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Lamotrigine in Breast Milk and Nursing Infants: Determination of Exposure

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Abstract

OBJECTIVE—Although lamotrigine use during pregnancy has substantially increased over the past decade secondary to accumulated reproductive safety data, systematic data on lamotrigine during breastfeeding remains sparse. We sought to characterize the determinants of lamotrigine concentrations in breast milk and nursing-infant plasma.

PATIENTS AND METHODS—Women who enrolled in a prospective investigation of perinatal medication pharmacokinetics, were treated with lamotrigine, and chose to continue lamotrigine while breastfeeding were included in the analysis. Breast milk samples were collected via breast

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pump from foremilk to hindmilk from a single breast to determine the excretion gradient and serial samples over 24 hours to determine the time course of excretion. Paired maternal/infant plasma samples were also collected. Lamotrigine concentrations in all of the samples were determined by using high-performance liquid chromatography with ultraviolet detection. Statistical analyses of breast milk and infant plasma concentrations and their determinants were conducted.

RESULTS—Thirty women and their nursing infants participated in the study, providing a total of 210 breast milk samples. The mean milk/plasma ratio was 41.3%. There was a nonsignificant trend for higher lamotrigine concentrations in breast milk 4 hours after the maternal dose. Infant plasma concentrations were 18.3% of maternal plasma concentrations. The theoretical infant lamotrigine dose was 0.51 mg/kg per day, and the relative infant lamotrigine dose was 9.2%. Mild thrombocytosis was present in 7 of 8 infants at the time of serum sampling. No other adverse events were observed or reported in the breastfed infants.

CONCLUSIONS—Consistent with previous investigations of medications in breast milk, the lamotrigine milk/plasma ratio is highly variable. The rate of lamotrigine excretion into human breast milk is similar to that observed with other antiepileptic drugs. These data expand the extant literature on lamotrigine in breastfeeding and demonstrate relatively comparable nursing-infant exposure to lamotrigine compared with other antiepileptic drugs.

Keywords

lactation; lamotrigine; antiepileptic drugs; epilepsy; bipolar disorder

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The clinical use of antiepileptic drugs (AEDs) has extended far beyond the treatment of seizures and assumed a significant role in the management of a variety of neuropsychiatric disorders including epilepsy, bipolar disorder, impulse-control disorders, migraine headaches, and pain syndromes. Lamotrigine is emerging as a first-line treatment for women with epilepsy during their reproductive years[1] and as a viable option for maintenance therapy for bipolar disorder during pregnancy.[2,3]

This transition is propagated by the burgeoning lamotrigine reproductive safety data. Briefly, the overall risk of major fetal malformations after first-trimester prenatal exposure to lamotrigine is 2.6% (83 of 3176 exposures, including 0.32% [8 of 2537] for midline cleft formations),[4–10] rates that are within the range of births not involving drug exposures. A recent report by the North American Pregnancy Registry noted a relatively high rate of midline facial clefts (0.89% of 564 exposures)[8]; however, the collective rate of orofacial clefts in the other registries was only 0.15% (2 of 1937 exposures).[4–7,9,10] The United Kingdom Epilepsy and Pregnancy Register reported higher risk of malformations at maternal daily doses exceeding 200 mg,[10] although this was not confirmed in a subsequent analysis of the manufacturer's registry.[7] The transplacental passage of lamotrigine both in placental perfusion and umbilical cord blood at delivery indicates that fetal exposure is equal to maternal plasma concentrations.[11,12]

Unfortunately, the data regarding excretion into human breast milk and effects of nursing-infant exposure for lamotrigine, as for all AEDs, lag far behind the pregnancy outcome literature,[13] leading to recommendations that are derived from a limited data set.[14,15] Initial

case reports[16,17] and case series,[7,11,18,19] collectively accounting for 25 lactating women, reported mean milk/plasma (M/P) ratios ranging from 0.40 to 0.61. Plasma/serum concentrations from a total of 20 nursing infants have been detectable in all but 3 of the infants and, excluding these infants, the ratio of infant/maternal plasma concentration has ranged from 6% to 40%. These data have led some authors to caution against lamotrigine use in breastfeeding.[15,18] It has been posited that an immature neonatal glucuronide metabolic system[20] may contribute to the relatively high infant/maternal plasma concentration ratios. Notably, no adverse effects were reported in any of the nursing infants.

The majority of professional and nutritional organizations support breast milk as the ideal form of nutrition for the infant in the first year of life. The American Academy of Neurology recommends that women with epilepsy nurse their children.[21] Similar to the concerns about prenatal medication exposure, the maternal use of medications during breastfeeding often occurs in the absence of adequate long-term follow-up data. Exposing breastfeeding infants to AEDs during the postnatal developmental period in the absence of such long-term outcome studies or established infant-monitoring guidelines remains a complex clinical decision. The purpose of the current study was to confirm and extend previous data on the use of lamotrigine during breastfeeding by providing a detailed investigation of the excretion of lamotrigine into human breast milk, estimates of infant exposure, and nursing-infant plasma concentrations that include both total and free lamotrigine concentrations.

