Q&A 400.3

Gabapentin and pregabalin—are they safe whilst breastfeeding?

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

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Background

Gabapentin is an anti-epileptic drug (AED) used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), it is neither a GABA agonist nor antagonist and its mechanism of action is unknown. Gabapentin is also used in the treatment of neuropathic pain, migraine prophylaxis and restless legs syndrome. (1, 2)

Pregabalin is an AED used as an adjunct in the treatment of partial seizures with or without secondary generalisation. It is also used in the treatment of generalised anxiety disorder, neuropathic pain, and fibromyalgia. (1, 2)

There are little data for the new AEDs, including gabapentin and pregabalin, regarding breastfeeding. The manufacturers state that these drugs are excreted into the breastmilk and the effects of this on the infant are unknown. The manufacturers of gabapentin recommend it should be used with caution in breastfeeding and only used where the benefits clearly outweigh the risks. (3) The manufacturers of pregabalin do not recommend use of pregabalin whilst breastfeeding. (4) This raises the question of the true compatibility of gabapentin and pregabalin whilst breastfeeding.

Answer

The following information relates to full term and healthy infants. If the infant is pre-term, of low birth weight or has other concomitant pathology or medical problems, then specialist advice should be sought as this answer may not apply.

Breastfeeding whilst taking AEDs is generally safe and should be encouraged. (5) In published reports of AED use during breastfeeding, most women were taking a combination of AEDs. Due to some drug-drug interactions affecting the metabolism of AEDs, the relationship of the maternal dosage to the concentration in breast milk can be quite variable. (6)

Gabapentin

Pharmacokinetic data can give a theoretical indication of transfer of a drug into breast milk. Gabapentin is a small molecule (molecular weight 171). (1) It is absorbed from the gastrointestinal tract by means of a saturable mechanism (1), with oral bioavailability decreasing with increasing dose. Oral bioavailability is about 60%. (3) It is only minimally bound to plasma proteins. Gabapentin is not appreciably metabolised and most of a dose is excreted unchanged in the urine. (1) Therefore, passage of gabapentin into breast milk with some infant absorption can be expected. (1)

Four women taking gabapentin 12 to 21 days postpartum, and a fifth who was 97 days postpartum had a single breast milk sample measured just before nursing and 10 to 15 hours after the previous evening's gabapentin dose. The average maternal dosage was 1.5 grams daily (range 0.6 to 2.1 grams daily) and the average milk level was 4.5 mg/L (range 1.2 to 8.7 mg/L) which was similar to maternal plasma levels. Four of the mothers breastfed their infants and infant serum levels were measured. One infant had an undetectable serum level, however low levels of gabapentin were detected in three of the breast fed infants. Assuming a daily milk intake of 150 mL/kg/day, the infant dose of gabapentin was estimated to be 0.2–1.3 mg/kg/day, which is equivalent to 1.3–3.8% of the maternal weight-adjusted dose. No adverse effects were observed in any of the 5 infants. (7)

A follow-up publication by the same authors found a similar degree of gabapentin excretion into

breast milk in 8 milk samples taken up to 2 days after delivery from 5 mother-infant pairs. The mean milk/maternal plasma concentration ratio was 1.11 (range 0.54—2.0). All of the breastfed infants had undetectable plasma concentrations of gabapentin. Again, no adverse effects were observed in the infants. (8)

A woman took gabapentin 600 mg 3 times daily plus amitriptyline 2.5 mg daily for 6 weeks beginning in the first few days postpartum for chronic back pain. She breastfed her infant 6 to 7 times daily with some additional bottle feeding at night. Eight milk samples (6 foremilk and 2 hindmilk) were obtained over 24 hours. The average concentration in milk was 5.7 mg/L. Using the average milk level, a fully breastfed infant would receive a dosage of 0.86 mg/kg daily or 2.34% of the maternal weight-adjusted dosage. At 1.6 months of age, the infant's plasma gabapentin concentration was 0.4 mg/L which was about 6% of the average maternal plasma concentration. The infant was found to be healthy with a weight between the 10th and 25th percentiles, having been at the 50th percentile at birth. His age on the Denver developmental test was the same as his chronological age. (9)

A study looking at the concentrations of levetiracetam in breast milk, described an exclusively breastfed 5-day-old infant whose mother was taking levetiracetam 2.5 grams daily and also gabapentin 1.2 grams daily during pregnancy and lactation. The infant appeared healthy to the investigators throughout the 6- to 8-week study period. (10)

