



Lithium

Revised: December 15, 2023.

CASRN: 554-13-2

Li +

Drug Levels and Effects

Summary of Use during Lactation

Lithium excretion into breastmilk and concentrations in infant serum are highly variable. Although lithium appears on some lists of drugs contraindicated during breastfeeding,[1] most sources do not consider it an absolute contraindication in healthy-full-term infants, especially in infants over 2 months of age and during lithium monotherapy.[2-9] Numerous reports exist of infants who were breastfed during maternal lithium therapy without any signs of toxicity or developmental problems. Most were breastfed from birth and some continued to nurse for up to 1 year of maternal lithium therapy. Some reports suggest that lithium in milk can adversely affect the infant acutely when its elimination is impaired, as in dehydration or in newborn or premature infants. Neonates may also have transplacentally acquired serum lithium levels. Lithium levels in these infants decline whether they are breastfed or not, although serum levels may fall more slowly in exclusively

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breastfed infants.[10] The long-term effects of lithium on infants are not certain, but limited data indicate no obvious problems in growth and development.[9-11]

Lithium may be used in mothers of full-term infants who are willing and able to monitor their infants. Because maternal lithium requirements and dosage may be increased during pregnancy, maternal serum levels should be monitored frequently postpartum and dosage reduced as necessary to avoid excessive infant exposure via breastmilk.[12] Infants with higher lithium levels at birth have more side effects and are more likely to be admitted to the NICU.[13] Discontinuing lithium 24 to 48 hours before Cesarean section delivery or at the onset of spontaneous labor and resuming the prepregnancy lithium dose immediately after delivery should minimize the infant's serum lithium concentration at birth.[14] Some investigators recommend monitoring infant serum lithium, serum creatinine, BUN, and TSH in intervals ranging from "periodic" to every 4 to 12 weeks during breastfeeding and maternal lithium therapy.[4,15] One group recommends monitoring maternal and infant serum lithium at 2 and 10 days postpartum in mixed-fed infants with additional monitoring at 30 and 60 days postpartum for exclusively breastfed infants.[10] A systematic review recommends infant lithium serum level, thyroid and renal function tests only at 10 days postpartum, then only if the infant's serum lithium is 0.3 mEq/L or greater or if clinical signs of toxicity appear.[16] However, others recommend close pediatric follow-up of the infant and only selective laboratory monitoring (i.e., serum lithium, TSH, BUN) if clinically indicated by unusual behavior, restlessness, feeding difficulties, sedation or abnormal growth and development. Infants who are preterm, dehydrated, or have an infection, should receive hydration and be assessed for lithium toxicity.[6,7] If the infant serum lithium level is elevated, reducing the percentage of breastfeeding can decrease it.[9]

Drug Levels

Maternal Levels. Most older reports of lithium levels in breastmilk did not characterize breastmilk lithium excretion in a rigorous manner. Random milk levels have been reported to range from 0.12 to 0.7 mEq/L and appear to be rather consistent at about 40 to 45% of the simultaneous maternal serum level.[17-20] The milk concentration of lithium in one woman was found to be inversely proportional to milk volume. The milk to plasma ratio was found to be directly proportional to serum lithium; the ratio was about 1 with low serum lithium and 1.5 with higher serum lithium levels, indicating disproportionately higher lithium excretion into milk with higher serum levels.[21]

From data in papers published up to 1990 concerning 6 infants, it is estimated that a fully breastfed infant would receive about 26% (range 11 to 42%) of the maternal weight-adjusted dosage of lithium.[18-23] However, many of these case reports were of poor quality.

A more recent case series of 11 mothers that used better techniques found the average infant dosage to be 12.2% (range 0 to 30%) of the maternal weight-adjusted dosage.[24] The reason for the difference between the older and more recent data is not apparent.

A case series reported 10 mothers taking lithium carbonate in an average daily dosage of 850 mg (range 600 to 1200 mg daily) for bipolar disorder. Lithium milk levels in 26 milk samples taken between 8.1 and 27.5 weeks postpartum averaged 0.35 mEq/L (range 0.19 to 0.48 mEq/L). No difference was found between concentrations in fore- and hindmilk samples.[15]

One woman who was taking 1200 mg of lithium carbonate daily (dosage schedule and product not reported) had a milk lithium concentration of 0.41 mmol/L at 20 hours after her previous dose. This was about the same as her simultaneous blood concentration.[25]