METHODS

Women referred to the Emory Women's Mental Health Program or the Emory Women's Epilepsy Program during pregnancy were recruited into a prospective observational study of the perinatal course of neuropsychiatric illness and the pharmacokinetics of neuropsychiatric medications during pregnancy and lactation. Women who chose to breastfeed during treatment with lamotrigine were eligible for the current analysis. Subjects were informed of the extant safety data regarding infant exposure to lamotrigine during lactation and the potential risks of untreated maternal epilepsy and/or untreated maternal mental illness. In addition, the risks and benefits of alternative treatments were reviewed. Inclusion criteria for the current analysis included (1) ≥18 years of age and able to provide informed consent, (2) on a stable daily dose of lamotrigine for >7 days, and (3) willing to collect breast milk samples and/or infant plasma (in addition to maternal plasma) for quantification of the lamotrigine concentration. Infant plasma collection was requested but was not a requirement of study participation. Written informed consent was obtained before data collection. The institutional review board of the Emory University School of Medicine approved the study.

Sample Collection

All of the plasma and breast milk samples were obtained after maternal plasma lamotrigine concentrations had achieved steady state (ie, >5 elimination half-lives). Maternal plasma, infant plasma, and breast milk were collected as described previously in detail.[22–24] Briefly, breast milk samples were collected from the same breast by using electric or manual breast pumps for time course analysis (foremilk collected every 4 hours for 24 hours) and

foremilk-to-hindmilk gradient analysis (10-mL aliquots from a single breast). The samples were coded and stored at −80°C until assay.

Determination of Lamotrigine Concentrations

Breast milk analysis for psychotropic medications has been described previously.[25] Breast milk samples were analyzed by using a modification of the Chromsystems (Munich, Germany) high-sensitivity assay system for the determination of AEDs. Standard curves were constructed by spiking lamotrigine into naive breast milk. Four-point standard curves were processed with every sample run. Two levels of quality control, again made from naive breast milk and different stock solutions, were processed in every run. Briefly, 100 μL of breast milk were mixed with 200 μL of methanol containing the internal standard. The mixture was centrifuged, and 100 μL of supernatant was mixed with 100 μL of stabilization reagent (included in the assay kit). Twenty μL of this mixture were injected on a high-performance liquid chromatograph for analysis. Recovery was assessed by using 5 different spiked breast milks and averaged 97.8% over the concentration range from 2.5 to 20.0 μg/mL. Coefficients of variation averaged 5% and 8.2% at 15 and 7.5 μg/mL, respectively, over all of the assays performed in this study. A high-performance liquid chromatography separation and ultraviolet detection method from Chromsystems was then performed to measure lamotrigine concentrations in the plasma samples and breast milk extracts. The system has a limit of detection of 0.3 μg/mL and is linear to 20 μg/mL of lamotrigine. Free lamotrigine was separated from bound by using Centifree YM-30 cartridges from Millipore Corp (Bedford, MA). Plasma samples were incubated at 37°C for 30 minutes before placement in the ultrafiltration cartridge. Samples were then spun at 2000 × *g* for 30 minutes at 35°C. The ultrafiltrate was assayed in the system described above without modification. By convention, all of the samples with concentrations below the limit of detection (<0.3 μg/mL) were converted to the limit of detection (0.3 μg/mL) for data analyses. This conversion provides an overestimate of exposure but is the most conservative approach. Laboratory personnel were masked to maternal daily dose and collection time of the sample.

Infant Outcomes

Infant well-being was ascertained by maternal report, review of pediatric records, and, for some children, clinical laboratory assessment, including complete blood cell counts, serum electrolytes, and hepatic profiles.

Data Analysis

The stages of data analysis include (1) demographic analysis to characterize the study sample, (2) analysis of breast milk concentrations including characterization of the potential foremilk-to-hindmilk excretion gradient and the 24-hour time course of excretion; calculation of M/P ratios at the minimum, maximum, and mean breast milk concentrations for each participant; estimation of theoretical infant dose (TID) and estimation of the relative infant dose (RID), (3) analysis of the determinants of breast milk concentrations, which were assessed by using univariate and multivariate analyses of maternal factors: maternal daily dose, maternal plasma concentrations, and time after maternal dose, (4) analysis of infant plasma concentrations including calculation of the infant/maternal plasma ratios for both

total and free lamotrigine concentrations and comparison of the free/total lamotrigine concentration ratio for each infant to the maternal free/total lamotrigine concentration ratio, and (5) review of infant outcomes.

