Brief Report

Lithium in Breast Milk and Nursing Infants: Clinical Implications

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Objective: Current practice guidelines discourage use of lithium during breast-feeding, despite limited data. This study aimed to quantify lithium exposure in nursing infants.

Method: In 10 mother-infant pairs, the authors obtained assays of lithium in maternal serum, breast milk, and infant serum and indices of infant renal and thyroid function.

Results: Maternal serum, breast milk, and infant serum daily trough concentrations of lithium averaged 0.76, 0.35, and 0.16 meq/liter, respectively, each lithium level lower than the preceding level by approximately one-half. No serious adverse events were observed, and elevations of thyroid-stimulating hormone, blood urea nitrogen, and creatinine were few, minor, and transient.

Conclusions: Serum lithium levels in nursing infants were low and well tolerated. No significant adverse clinical or behavioral effects in the infants were noted. These findings encourage reassessment of recommendations against lithium during breast-feeding and underscore the importance of close clinical monitoring of nursing infants.

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In clinical practice, use of lithium during lactation has been discouraged and typically considered contraindicated in breast-feeding (1–3). These cautious recommendations arise from concerns that lithium may be secreted at high levels in breast milk and infants may inefficiently clear lithium, thereby increasing their risk for significant drug exposure and toxicity (1–4). However, the evidence underlying such concerns is limited. Typically, milk/maternal plasma levels are used as a proxy for infant exposure instead of infant serum lithium levels (1–4). Accordingly, we now report on concentrations of lithium in breast milk paired with *both* maternal and infant serum and also examine renal and thyroid indices in 10 lithium-exposed infants.

Method

Ten mother-infant pairs were enrolled from the Perinatal and Reproductive Clinical Research Program at Massachusetts General Hospital in Boston between November 2002 and September 2004. The institutional review board approved all study procedures, and the subjects provided written informed consent after review of the risks and benefits of using lithium during nursing. Most subjects were married, well educated, and stable while receiving lithium monotherapy for DSM-IV bipolar disorder. All mothers used lithium during the index pregnancy (nine throughout pregnancy and one from gestational week 34); all infants were exclusively breast-fed.

We assayed lithium concentrations in maternal and infant sera, as well as infant serum concentrations of thyroid-stimulating hormone (TSH), blood urea nitrogen, and creatinine by standard commercial laboratory methods. Breast milk samples were assayed for lithium in the research laboratory of Emory Women's Mental Health Program at Emory University School of Medicine with ion-selective electrode detection (Beckman Coulter, Fullerton, Calif.) with blinding to the sample source.

The samples were collected within 10–14 hours of each mother's last daily dose of lithium between an average of 8 to 27 weeks postpartum. Six mother-infant pairs provided two or more samples, and four women provided segmented milk samples across a single breast-feeding to test for a gradient of lithium excretion.

Repeated measurements were pooled to provide individual subject averages and then across subjects to provide sample means and standard deviations. In addition, we calculated within-subject-pair ratios for: 1) lithium concentrations in milk/maternal serum, 2) lithium in infant serum/breast milk, and 3) lithium in infant/maternal serum. We also examined correlations (Pearson's r) of lithium dose (mg/day) with maternal serum, breast milk, and infant serum lithium concentrations and of infant serum levels with TSH, blood urea nitrogen, and creatinine based on within-subjects means. Analyses used commercial microcomputer programs (STATA, College Station, Tex.).

Results

The 10 mother-infant pairs contributed a total of 26 samples between 8.1 weeks postpartum (SD=8.8, range=1–32) and 27.5 weeks (SD=19.6, range=7–55) (Table 1). Infants were breast-fed an average of 4.03 months (SD=2.28). The maternal lithium dose averaged 850 mg/day (SD=220, range=600–1200), with corresponding daily trough serum concentrations of 0.76 meq/liter (SD=0.29, range=0.41–1.31). Breast milk lithium concentration averaged 0.35 meq/liter (SD=0.10, range=0.19–0.48), with paired infant serum concentrations of 0.16 meq/liter (SD=0.06, range=0.09–0.25). Infant blood urea nitrogen concentration averaged 6.2 mg/dl (SD=2.1, range=3.0–9.2) and creatinine averaged 0.28 mg/dl (SD=0.6, range=0.18–0.40 mg/dl), and the mean blood urea nitrogen/creatinine ratio was 23.0 mg/dl (SD=11.5, range=10.0–51.1). Serum TSH was 2.4