A further unpublished single dose study of 6 lactating women evaluated gabapentin concentrations in breast milk. Each woman received a single 400 mg dose of gabapentin. Blood, urine and breast milk samples were collected for 36 hours following gabapentin administration. Five of the 6 subjects were able to produce milk during the collection periods and were included in the pharmacokinetic analysis. Results indicated that gabapentin is secreted into breast milk at concentrations equal to or significantly less than corresponding plasma concentrations. The authors concluded that an infant would be expected to receive 1.2 mg/kg/day gabapentin via breast milk from a mother receiving 4.8 grams of gabapentin daily. (11)

Pregabalin

Pregabalin is a small molecule (molecular weight 159). It is rapidly absorbed after oral doses and peak plasma concentrations occur within 1.5 hours. Oral bioavailability is about 90%. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug with a mean elimination half-life of 6.3 hours. (1) Therefore, passage of pregabalin into breast milk and absorption by the breastfed infant should be expected.

The breastfed infant of a woman who was taking pregabalin (dose not specified) as an AED during pregnancy and breastfeeding had a pregabalin serum concentration of 429 micrograms/L at 48 hours postpartum, which was about 8% of the mother's serum concentration. However, some of the infant's serum concentration could have been derived from transplacental passage. The authors concluded that although extensive passage of pregabalin into breast milk occurs, with milk levels almost equalling maternal serum levels, low concentrations are seen in the breastfed infant’s serum. No adverse effects were observed. (12)

After a thorough literature search no further data regarding excretion of pregabalin into human breast milk were located. Distribution into milk has been found in rat studies (13).

Summary

- Limited data indicate that gabapentin passes into breast milk, with low or negligible concentrations measured in the breastfed infant's serum.
- Assuming a daily milk intake of 150 mL/kg/day, the infant dose of gabapentin via breast milk has been estimated to be 0.2–1.3 mg/kg/day, and 1.3–3.8% of the maternal weight-adjusted dosage.
- A single study reported extensive passage of pregabalin (dose not specified) into breast milk but low levels in the breastfed infant. Therefore, due to limited data alternative agents for which more data exists should be used preferentially, especially in a newborn infant.
- No adverse effects have been attributed to infant exposure to gabapentin or pregabalin through the breast milk
- Gabapentin and pregabalin are almost entirely renally excreted; therefore use should be avoided in infants with impaired renal function and premature infants.
- If gabapentin or pregabalin is used by a breastfeeding mother, monitor the infant for gastrointestinal adverse effects, appetite changes, adequate weight gain, drowsiness and normal developmental milestones. If the infant becomes unwell then consider withholding breastfeeding until a cause can be identified.
- Long-term data on the developmental effects of exposure to gabapentin or pregabalin through the breast milk is not available.

Limitations

- Evidence of the secretion of gabapentin and pregabalin into breast milk, and its safety in breastfed infants, is limited to relatively small short term studies with limited numbers of mothers and infants.
- The information relates to full term and healthy infants. Evidence in preterm infants is lacking. If the infant is preterm, of low birth weight or has other concomitant pathology or medical problems, then specialist advice should be sought as this answer may not apply. Contact the UK Drugs in Lactation Advisory Service (UKDILAS) provided by the Trent and West Midlands Medicines Information Services (Telephone: 0116 258 6491 or 0121 311 1974).

References

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Quality Assurance

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Search strategy
For lactation evidence:

- In-house UKDILAS database
- Embase and Medline (Standard UKDILAS Search Patterns) [link]
- Drugs and Lactation Database (LactMed). Toxnet Toxicology Data Network, United States National Library of Medicine. Available from http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. Gabapentin and pregabalin monographs
- Medications and Mothers' Milk Online. Available from www.medsmilk.com: gabapentin and pregabalin
- Martindale: The Complete Drug Reference: gabapentin and pregabalin
- National Institute for Health and Care Excellence (online): CG 137
- British National Formulary (online): gabapentin and pregabalin
- Manufacturers (eMC) of gabapentin and pregabalin products
- Drugs in Pregnancy and Lactation (Briggs)
- Drugs for Pregnant and Lactating Women (Weiner)
- Drugdex (online): gabapentin and pregabalin