Analysis of Breast Milk Concentrations

To determine the foremilk-to-hindmilk excretion gradient, the concentration for each fraction was divided by that of the minimum observed concentration and presented as a ratio for each 10-mL aliquot from foremilk to hindmilk. Linear regression was performed to characterize the foremilk-to-hindmilk excretion gradient curve. The time course of excretion was calculated in a similar fashion by using the minimum breast milk concentration.

Breast milk lamotrigine concentration was divided by the total lamotrigine concentration in maternal plasma to provide the M/P ratio. Because each participant provided multiple breast milk samples (to complete the excretion and time course analyses), we were able to calculate the M/P ratio not just for a single spot sample (a typical limitation of previous investigations) but for the minimum, maximum, and mean breast milk concentrations over a 24-hour period for each participant.

The lamotrigine breast milk concentrations were used to calculate 2 conventional estimates of infant drug exposure during lactation, that is, the TID and RID.[15] The TID, estimated in milligrams per kilogram per day, was calculated by using the formula put forth by Atkinson et al[26] (TID = daily breast milk intake [150 mL/kg per day] × breast milk concentration of medication). Each subject's mean breast milk concentration was divided by 1000 (to convert the concentration units from micrograms per milliliter to milligrams per milliliter) and then multiplied by the estimated infant daily breast milk intake of 150 mL/kg per day. The RID, expressed as a percentage, was calculated by dividing the TID by the maternal daily dose (also reported in milligrams per kilogram per day).

Determinants of Breast Milk Concentrations

Pearson correlation coefficients were calculated in an initial univariate analysis of the maternal characteristic predicting breast milk concentration. Subsequently, multiple regression analyses were performed. Candidate predictors of breast milk lamotrigine concentration included maternal daily dose, maternal plasma concentration of lamotrigine, hours after maternal dose when the breast milk sample was collected, and the sequential aliquot number for those samples collected as part of a foremilk-to-hindmilk gradient analysis. Raw data were normalized via logarithmic transformation, and a backward elimination procedure with an α at .05 for retention was used.

Analysis of Infant Plasma Concentrations

Although breast milk concentrations can be used to derive TID and RID estimates of infant exposure during lactation, actual infant exposure may be better represented by infant plasma concentrations. Infant plasma/ maternal plasma ratios of both free and total lamotrigine concentrations were calculated to provide an index of actual infant exposure relative to maternal exposure. The ratio of free lamotrigine concentration to total lamotrigine concentration was calculated for both infant and mother. Finally, to assess concerns raised

regarding the potential for lamotrigine accumulation in breastfed infants as a theoretical consequence of immature glucuronidation systems in early infancy,[20] a paired *t* test was conducted to assess differences between free and total lamotrigine concentrations for each infant for whom plasma lamotrigine concentrations were available both at delivery (via umbilical cord collection) and during nursing within the first 4 weeks after delivery.

RESULTS

Demographic Analysis

A total of 30 women and their nursing infants participated in the current study. Of these, 80.0% (*n* = 24) were white, 10.0% (*n* = 3) were Asian, and 10.0% (*n* = 3) were black. Eighty percent (*n* = 24) were married, and 20.0% (*n* = 6) had never been married. The participants were 32.2 years old (95% confidence interval [CI]: 30.0 to 34.4 years) and had 15.3 years of education (95% CI: 14.6 to 16.1 years of education). Treatment with lamotrigine was for epilepsy (63.3% [*n* = 19]) and bipolar disorder (36.7% [*n* = 11]). Women and infants were taking no concomitant medications known to interact with lamotrigine metabolism or protein binding.

Breast milk samples (*n* = 210) were provided by 25 participants. One participant completed the breast milk collection on 2 occasions producing a total of 26 breast milk collections (Table 1). The 210 breast milk samples were composed of 94 samples collected by 17 women for foremilk-to-hindmilk gradient analysis, 107 samples collected by 16 women for 24-hour time course analysis, and 9 spot samples. On average, breast milk was collected 13.0 weeks postpartum (95% CI: 7.6 to 18.4 weeks) at a maternal daily dose of 386.5 mg (95% CI: 311.1 to 461.8 mg).

Paired infant and maternal plasma samples were provided by 12 mother-infant dyads (Table 2). Five of these 12 participants did not provide breast milk samples.

Analysis of Breast Milk Concentrations

A significant volume- and aliquot-dependent rate of excretion, with lower concentrations in later aliquots of breast milk (hindmilk), was observed (Fig 1). The excretion gradient data were best fit by a second-order polynomial regression ($R = 0.83$; $F = 8.05$; $df = [2,7]$; $P < .02$). The time course data were also best fit by a second-order polynomial regression (Fig 2), although this analysis failed to achieve statistical significance ($R = 0.86$; $F = 4.36$; $df = [2,3]$; $P < .13$).