TABLE 1. Lithium Concentration in Maternal and Infant Serum and Breast Milk and Infant Renal and Thyroid Function in 10 Nursing Infant-Mother Pairs

Infant-Mother Pair	Infant Age at Sampling (week)	Maternal Dose of Lithium Carbonate (mg/day)	Maternal Serum Lithium Concentration (meq/liter)	Breast Milk Lithium Concentration (meq/liter)	Infant Serum Lithium Concentration (meq/liter)	Infant Serum Urea Nitrogen (mg/dl)[a]	Infant Serum Creatinine (mg/dl)[b]	Infant Serum Thyroid-Stimulating Hormone (μU/ml)[c]
A	7	600	0.43	0.30	0.10	3.00	0.3	2.10
B	10	600	0.70	0.28	0.20	6.00	0.3	1.60
B	21	600	0.70	—	0.22	6.00	0.3	0.88
B	52	600	0.60	0.10	0.10	6.00	0.2	1.21
C	1	625	0.80	—	0.30	6.00	0.3	—
C	8	625	0.70	—	0.30	5.00	0.3	1.87
C	14	625	0.70	—	0.30	8.00	0.4	2.52
C	24	725	0.60	0.44	0.10	8.00	0.4	1.35
C	30	725	0.60	—	—	—	—	—
C	55	750	0.70	0.46	—	19.00	0.6	1.32
D	32	700	0.60	0.36	0.09	—	—	—
E	4	900	0.90	0.39	0.30	5.00	0.3	2.80
E	12	900	1.00	0.25	0.10	3.00	0.2	1.30
F	7	900	0.41	0.25	0.23	7.00	0.3	7.31
G	2	900	0.80	—	0.10	9.00	0.2	2.89
G	5	900	0.80	0.51	0.13	5.00	0.2	2.02
G	14	900	0.92	0.40	0.10	5.00	0.2	2.60
G	32	900	0.92	—	0.20	5.00	0.0	2.30
G	52	900	—	—	0.10	22.00	0.3	1.38
H	8	900	1.31	—	0.14	7.00	0.3	1.71
I	6	1200	1.16	0.48	0.19	4.00	0.3	1.40
I	25	1200	1.03	—	0.05	6.00	0.3	1.75
J	4	1200	0.55	0.37	0.10	5.00	0.2	1.67
J	10	1200	0.55	—	0.10	5.00	0.2	1.61
J	14	1200	0.67	0.40	0.18	6.00	0.3	1.23
J	25	1200	0.65	—	0.14	5.00	0.3	1.07

[a] Normal blood urea nitrogen range for newborn to 2-year-old children: 5–15 mg/dl (5).
[b] Normal creatinine range—1–30-day-old infants: 0.2–1.0 mg/dl; 1-month to 1-year-old infants: 0.2–0.6 mg/dl (5).
[c] Normal thyroid-stimulating hormone range—1–30-day-old infants: 0.52–16.00 μU/ml; 1-month to 5-year-old children: 0.55–7.10 μU/ml (5).

mg/dl (SD=1.88, range=1.23–7.30). No statistically significant correlations of these measures with any measure of lithium concentration were found (data not shown).

The ratio of breast milk to maternal serum lithium concentration averaged 0.53 meq/liter (SD=0.15, range=0.34–0.70), the infant serum/breast milk lithium ratio was 0.50 (SD=0.27, range=0.25–0.92), and the infant/maternal serum lithium concentration ratio was 0.24 (SD=0.14, range=0.11–0.56). Analysis of segmented breast milk in four mothers demonstrated no concentration gradient from foremilk to hindmilk for lithium.

No acute observable growth or developmental delays were reported by mothers for any infants. However, there were several instances of elevated infant serum concentrations of TSH, blood urea nitrogen, and creatinine. One male infant had a slightly elevated TSH level (7.31 μU/ml) (normal infant levels=0.5–6.3 μU/ml [5]) at 8 weeks following exposure during pregnancy from week 34 to delivery. Because thyroid function had been normal at neonatal screening, cessation of breast-feeding was recommended for this infant. No significant changes in the infant's behavior were noted, but the mother decided to discontinue taking lithium and to nurse her infant. When retested 8 weeks later, TSH was normal (TSH=2.07 μU/ml). Two other infants had slightly elevated blood urea nitrogen levels (19–22 mg/dl versus a normal infant range of 5–15 mg/dl [5]) but with no clinical signs of hypovolemia. In a fourth infant, the creatinine level rose slightly over several months, from 0.3 to 0.6 mg/dl (normal infant range=0.2–0.4 mg/dl [5]), and returned to normal a year later (creatinine=0.2 mg/dl).