Infant Levels. The serum lithium levels in the breastfed infants of mothers taking lithium have ranged from 10 to 50% of simultaneous maternal serum lithium levels.[18,22,24,26] One infant, who previously had a serum level about 50% of the mother's, became dehydrated and developed a serum level that was double that of the mother's.[26]

A 5-day-old infant developed cyanosis, lethargy, ECG T-wave inversion probably caused by lithium in breastmilk. The infant's serum lithium concentration was 0.6 mEq/L at 5 days of age and 0.21 mEq/L on day 7, 2 days after breastfeeding was discontinued.[22]

Ten exclusively breastfed infants whose mothers were taking an average of 850 mg daily of lithium carbonate had serum levels of 0.16 mEq/L or 24% (range 11 to 56%) of maternal serum levels.[15]

Two breastfed infants (extent not stated) were reported whose mothers were taking lithium carbonate during pregnancy and postpartum. The first mother was taking 1200 mg daily and the infant's serum concentrations were 0.11 mmol/L on day on day 4 and undetectable (<0.1 mmol/L) on days 6 and 10 postpartum. The second mother was taking 900 mg daily and her breastfed infant's serum lithium concentration was undetectable (<0.3 mmol/L) on day 3 of life. Both infants had other serum concentration measurements that were in the therapeutic or toxic ranges but displayed no symptoms. These samples apparently had been collected in tubes containing lithium heparin.[25]

A woman took lithium carbonate orally 800 mg daily during pregnancy and postpartum while exclusively breastfeeding her infant. The mother had a serum lithium concentration of 0.74 mmol/L at 15 days postpartum. The infant's serum lithium concentration was 0.26 mmol/L at this time. Further serum lithium concentrations in the infant were 0.23 mmol/L at 1 and 2 months of age and 0.17 mmol/L at 6 months of age.[27]

Three mothers took lithium carbonate during pregnancy and breastfeeding. One mother took a dosage of 900 mg daily during 2 pregnancies. Her infants' serum lithium concentrations were 0.08 mEq/L at 31 days and 183 days postpartum in the first pregnancy and 0.11 mEq/L at 43 days of age in the second pregnancy. These values were 11%, 17% and 15% of the mother's simultaneous serum lithium concentrations, respectively. The second mother also took a dosage of 900 mg daily. Her infant's serum lithium concentration was 0.08 mEq/L at 39 days postpartum, or 10% of the mother's simultaneous serum lithium concentration. The third mother took a dosage of 1350 mg daily. Her infant's serum lithium concentration was 0.11 mEq/L at 31 days postpartum, or 11% of the mother's simultaneous serum lithium concentration.[14]

A woman with bipolar disorder was taking lithium 600 to 900 mg daily during pregnancy and postpartum. At 10 days postpartum, her infant's serum lithium level was 0.26 mmol/L, which was 58% of the maternal trough serum level. Lithium was discontinued. First quetiapine then aripiprazole were substituted for lithium, but after 2 to 3 weeks she switched back to lithium at an unspecified dosage. After several weeks of treatment, her infant's lithium level was 0.2 mmol/L.[28]

A woman with bipolar disorder took prolonged-release lithium carbonate 400 mg (Plenur-Faes Pharma, Spain) every 12 hours during pregnancy and postpartum. She breastfed her infant exclusively for 33 days but introduced supplements for 16 days because of slow weight gain. After the 16 days, she exclusively breastfed her infant until 2.5 months of age, when mixed feeding was begun. The infant's serum lithium levels were monitored at 17 days, 1 month, 3.5 months and 5.5 months of age. Lithium levels were less than 0.2 mmol/L at all these time points.[29]

A case series from Germany reported 3 breastfed infants whose mothers were taking lithium. The first infant's mother was taking 1000 mg daily of lithium carbonate (Hypnorex ret., Essential Pharma Ltd.). The infant's serum lithium levels were 0.09 and 0.12 mEq/L at 1 and 2 months postpartum, respectively. These levels corresponded to 12.5% and 13.5% of the mother's serum lithium levels on those days. The second woman was taking 450 mg daily of lithium (Quilonum® retard, Teofarma S.R.L. or GlaxoSmith Kline) and partially (about 50%) breastfed her infant for the first 4 months postpartum. At 2 months of age, the infant's serum lithium level was <0.1 mEq/L. The third mother was taking lithium 225 mg daily (also Quilonum® retard) postpartum and exclusively breastfed her infant. At 11 days postpartum, the infant's serum lithium concentration was 0.11 mEq/L, which was 42.3% of the mother's serum lithium concentration.[30]