M/P ratios demonstrated wide variability ranging from a low of 5.7% to a peak of 147.1%. At the mean breast milk concentration for each participant, the M/P ratio was 41.3% (95% CI: 33.0 to 49.6). M/P ratios equaled 26.5% (95% CI: 20.2 to 32.9) when calculated by using the minimum breast milk concentration for each participant and were 2.4 times higher at 63.1% (95% CI: 47.3 to 78.9) when determined by using the maximum breast milk concentration. The mean breast milk concentrations for each individual were used to calculate the TID and RID. The TID was 0.51 mg/kg per day (95% CI: 0.37 to 0.65 mg/kg per day), and the RID was 9.2% (95% CI: 7.4% to 10.9%).

Determinants of Breast Milk Concentrations

Univariate Pearson correlation coefficients demonstrated that the concentration of lamotrigine in breast milk was positively correlated with maternal daily dose of lam-otrigine ($r = 0.63$; $P < .0001$), the total lamotrigine concentration in maternal plasma ($r = 0.37$; $P < .0001$), and the free lamotrigine concentration in maternal plasma ($r = 0.51$; $P < .0001$). The multiple regression analysis of lamotrigine concentration in breast milk was calculated by using the 151 breast milk samples for which all of the predictor data were available. Significant predictors of lamotrigine breast milk concentration were maternal dose ($F_{1,147} = 25.62$; $P < .0001$), free lamotrigine concentration in maternal plasma ($F_{1,147} = 17.31$; $P < .0001$), and the interaction of these 2 predictors ($F_{1,147} = 6.44$; $P < .02$). Hours after maternal dose and foremilk-to-hindmilk aliquot number were not significant predictors of lamotrigine breast milk concentration. The final regression model was significant ($F_{3,147} = 41.11$; $P < .0001$) and explained 45.6% of the variability in lamotrigine breast milk concentrations.

Analysis of Infant Plasma Concentrations

Paired plasma samples were collected from 12 breast-feeding women and their infants. The infant/maternal ratio of total lamotrigine concentration equaled 18.3% (95% CI: 9.5% to 27.0%); however, the infant/maternal ratio of free lamotrigine concentration was 1.7 times higher at 30.9% (95% CI: 13.4% to 48.3%), presumably as a consequence in part of lower plasma protein binding in the infants as evidenced by the fact that the ratio of free lamotrigine concentration/total lamotrigine concentration was 1.8 times higher in the infants than their mothers (53.5% vs 29.5%; paired $t = 2.91$; $P < .02$).

Complete sets of infant and maternal plasma concentrations at delivery, coupled with infant and maternal plasma concentration while nursing during the first 4 weeks of life (mean: 2.5 weeks postpartum [95% CI: 0.7 to 4.3 weeks]), were available for 4 infant-mother dyads. Among these 4 dyads, the neonate/mother ratio for total lamotrigine concentration at delivery was 12.2 times higher than that observed during lactation (96.5% [95% CI: 75.3% to 117.7%] vs 7.9% [95% CI: −3.3% to 19.2%]; paired $t = -5.23$; $P < .02$). Similarly, the infant/mother ratio for free lamotrigine concentration at delivery was 6.2 times higher than that observed during lactation (105.0% [95% CI: 91.9% to 118.1%] vs 17.1% [95% CI: 10.8% to 23.5%]; paired $t = -5.24$; $P < .02$).

Review of Infant Outcomes

Maternal report and pediatric records revealed no adverse events among either the mothers or their nursing infants. Specifically, no nursing infant developed a rash or demonstrated evidence suggestive of Stevens Johnson Syndrome, a concern noted in the *Physician's Desk Reference* insert. Clinical laboratory results were available for 10 infants. All of the hepatic profiles ($n = 10$), serum electrolyte values ($n = 10$), and hematocrit values ($n = 8$) were within normal limits. However, elevated platelet counts (mean: 520.5 [range: 329.0–652.0]) were observed in 7 of 8 children. Platelet counts were collected at 3.8 weeks after delivery (range: 2–10 weeks). No adverse clinical consequences were observed in any of the 7 infants with elevated platelet counts.

DISCUSSION

There has been considerable debate regarding the relative safety of medications during lactation and the optimal means for determining nursing-infant exposure, that is, M/P ratio, TID, RID, nursing-infant plasma concentrations, and reported adverse events. The principal reference sources for information regarding medication use during lactation, *Medications in Mothers Milk*[15] and the American Academy of Pediatrics Committee on Medications in Breast Milk Report,[27] rely on these parameters when determining lactation safety classifications for specific medications. The current investigation extends the previous literature by providing the largest and most detailed study of lamotrigine excretion into human breast milk and presents results in the context of the parameters noted above.