Discussion

To our knowledge, this is the largest available study of maternal-infant pairs examining serum and breast milk concentrations of lithium and concurrent infant thyroid and renal function. The study is limited in size and duration and includes a selected sample of well educated, motivated, and clinically stable women with bipolar disorder receiving lithium monotherapy. Our findings, therefore, may not generalize to more heterogeneous populations of nursing women with bipolar disorder. In addition, other monitoring procedures, such as baseline infant ECG assessments, 24-hour creatinine clearance, and formal neurobehavioral testing, were not included and may be important to consider.

Despite the study's limitations, the findings suggest that serum lithium concentrations are substantially lower in nursing infants than previous estimates (1, 6). Lithium concentrations in infant serum (0.16 meq/liter), breast milk (0.35 meq/liter), and maternal serum (0.76 meq/liter) followed an approximate "rule of halves." Breast milk contained about half the concentration of maternal serum,

and infant serum had about half the level in breast milk, so that infant serum contained about one-quarter the concentration of lithium in maternal serum.

In contrast to many lipophilic psychotropic drugs that appear at their highest concentrations in relatively lipid-rich subsamples of hindmilk, hydrophilic lithium showed no such concentration gradient. Previous studies have failed to control for milk sampling when calculating the milk/maternal plasma ratio for psychotropics as a measure of infant exposure, which may misleadingly suggest that lithium is present in higher concentrations in foremilk, based on experience with lipophilic drugs (2).

Overall, moderate exposure to lithium through breast milk was well tolerated, with infant levels averaging 0.16 (never >0.25) meq/liter and with no obvious adverse effects on development. There were only occasional, minor, and transient laboratory abnormalities even after prolonged exposure to lithium through breast milk. We caution, however, that the risk for thyroid dysfunction and renal impairment from exposure to lithium through breast milk cannot be quantified securely. Infant hypothyroidism is a serious condition and can lead to mental and growth retardation, impaired tissue perfusion, constipation, and poor muscle tone. Moreover, even though early thyroid hormone replacement can avoid these adverse outcomes, in most cases, clinical signs of hyperthyroidism are not obvious soon after birth. Currently, some state laws mandate that all newborns be screened for hypothyroidism and other disorders. It is noteworthy that all newborns in our sample had normal neonatal thyroid assays despite prolonged exposure to lithium in utero and the complete passage of maternal lithium across the placenta (6).

The elevated serum blood urea nitrogen level noted in two of 10 infants highlights the importance of infant fluid status. Because renal function and lithium clearance are sensitive to perturbations in fluid volume, we recommend added vigilance during exposure to lithium through nursing, especially with fever, gastrointestinal illness, or other loss of fluid and electrolytes. Severe fluid loss could lead to toxic retention of lithium as sodium is lost, and lithium clearance can be compromised further by co-administration of nonsteroidal analgesic-antipyretic agents such as ibuprofen. Clinical signs of lithium toxicity, including lethargy, poor feeding, and hypotonia, are generally reversible with early aggressive treatment with intravenous hydration (1, 2).

Currently, formal guidelines for therapeutic drug monitoring of mood stabilizers are not available (1, 2). However, because monitoring of indices of thyroid and renal function is standard for adults treated with lithium, similar recommendations are appropriate for nursing infants exposed to lithium. Laboratory monitoring should include assays of infant serum lithium and TSH, blood urea nitrogen, and creatinine levels, preferably in the immediate postpartum period up to 6 weeks of age. Based on clinical experience, we recommend using an experienced pediatric phlebotomist and favor obtaining laboratory values between 4 and 6 weeks of age, when venous access is easier and potentially less stressful for the infant. Of note, we found no negative consequences of obtaining laboratory values after the immediate postpartum period. As long as an infant is breast-fed by a woman taking lithium, laboratory monitoring should continue—on average every 8–12 weeks or as clinically indicated.

Despite the absence of treatment-emergent adverse events in our small cohort, we caution that breast-feeding while taking lithium should be considered appropriate *only* for carefully selected women with bipolar disorder. Suitable clinical characteristics include the following: 1) stable maternal mood, 2) lithium monotherapy or at least a simple medication regimen, 3) and adherence to infant monitoring recommendations, as well as a 4) a healthy infant and 5) a collaborative pediatrician. Further studies assessing larger cohorts of nursing infants are needed to quantify lithium exposure during lactation and to examine the spectrum of possible adverse effects as well as to define optimal monitoring requirements.

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