Nine exclusively breastfed infants whose mothers were taking lithium carbonate twice daily had blood samples taken once on days 1 to 5, 7 to 11, at one month and monthly thereafter. A cord blood sample was also taken. Mothers were taking a mean dosage of 956 mg (range 600 and 1600 mg) daily. The cord blood lithium level ranged from 1.05 to 1.3 times the maternal blood level. Excluding the cord blood samples, the overall average infant blood to maternal blood ratio was 0.58 (range 0.12 to 1.09) The infant to maternal blood ratio decreased in all infants postpartum, by an average of 44% at 1 month and 59% at 3 months of age.[31]

Twenty-four women taking lithium during pregnancy for bipolar disorder were divided into 3 groups: exclusive breastfeeding, partial (50 to 80%) breastfeeding and exclusive formula feeding postpartum. Lithium was discontinued at the onset of labor for a spontaneous delivery or 12 hours before a scheduled caesarean section or induction. Breastfeed was reinitiated at the same dose 6 hours after vaginal delivery or 12 hours after caesarean section. Infant serum lithium concentrations were obtained at approximately 2, 7, 15, 30 and 60 days. The median times for infant serum concentrations to fall to 0.2 mEq/L were 6 to 8 days for formula-fed infants, 7 to 8 days for mixed-fed infants, and 53 to 60 days for exclusively breastfed infants. No accumulation of lithium was observed in exclusively breastfed infants.[10]

A 15-year retrospective study from two hospitals in Sweden observed 30 infants who had been breastfed by mothers taking lithium. Infants were mostly breastfed greater than 50% with 3 exclusively breastfed. A total of 66 infant serum levels were recorded. The mean lithium serum concentration was 0.19 mmol/L in the first two weeks of life, 0.16 mmol/L in week 2 to 4 (range <0.05-1.2 mmol/L), 0.07 mmol/L in the second month of life (range <0.05-0.2 mmol/L) and 0.08 mmol/L after 2 months of age (range <0.05-0.2 mmol/L). Concentrations measured before one month of age were significantly higher than those measured after one month of age. The mean infant to mother serum lithium concentration ratio was highest at 1 to 2 weeks of age at 0.37, about 0.18 from 2 to 4 weeks of age, and about 0.1 thereafter. Two infants had elevated serum lithium concentrations. One infant, born at 35+2 weeks of gestation, had a serum lithium concentration of 0.7 mmol/L at 12 days of age and had been about 75% breastfed. The level was 17% higher than the maternal concentration. The mother was recommended to reduce breastfeeding to around 50%, and 4 days later the infant's lithium concentration was undetectable (<0.05 mmol/L). Another infant had a serum lithium concentration of 1.2 mmol/L at the first follow-up visit at 29 days of age. Breastfeeding was discontinued and no clinical complications were noted.[9]

In a retrospective chart review, 25 breastfed infants who were exposed to lithium in utero and were born with detectable serum lithium levels at birth were followed postpartum. At hospital discharge, 46% were exclusively breastfed and at 2 to 4 weeks of age, 58% were exclusively breastfed. Infants with high serum concentrations (average 0.9 mEq/L; n = 7) at birth had higher median serum concentrations at follow-up of 0.20 mEq/L (range 0.10 to 1.20 mEq/L) than those in the low serum level group of 0.06 mEq/L (range <0.05 to 0.3 mEq/L).[13]

Effects in Breastfed Infants

In older reports, at least 24 infants have been reported to have been breastfed during maternal lithium therapy without any signs of toxicity or developmental problems. All were breastfed from birth and some continued to nurse for up to 6 months of maternal lithium therapy.[15,18-20,24,25,27]

A 5-day-old infant developed cyanosis, lethargy, ECG T-wave inversion probably caused by lithium in breastmilk.[22] The mother had been receiving the long-acting diuretic chlorthalidone prior to delivery which probably decreased the infant's lithium elimination and increased the neonate's lithium serum levels. Another case of probable infant lithium intoxication appeared only after the infant had a cold which may have led to dehydration and decreased lithium excretion.[26,32] Two other infants had slight increases in thyrotropin (TSH) levels at 8 and 4 weeks of age, respectively, after lithium exposure that began during pregnancy. Elevated TSH continued until maternal lithium was stopped in one,[15] and normalized by 2 months postpartum in the other, despite continued exclusive breastfeeding.[27]