Lamotrigine concentrations in breast milk and M/P ratios were highly variable, ranging from 0.5 to 11.77 μg/mL and 5.7% to 147%, respectively. These results are consistent with our previous investigations of anti-depressants demonstrating the imprecision and subsequent limited use of M/P ratios derived from spot breast milk analysis as an estimate of exposure during lactation.[22–24,28] Given the considerable variability in lamotrigine breast milk concentrations, it was initially surprising that neither hours after dose nor aliquot sequence within the foremilk-to-hindmilk gradient analysis significantly predicted lamotrigine concentrations. Closer scrutiny (Table 1), however, reveals that, whereas the time course and excretion gradients convey considerable intraindividual variability (thereby rendering superfluous any results derived from spot breast milk sampling), there are even larger between-subject differences in rates of breast milk excretion in this cohort that are likely a product of other sources of variability. Maternal pharmacogenetic profiles, for example, may prove to be key determinants of the rates of breast milk excretion of specification medications. If so, they could ultimately contribute to the development of pharmacogenetically informed and individually tailored guidelines that will inform maternal medication selection and produce lower rates of medication exposure to nursing infants.

The mean RID in this sample (9.2% [95% CI: 7.4% to 10.9%]) was lower than reported previously (22.7%).[15] This disparity may be a because of distinct methods for collection and characterization of the breast milk sample (eg, reliance on spot sampling as described above). In addition, previous studies have relied on fixed estimates of maternal weight when calculating the TID and RID, whereas the actual maternal weight at the time of breast milk sampling was used in the current study (potentially providing a more precise estimate). The literature is replete with references to a 10% RID as an empiric cutoff for assuming medication safety during lactation.[29] Although the 9.2% RID for lamotrigine falls within this de facto 10% guideline, clinicians should be advised that this rule of thumb is without objective verification of relative safety.

It is perhaps noteworthy that the 0.51 mg/kg per day TID calculated in the present study is considerably less than the lamotrigine dose of 4.4 mg/kg per day administered beginning at 17 days of age to a child with neonatal seizures,[30] the 2 mg/kg per day administered to a series of neonates (n = 13) during the first month of life,[31] and the 3.1 mg/kg per day administered to infants aged 1 to 24 months (n = 51) as an adjunctive therapy with other nonenzyme-inducing AEDs.[32]

The current study sought to extend previous investigations by incorporating both total and free lamotrigine concentrations in nursing infants. Infant plasma monitoring is arguably the most direct means for ascertaining infant exposure, although this method remains to be validated. Because plasma concentrations are not consistently indicative of tissue concentrations, they may not be a fully reliable measure of the degree of an infant's central nervous system exposure to a drug.

Both total (11 of 12) and free (7 of 11) lamotrigine concentrations were above the limit of detection in the majority of infants. Although the importance of plasma proteins in governing the effects of AEDs is an emerging literature, the role(s) of plasma proteins in determining neonatal exposure has received scant attention. In the present study, we observed that the ratio of infant/ maternal plasma concentration for free lamotrigine (30.9%) was higher than that for total lamotrigine (18.3%). These data suggest that the drug's free fraction is higher in the plasma of nursing infants than their mothers. Theoretically, this could result in greater penetration of target tissues, including the central nervous system. It is noteworthy that carbamazepine and valproate, 2 AEDs with favorable lactation safety classifications, that is, L2[15] and compatibility with breastfeeding,[27] have also shown considerable variability in the ratio of infant/maternal plasma concentrations. In nursing infants, total carbamazepine concentrations have ranged from undetectable to 65% of the maternal level.[33–39] Total valproate concentrations in nursing infants have ranged from 2% to 40% of maternal concentrations.[40–43]

The absence of acute adverse effects, reported via maternal interview or pediatric records, during the first postnatal year was reassuring. In contrast, clinical laboratory assessment in 7 of 8 infants demonstrated elevated platelet counts consistent with criteria for mild thrombocytosis.[44] Secondary thrombocytoses during infancy are common and presumably benign occurrences, affecting ≤36% of neonates[44,45] in association with prematurity, infection, and exposure to pharmacological agents. The clinical significance and/or direct relationship to lamotrigine exposure warrants additional investigation. Previous studies of AEDs in breastfeeding have been inconsistent in the laboratory indices assessed; however, ≥1 report posited an association of nursing-infant thrombocytosis with maternal phenytoin treatment.[46] Overall, the acute infant outcomes in the current study compare favorably to reports with other commonly used AEDs that have noted potential adverse effects of nursing exposure.[35,38,40,46]

CONCLUSIONS

Our investigation confirms and extends previous investigations of lamotrigine nursing exposure. Depending on the index used, lamotrigine exposure during lactation is either equivalent to or marginally higher than that of alternative AEDs, notably carbamazepine and valproate. Like all of the AEDs studied, lamotrigine exposure during lactation was considerably less than placental transfer. Many, if not most, postpartum women who are taking lamotrigine will have already been treated with the agent during pregnancy (ie, epilepsy and bipolar disorder seldom remain untreated throughout gestation).

