events.

BACKGROUND
Lamotrigine is an antiepileptic drug (AED) of the phenyltriazine class that is indicated for adjunctive therapy for epilepsy in patients $\geq 2$ years of age, monotherapy for epilepsy in patients $\geq 16$ years of age, and maintenance treatment for Bipolar I Disorder in patients $\geq 18$ years of age. The precise mechanism of action is unknown. Lamictal (lamotrigine) was initially approved on December 27, 1994, and is widely used in women of childbearing potential for the treatment of both epilepsy and bipolar disorder. The current Nursing Mothers subsection of lamotrigine labeling states:

8.3 Nursing Mothers
Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL XR is not recommended.

Pharmacokinetics of Lamotrigine
Lamotrigine is a weak lipophilic base (pKA 5.7) with a molecular weight of 256.09 that is rapidly orally absorbed with high bioavailability. There is a linear relationship between dose and plasma concentrations at steady state following doses of 50 to 350 mg twice daily. Lamotrigine is not highly bound to plasma proteins (55%) and is metabolized predominately by glucuronic acid conjugation and is renally excreted. The half-life and clearance vary depending on concomitant medications. The half-life in adults varies from 6 to 103 hours and from 7 to 45 hours in pediatric patients ages 10 months to 18 years of age.

1 OSE PREA: Pediatric Postmarketing Adverse Event Review for lamictal XR Tablets, September 14, 2010
The approved pediatric lamotrigine starting dose in patients 2 to 12 years of age is 0.15 to 1.2 mg/kg/day and usual maintenance dose is 1 to 15 mg/kg/day, depending on concomitant medications. The use of concomitant medications that either induce or inhibit glucuronidation and genetic differences in glucuronidation that are due to different isoenzymes may lead to a wide variability in drug metabolism between patients. In addition, there is a significant transfer of lamotrigine into breast milk.

Pharmacokinetics of Drugs in Human Milk
The transfer of substances, including drugs, into human milk can occur by passive diffusion and/or active transport. Factors that influence the amount of a systemically absorbed drug present in human milk include:

- Higher maternal plasma levels
- Plasma protein binding – higher protein binding decreases the amount of drug excreted into human milk; however, high milk protein binding results in a sustained presence of the drug in human milk
- Lipophilicity – high lipophilicity of a drug leads to its accumulation in human milk
- Molecular weight – drugs with low molecular weights are transferred more easily into human milk
- pKA (ionization in plasma and human milk pH) – higher pKAs increase the amount of drug excreted into human milk

Calculation of Infant Drug Doses Received through Human Milk
There are two conventional ways to estimate infant drug exposure during lactation, the theoretical infant dose (TID) and the relative infant dose (RID). These estimates can be used for determining drug safety during lactation. The TID (expressed as mg/kg/day) = daily breast milk intake [150 mL/kg/day] x drug human milk concentration. This calculation can be used to compare the drug amount received through human milk to a known infant/pediatric therapeutic drug dose. The RID (expressed as a percentage) = TID/maternal daily dose (mg/kg/day). A classification system was developed using the RID to provide a rational basis for making therapeutic decisions for women who want to human milk-feed their infants. Drugs are classified as acceptable, caution, or unacceptable with use during lactation based on their RID; however, the RID cut-offs for the three categories were randomly chosen and not based on any scientific method. By this classification system, the RID cut-off for assuming safety of a drug during lactation is 10%.

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2 See current approved Lamictal XR labeling, April 4, 2010
5 Bennett PN, ed. Drugs and Human Lactation, 2nd ed. 1996, Elsevier B.V.
LITERATURE REVIEW
Following is a brief summary of the relevant available literature regarding lamotrigine use and lactation.