Three mothers took lithium carbonate during pregnancy and breastfeeding. The first infant was born to a mother who also took bupropion 300 mg and levothyroxine 50 to 75 mcg daily. She breastfed beyond 1 year of age. Her infant did not regain birth weight by 15 days of age, was somewhat hypotonic at 2 months of age, and was treated for gross and fine motor delay for the first year of life. The mother had a second infant on the same drug regimen. She exclusively breastfed her infant who developed normally without hypotonia. A second mother was taking a lithium dosage of 900 mg daily. Her infant gained weight slowly, but weight gain increased with breastfeeding support and she exclusively breastfed her infant for 4 months. A third mother was taking 1350 mg of lithium daily as well as escitalopram 10 mg, levothyroxine 25 mcg and heparin (dosage not stated) daily during pregnancy and breastfeeding. Her infant was normal and was exclusively breastfed until 8 weeks of age when the maternal serum lithium concentration was excessive at 2.0 mEq/L. Breastfeeding was withheld for 2 days and the dosage lowered to 600 mg daily. She then breastfed successfully until 7 months of age.[14]

A woman with bipolar disorder took prolonged-release lithium carbonate 400 mg every 12 hours during pregnancy and postpartum. She breastfed her infant exclusively for 33 days but introduced supplements for 16 days because of slow weight gain. After the 16 days, she exclusively breastfed her infant until 2.5 months of age, when mixed feeding was begun. The infant was monitored at 17 days, 1 month, 3.5 months and 5.5 months of age. No infant side effects were observed at any time. Lithium levels were not detectable, and serum creatinine and thyroid-stimulating hormone levels were normal.[29]

Three infants were breastfed (2 exclusive, one 50%) during maternal lithium therapy. The infants were breastfed for 5 to 21 months. All had normal growth and development, as well as normal renal and thyroid levels.[30]

Nine infants whose mothers were taking lithium in an average dosage of 956 mg daily were exclusively breastfed for an average of 93 days (range 15 to 189 days). After routine follow-up examinations by a pediatrician, no acute growth or developmental delays were reported in any infant during the follow-up period.[31]

Twenty-four women taking lithium during pregnancy and postpartum for bipolar disorder were divided into 3 groups: exclusive breastfeeding, partial (50 to 80%) breastfeeding, and exclusive formula feeding. Infants were followed for up to 60 days of age. During the follow-up period, pediatricians found no observable growth or developmental delay in infants in any of the three groups.[10]

A 15-year retrospective study from two hospitals in Sweden observed 30 infants who had been breastfed by mothers taking lithium. None of the infants experienced an adverse event from lithium. All the serum sodium, potassium, creatinine, thyroid stimulating hormone and thyroid hormone (values measured were within the normal range, except for one sodium and one potassium level that were 0.1 mmol/L outside of the normal range, without any clinical consequence. No infants were described as irritable and all had normal muscle tone. About 25% of the infants had inadequate growth during their first month of life. Four mothers were advised to reduce breastfeeding and to increase the amount of formula given because of poor infant growth (n = 1), polypharmacy (n = 1) or elevated serum lithium concentrations in the infants (n = 2). Two infants were described as tired at their first outpatient visits, but their serum lithium concentration was only 0.2 mmol/L. One of them also had poor weight gain and hyperbilirubinemia at nine days of age, but one week later the baby was healthy and growing well.[9]

In a retrospective chart review, 25 breastfed infants who were exposed to lithium in utero and were born with detectable serum lithium levels at birth were followed postpartum. At hospital discharge, 46% were exclusively breastfed and at 2 to 4 weeks of age, 58% were exclusively breastfed. Infants with high serum concentrations (average 0.9 mEq/L; n = 7) at birth had more complications than those with low serum concentrations (average 0.4 mEq/L; n = 18). At follow-up, the rate of neonatal symptoms was 28.6% in the infants with high serum levels at birth and 11.8% in those with low levels.[13]

Effects on Lactation and Breastmilk

Lithium increases serum prolactin.[33-35] Galactorrhea was reported in a woman taking lithium carbonate for 50 days. Lactation ceased with lithium discontinuation.[35] The prolactin level in a mother with established lactation may not affect her ability to breastfeed.

Alternate Drugs to Consider

(Bipolar Disorder) *Divalproex, Olanzapine, Quetiapine, Risperidone, Valproic Acid*

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Substance Identification

Substance Name

Lithium

CAS Registry Number

554-13-2

Drug Class

Breast Feeding

Lactation

Milk, Human

Lithium