Expanding the extant knowledge base on the use of lamotrigine in women choosing to breastfeed enhances the clinician's ability to inform women regarding the risk and benefits of breastfeeding. Similarly, by understanding the methodologic limitations and differences across investigations, the clinician is equipped to interpret future investigations and apply such data to clinical scenarios.

Despite the acknowledged benefits of breastfeeding and general support for nursing by professional organizations, the decision regarding exposure to AEDs warrants careful deliberation. For women choosing to nurse, the patient and her clinician must consider (1) the extent of nursing-infant exposure during continued central nervous system development, (2) the potential hazards of switching medications for breastfeeding women (thereby exposing the neonate to multiple medications and the risk of relapsing maternal illness), and (3) appropriate monitoring of nursing infants exposed to AEDs.

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Abbreviations

AED	antiepileptic drug
M/P	milk/plasma
TID	theoretical infant dose
RID	relative infant dose
CI	confidence interval

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What's Known on This Subject

The information on lamotrigine in breastfeeding is very limited. There are no established infant-monitoring guidelines and limited methodologic rigor in previous studies.

What This Study Adds

This was the largest single data set on lamotrigine use during breastfeeding. It serves as a foundation of methodologic clarification for colleagues to evaluate previous medication studies.

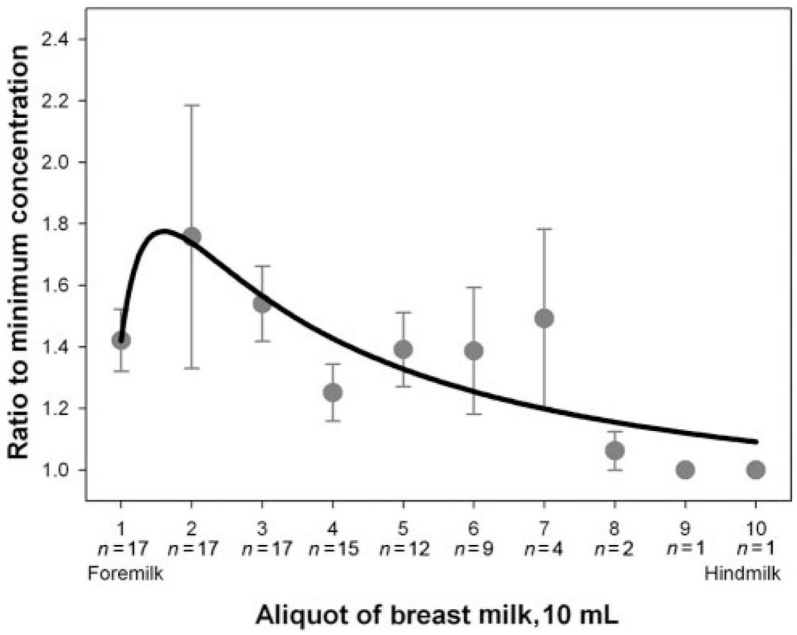

FIGURE 1.

Gradient for lamotrigine excretion into human breast milk: mean ratio of lamotrigine concentration to the minimum breast milk concentration in each set of samples plotted by the aliquot of breast milk obtained from 17 women. These 17 women submitted breast milk samples (≥3 samples each; n =94) for determination of gradient effects from foremilk to hindmilk. The data shown represent breast milk samples collected from a single breast 8 to 12 hours after maternal ingestion of lamotrigine. These data were significantly defined by a second-order polynomial regression (R =0.83; F =8.05; df = [2,7]; P <.02).