Summary: The authors conducted a study to prospectively analyze the pharmacokinetics of lamotrigine during pregnancy and lactation in a consecutive series of 9 epileptic pregnant women. During pregnancy, lamotrigine clearance increased 197% during the first trimester, 236% during the second trimester, and 248% during the third trimester (median levels). The average lamotrigine dose required a 250% increase during pregnancy to maintain therapeutic serum levels. Preconception lamotrigine levels were achieved approximately 3 weeks postpartum. The lamotrigine concentration ratio of umbilical cord blood to maternal serum ranged from 0.56 to 1.42, and the lamotrigine concentration ratio of breast milk to maternal serum ranged from 0.35 to 0.86. The lamotrigine serum concentration in the newborn ranged between 1.7 and 3.3 μg/mL in the first 12 weeks of life corresponding to 25 to 28% of the maternal serum concentration. These findings for lactation imply that close monitoring of breastfed infants is required due to therapeutic levels of lamotrigine occurring for several weeks in the newborn infant. The authors found no adverse events in any infants from exposure to lamotrigine in-utero or through breast milk, and no abnormalities were detected in short-term neuropsychological development testing.


Summary: The authors report that the safety of lamotrigine in pregnancy and breastfeeding remains controversial. A considerable amount of lamotrigine is excreted in human milk and in some cases human milk-fed infants have lamotrigine serum levels that reach therapeutic ranges. Human milk-fed infants should be closely monitored for adverse events, including sedation, poor suckling and life-threatening rashes.


Summary: The authors report that current practice guidelines suggest that women with epilepsy can breast-feed their infants; however, no consideration is given for infant metabolism of drugs. Lamotrigine is extensively metabolized by glucuronidation, a process which is immature in neonates and may lead to drug accumulation. The authors reported on lamotrigine serum levels in four full-term nursing newborns on day 10 of life that were born to mothers with epilepsy on lamotrigine monotherapy (lamotrigine serum levels were also obtained in the mothers). Infant serum lamotrigine levels ranged from <1.0 to 2.0μg/mL and these serum levels were 20 to 43% of the maternal drug levels. The infant serum lamotrigine levels were higher than expected and reached therapeutic ranges in some infants. As all infant serum levels were not high, there may be considerable genetic variability in infant
lamotrigine metabolism. The authors conclude, that based on this limited data, lamotrigine levels should be monitored in nursing infants and mothers with epilepsy should be counseled regarding the potential risks and benefits of breastfeeding their infants.


Summary: Lamotrigine use has increased over the past decade and breastfeeding data is sparse. The authors conducted a study to characterize the determinants of lamotrigine concentrations in breast milk and nursing-infant plasma. Paired infant and maternal plasma samples were provided by 12 mother-infant pairs and breast milk samples were provided by 7 mothers (8 infants). Maternal milk/plasma concentrations ranged from 5.7% to 147.1% (mean was 41.3%). Infant plasma concentrations ranged from 6 - 40% of the mothers plasma level (mean was 18.3%). The calculated infant theoretical infant lamotrigine dose was 0.51 mg/kg/day and the relative infant lamotrigine dose was 9.2% (RID cut-off for assuming safety during lactation is 10%). Mild thrombocytosis was reported in 7/8 infants. No other adverse events were reported. Lamotrigine milk/plasma ratio is highly variable and lamotrigine excretion into breast milk is comparable to other AEDs. The authors concluded that women who choose to nurse while taking lamotrigine must consider the extent of infant exposure during central nervous system development and appropriate monitoring of their nursing infants.


Summary: The authors reported on a case of severe apnea requiring resuscitation in a 16 day old infant exposed to lamotrigine through breastfeeding. The infant experienced several mild apnea episodes leading up to the severe event. Lamotrigine clearance increases through pregnancy, requiring increasing doses to maintain therapeutic serum levels. Clearance returns to preconception levels usually within 2 to 3 weeks of delivery and lamotrigine doses are generally decreased during this time period to avoid increased drug serum levels. The mother reported in this article had been on increasing doses of lamotrigine during pregnancy (875 mg/day) and had a seizure at 5 months. A second seizure occurred a number of hours post-delivery, and due to that event, her lamotrigine dose was slowly decreased post-delivery. At the time of the infant apnea episodes, the mother’s lamotrigine dose was 850 mg/day, maternal serum concentration was 14.93 μg/mL, and the infant’s serum concentration was 4.87 μg/mL (theoretical infant dose of 1.96 mg/k/day). The authors conclude that this case highlights the importance of individual risk/benefit decision making regarding breast feeding when a mother is taking lamotrigine. If a mother chooses to breastfeed while taking lamotrigine, careful observation and serum monitoring should be performed in both mother and infant, and caution is advised if a mother is taking a high dose or has any adverse effects.