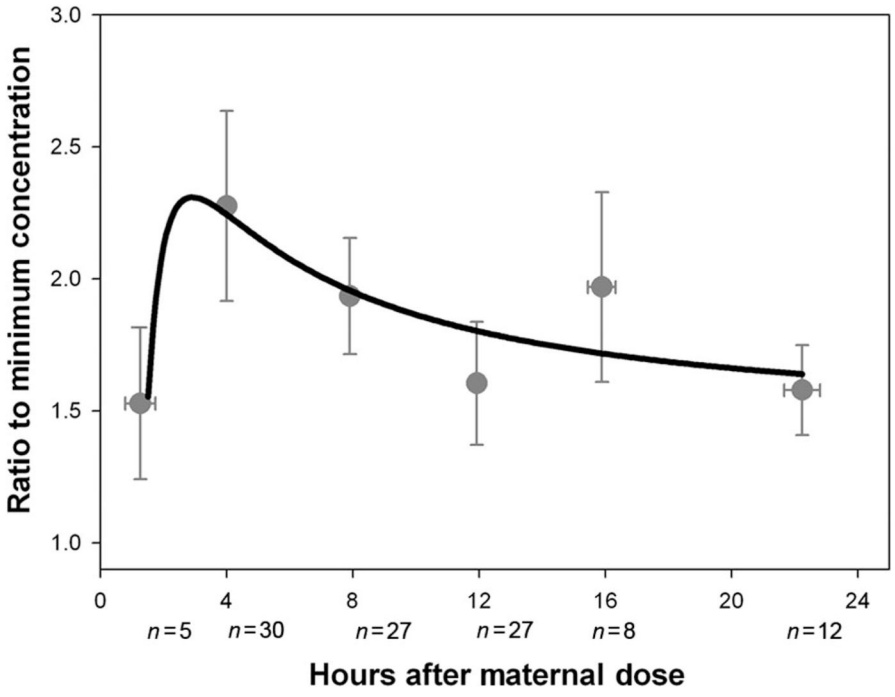

FIGURE 2.

Time course of lamotrigine excretion into human breast milk: mean ratio of lamotrigine concentration to the minimum breast milk concentration in each set of samples plotted by the time after maternal ingestion of lamotrigine aliquot of breast milk obtained from 16 women. These 16 women submitted breast milk samples (≥3 samples each; n =107) for determination of the time course of excretion into breast milk. These data were best fit by a second-order polynomial regression, although the regression analysis did not achieve statistical significance (R =0.86; F =4.36; df =[2,3]; P <.13).

TABLE 1

Lamotrigine Concentrations in Maternal Plasma and Breast Milk With Infant Dose Estimates (Ordered According to Maternal Daily Dose)

Subject	Infant Age, wk	Maternal Weight, kg	Maternal Daily Dose		Maternal Plasma Lamotrigine, μg/mL	Breast Milk Lamotrigine, μg/mL						Infant Daily Dose	
						Minimum		Maximum		Mean			
			mg/d	mg/kg per d		Lamotrigine	M/P, %	Lamotrigine	M/P, %	Lamotrigine	M/P, %	TID, mg/kg per d	RID, %
A	NA	NA	50	NA	1.7	1.0	58.8	2.5	147.1	1.79	105.0	0.27	NA
B	9.4	101.2	100	0.99	2.6	0.7	26.9	1.3	50.0	1.02	39.2	0.15	15.4
C	51.7	78.5	100	1.27	3.0	0.5	16.7	<0.5	16.7	0.5	16.7	0.08	5.9
D	4.1	95.7	150	1.57	4.6	0.5	10.9	0.7	15.2	0.59	12.8	0.09	5.7
E	3.9	71.2	150	2.11	7.7	2.6	33.8	2.6	33.8	2.6	33.8	0.39	18.5
F	25.4	86.6	200	2.31	3.4	0.5	14.7	2.1	61.8	1.29	38.1	0.19	8.4
G	7.1	60.8	300	4.94	4.9	1.0	20.4	4.8	98.0	2.07	42.2	0.31	6.3
H	17.7	63.5	300	4.72	6.2	2.2	35.5	2.9	46.8	2.58	41.6	0.39	8.2
I_1[a]	7.2	73.0	300	4.10	8.7	4.2	48.3	7.9	90.8	5.77	66.3	0.87	21.1
J	3.0	62.6	350	5.59	5.9	0.9	15.8	7.9	133.4	2.82	47.8	0.42	7.6
K	20.5	73.0	350	4.79	12.0	2.8	23.3	4.0	33.3	3.40	28.3	0.51	10.6
L	2.9	78.5	400	5.10	7.8	2.9	37.2	3.5	44.9	3.20	41.0	0.48	9.4
M	8.7	68.5	400	5.84	8.6	2.4	27.9	4.0	46.5	3.02	35.1	0.45	7.7
N	12.9	47.6	400	8.40	17.5	1.0	5.7	7.0	36.4	3.99	22.8	0.60	7.1
O	1.9	55.3	450	8.13	9.9	0.7	7.1	7.3	73.7	3.90	39.4	0.59	7.2
P	33.4	64.9	450	6.94	10.6	2.8	26.4	13.4	126.4	6.25	59.0	0.94	13.5
Q	2.7	74.8	450	6.01	NA	NA	NA	NA	NA	2.6	NA	0.39	6.5
R	3.0	79.4	500	6.30	4.3	NA	NA	NA	NA	1.3	30.2	0.20	3.1
I_2[a]	35.6	73.0	500	6.85	6.6	3.1	47.6	4.2	63.3	3.56	53.9	0.53	7.8
S	13.9	89.8	500	5.56	8.1	2.8	34.6	3.6	44.4	3.13	38.7	0.47	8.4
T	29.6	86.6	500	5.77	8.7	4.2	48.3	6.3	72.4	4.96	57.0	0.74	12.9
U	15.6	78.9	500	6.34	NA	1.2	NA	3.0	NA	2.16	NA	0.32	5.1
V	1.8	55.8	550	9.86	17.4	1.6	9.2	4.7	27.0	2.62	15.0	0.39	4.0
W	2.1	60.8	600	9.87	10.9	3.1	28.3	8.8	80.3	5.85	53.7	0.88	8.9
X	9.9	66.2	700	10.57	22.8	3.0	13.2	7.1	31.1	5.05	22.1	0.76	7.2
Y	1.0	55.8	800	14.34	23.1	4.6	19.9	18.1	78.4	11.77	51.0	1.77	12.3