Summary: The authors conducted a study to investigate the pharmacokinetics of lamotrigine during delivery, the neonatal period, and lactation in 9 women and their 10 infants. At 2 to 3 weeks after delivery, maternal milk/plasma concentration ratios were 0.47 to 0.77 and the nursing infants maintained plasma concentrations of 23 to 50% of the mother’s plasma levels. Lamotrigine is excreted in considerable amounts in breast milk and eliminated slowly in infants. The dose of lamotrigine to a nursing infant at 2-3 weeks is estimated at ≥0.2-1 mg/kg/day (up to and above therapeutic levels).


Summary: The authors conducted a study in 6 nursing women/infant pairs to present additional data to inform decision making with lamotrigine use and breastfeeding. Findings were similar with other small studies. The mean absolute infant dose was 0.45 mg/kg/day, the mean relative infant dose was 7.6%, and the mean infant serum concentration was 18% of the maternal serum concentration. No adverse events were noted in infants. The authors concluded that use of lamotrigine during breastfeeding should be subject to an individual risk-benefit analysis and infant observation and occasional monitoring of both infant and maternal lamotrigine serum levels should be performed.


Summary: The authors report that knowledge of pharmacokinetics of AEDs during pregnancy and lactation is important to enable optimal treatment. Therapeutic drug monitoring is advisable during pregnancy and appropriate observation of breast fed infants is recommended with maternal use of AEDs. Lamotrigine is eliminated by glucuronidation and may accumulate in breast fed infants due to immature drug metabolizing pathways. Infant plasma concentration levels up to 40% of the maternal plasma concentration have been reported, and the free fraction appears to be higher in the plasma of a breast fed infant that in the mother. No clinically adverse events have been reported in breast fed infants.


Summary: The authors present 3 cases of women with bipolar disorder who were exposed to lamotrigine through pregnancy and breastfeeding and infant follow-up through 15 to 18 months. No adverse events attributable to lamotrigine were observed in the 3 infants and growth and development were normal through 16 months. No drug serum levels were provided in the mothers or infants.
The Drugs and Lactation Database (LactMed) summary of lamotrigine use during lactation: 6

_Lamotrigine_
_Summary of Use during Lactation:_
_Breastfed infants whose mothers are taking lamotrigine have relatively high plasma lamotrigine levels, averaging 30 to 35% of maternal serum levels; infant plasma levels up to 50% of maternal levels have been reported. Neonates are particularly at risk for high plasma levels because their ability to metabolize the drug by glucuronidation is limited, 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 prepregnancy dosage. Mild thrombocytosis has been reported in some infants and withdrawal symptoms can occur if breastfeeding is abruptly discontinued. One case of severe apnea occurred in a breastfed 16-day-old whose mother was taking a high dose of the drug. Additionally, lamotrigine can cause rare, but potentially fatal skin reactions, although none has been reported in breastfed infants.

If lamotrigine is required by the mother, it is not necessarily a reason to discontinue breastfeeding, because many infants have been breastfed without adverse reactions. However, breastfed infants should be carefully monitored for side effects such as apnea, rash, drowsiness or poor sucking, including measurement of serum levels to rule out toxicity if there is a concern. Monitoring of the platelet count may also be advisable. If an infant rash occurs, breastfeeding should be discontinued until the cause can be established.

**DISCUSSION**

Lamictal XR will be discussed at the December Pediatric Advisory Committee Meeting as required by PREA and BPCA. The OSE review of pediatric adverse events in the year since approval of this product on May 29, 2009, reported on an unlabeled and serious adverse event of “cyanosis neonatal” in which a 16 day old nursing infant whose mother was taking Lamictal 850 mg/day for seizures, experienced several apnea episodes, one of which required basic cardiac life support. The infant had a serum lamotrigine level of 4.87 μg/mL upon hospital admission.

Human milk is the most complete form of nutrition for infants and offers a range of health benefits for human milk-fed infants and lactating women. For infants, human milk-feeding decreases risks for many early life diseases and conditions, including a reduction in the risk of sudden infant death syndrome, and mortality from gastrointestinal and respiratory infections. The benefits of human milk feeding are well documented, and the American Academy of Pediatrics encourages human milk feeding up to at least one year of age if possible. 7 The developmental and health benefits of human milk feeding should be

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6 LactMed, part of the National Library of Medicine's (NLM) Toxicology Data Network (TOXNET®), is a database of drugs and other chemicals to which breastfeeding mothers may be exposed

considered along with the woman’s clinical need for a drug, any underlying maternal condition, and the risk for potential adverse effects in the human milk-fed child.

Lamotrigine is a widely used antiepileptic drug (AED) and is used frequently in women of childbearing potential for both the treatment of epilepsy and bipolar disorder. Lamotrigine’s pharmacokinetics and use during pregnancy have been well characterized. Pregnancy is associated with physiological changes that affect drug disposition and maternal plasma concentrations. Plasma concentrations of many drugs, including lamotrigine, decrease during pregnancy because of increased drug clearance; and therefore, maternal dosing requirements increase to maintain therapeutic drug levels. Lamotrigine crosses the placenta rapidly and easily, resulting in considerable fetal exposure. One study found the median lamotrigine concentration ratio of umbilical cord blood to maternal serum approximately 1.01 (range: 0.56-1.42). Drug plasma levels rapidly return to preconception levels as drug elimination rates decrease and normalize during the postpartum period. Lamotrigine maternal plasma concentrations return to preconception levels within the first 2-3 weeks postpartum and dosing must be adjusted accordingly to avoid maternal dose-related adverse reactions.

Despite its wide use in women of childbearing potential, only limited information is available on lamotrigine use during lactation. Current approved lamotrigine labeling recommends against use during lactation because of the drug’s known excretion into breast milk and lack of knowledge on the effects to the human milk-fed infant. MHT conducted a lamotrigine lactation literature review and found limited data from small studies that have been conducted in order to provide some information for women and clinicians to inform risk/benefit decision making of the drug’s use during lactation. The one case report of “cyanosis neonatal” that stimulated this consult is the only serious adverse event that has been reported in the literature in infants exposed to lamotrigine through human milk. Mild thrombocytosis was reported in human milk-fed infants in one study and no other clinically relevant adverse events, including life-threatening rashes have been reported in human milk-fed infants exposed to lamotrigine. No abnormalities were detected in short-term neuropsychological development in a small sample of infants exposed to lamotrigine through human milk; however, no data are available on the long-term neuropsychological and developmental outcomes in any infant exposed to lamotrigine in-utero or through human milk.

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As mentioned earlier in this review, lamotrigine is metabolized predominantly by hepatic glucuronidation and is renally eliminated. Lamotrigine’s half-life and clearance vary depending on genetic differences in glucuronidation due to different isoenzymes and the use concomitant medications that induce or inhibit glucuronidation. Lamotrigine’s half-life in adults varies from 6 to 103 hours and from 7 to 45 hours in pediatric patients ages 10 months to 18 years of age. The approved pediatric lamotrigine starting dose in patients 2 to 12 years of age is 0.15 to 1.2 mg/kg/day and usual maintenance dose is 1 to 15 mg/kg/day, depending on concomitant medications. The safety of lamotrigine has not been systematically assessed in neonates, infants, or in children <2 years of age. Glucuronidation enzymes are immature in neonates and young infants and generally reach adult levels around 4 months of age (range is 3 - 6 months) in a full-term infant. Because of the immaturity of glucuronidation enzymes in neonates and young infants, lamotrigine is likely to accumulate and the half-life is expected to be longer than in older children. Based on this information, the neonate/young infant therapeutic dose is expected to be lower than for an older child. In the lactation literature reviewed, the estimated or calculated infant lamotrigine daily dose through human milk ranged from .2 to 1.96 mg/kg/day, doses that are at or above therapeutic starting doses in patients 2 to12 years of age.