Subject	Infant Age, wk	Maternal Weight, kg	Maternal Daily Dose		Maternal Plasma Lamotrigine, μg/mL	Breast Milk Lamotrigine, μg/mL						Infant Daily Dose	
			mg/d	mg/kg per d		Minimum		Maximum		Mean		TID, mg/kg per d	RID, %
						Lamotrigine	M/P, %	Lamotrigine	M/P, %	Lamotrigine	M/P, %		
Mean	13.0	72.1	386.5	5.93	9.0	2.1	26.5	5.3	63.1	3.38	41.3	0.51	9.2
95% CI	7.6 to 18.4	66.6 to 77.6	311.3 to 461.8	4.63 to 7.23	6.6 to 11.5	1.6 to 2.6	20.2 to 32.9	3.6 to 7.0	47.3 to 78.9	2.44 to 4.32	33.0 to 49.6	0.37 to 0.65	7.4 to 10.9

Subjects who provided both breast milk samples and paired infant/maternal plasma samples are identified by the same letter in Tables 1 and 2. Subjects who provided plasma samples but not breast milk samples appear only in Table 2 and are identified by letters AA through AE. NA indicates that data were not available.

[a]Subject “I” provided a series of breast milk samples on 2 occasions.

TABLE 2

Infant/Maternal Paired Plasma Samples: Free and Total Lamotrigine Concentrations and Ratios (Ordered According to Infant Age at Time of Sampling)

Subject	Infant Age, wk	Nursing %	Infant Daily Dose[a]		Infant Plasma Lamotrigine		Maternal Dose, mg/d	Maternal Plasma Lamotrigine		Infant/Maternal Plasma Lamotrigine Ratio	
			TID, mg/kg per d	RID, %	Total, μg/mL	Free, μg/mL		Total, μg/mL	Free, μg/mL	Total, %	Free, %
A	NA	NA	0.27	NA	<0.3	NA	50	1.7	0.4	17.6	NA
AA	1.7	100	NA	NA	1.0	0.5	400	10.8	2.6	9.3	19.2
W	2.9	100	0.39	4.0	0.5	0.5	550	17.4	2.8	2.9	17.9
K	3.0	100	NA	NA	2.0	1.0	400	18.2	6.0	11.0	16.7
R	3.0	100	0.20	3.1	0.5	<0.3	500	4.3	2.1	11.6	14.3
AB	3.7	100	NA	NA	1.0	<0.3	125	5.9	1.6	16.9	18.8
AC	5.9	100	NA	NA	1.3	0.6	350	7.6	2.4	17.1	25.0
I	7.4	100	0.87	21.1	3.9	1.4	300	8.7	3.3	44.8	42.4
B	8.0	100	0.15	15.4	1.2	<0.3	100	2.6	0.6	46.2	50.0
Y	9.9	75	0.76	7.2	1.7	0.7	700	22.8	7.9	7.5	8.9
AD	19.6	50	NA	NA	0.5	0.5	400	4.5	1.9	11.1	26.3
AE	30.4	100	NA	NA	0.6	<0.3	100	2.6	<0.3	23.1	100.0
Mean	8.7	93.2	NA	NA	1.2	0.6	325.0	8.9	2.7	18.3	30.9
95% CI	2.8 to 14.6	82.3 to 104.0	NA	NA	0.6 to 1.8	0.3 to 0.8	182.3 to 467.7	4.5 to 13.4	1.2 to 4.1	9.5 to 27.0	13.4 to 48.3

Subjects who provided both breast milk samples and paired infant/maternal plasma samples are identified by the same letter in Tables 1 and 2. Subjects who provided plasma samples but not breast milk samples appear only in Table 2 and are identified by letters AA through AE. NA indicates that data were not available.

[a]The estimates of infant daily dose were derived from breast milk data (Table 1) where available.