CONCLUSIONS
The MHT finds the limited available lamotrigine lactation data are concerning due to the potential therapeutic and super-therapeutic dose that an infant may receive through human milk. Lamotrigine is rapidly adsorbed after oral dosing; it has high bioavailability; there is a linear relationship between dose and serum levels; and there is a significant transfer of lamotrigine into breast milk. Maternal lamotrigine serum levels vary widely between patients because of genetic differences in glucuronidation mainly due to different isoenzymes and the use of concomitant medications that either induce or inhibit glucuronidation. Glucuronidation enzymes are immature in neonates and young infants. Because of the immature metabolic pathway, lamotrigine is likely to accumulate, and the half-life is expected to be longer in neonates and young infants than in older children. The immaturity of drug-metabolizing enzymes in infants is a leading cause of adverse drug reactions in this age group.15

By convention, drugs are generally assumed safe for use during lactation if the relative infant dose (RID) is <10% [The RID (expressed as a percentage) = TID/maternal daily dose (mg/kg/day)]. The lamotrigine RID was calculated at less than 10% in a few of the small studies from the literature reviewed; however, the theoretical infant doses used in these RID calculations, generally fell within or above the labeled therapeutic doses for children 2 to 12 years of age, and it is generally not considered acceptable for an infant to receive therapeutic drug doses through human milk. Furthermore, the safety of lamotrigine has not been systematically assessed in neonates, infants, or in children <2 years of age.

14 See current approved Lamictal XR labeling, April 4, 2010
15 Miyagi S, Collier A. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. Drug Metabolism and Disposition. 2007, 35 1587-1592
16 Bennett PN, ed. Drugs and Human Lactation, 2nd ed. 1996, Elsevier B.V.
It is somewhat reassuring, that despite the high infant lamotrigine doses received through human milk, there has been only one serious adverse reaction reported in a human milk-fed infant; however, the reports are limited and no data exists on the long-term neuropsychological and developmental outcomes in infants exposed to lamotrigine through human milk (or in-utero).

Mothers desiring to human milk-feed their infants while taking lamotrigine should be counseled about the benefits of human milk-feeding as well as the potential risks of lamotrigine to a human milk-fed infant, including potential exposure to clinically significant drug levels, and a lack of data on the long-term effects of lamotrigine exposure on neuropsychological development.

**RECOMMENDATIONS**

MHT recommends that Lamictal XR and all lamotrigine nursing mothers labeling be revised to include the available lactation data from literature to better inform lactation risk/benefit decision making for clinicians and for mothers desiring to human milk-feed their infants while taking lamotrigine. Lamotrigine nursing mothers labeling revisions should include information on monitoring human milk-fed infants for adverse events that are associated with lamotrigine use and toxicity. In addition, nursing mothers labeling should include a recommendation for regular monitoring of maternal lamotrigine serum levels during lactation and a recommendation or consideration for lamotrigine serum monitoring in the human milk-fed neonate/or young infant. If lamotrigine serum levels are found to be high in the mother and/or infant, then nursing mothers labeling should contain information that human milk-feeding is not recommended under these conditions.

MHT would be happy to assist DNP with revisions to the nursing mothers section of lamotrigine labeling.
I agree with the discussion and recommendations in this review. Lamictal lactation labeling should be well informed and include appropriate information to inform infant monitoring in the clinical setting.

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10/19/2010