

Histamine H₂-receptor antagonists - are they safe in breastfeeding?

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Background

Gastro-oesophageal reflux disease is a common problem during pregnancy and usually resolves after delivery. However some women continue to experience symptoms post partum. First line choices of management for breastfeeding mothers are lifestyle and dietary modifications followed by use of simple antacids. If this does not suffice an H₂-receptor antagonist or a proton pump inhibitor may be considered (1,2). Four H₂-receptor antagonists are licensed in the UK: ranitidine, cimetidine, famotidine and nizatidine, and all can be obtained over-the-counter (3). The use of over-the-counter H₂-receptor antagonists should be discouraged in this patient group.

Answer

Ranitidine

In a case study a breastfeeding mother was initiated on ranitidine 150 mg twice daily. Breastfeeding was interrupted for 12 hours after her fifth dose. The ranitidine concentration in breast milk before the 5th dose was 993 nanograms/mL. Post dose concentrations were 722 nanograms/mL, 2,610 nanograms/mL and 1,569 nanograms/mL at 1.5 hours, 5.5 hours and 12 hours respectively. The milk to serum ratios were 6.81, 8.44 and 23.77 at the same times. The results show an accumulation of ranitidine in milk with the highest milk to serum ratio occurring 12 hours post dose. The difference in breast milk concentration pre-dose and 12 hours post dose suggests that steady state concentrations in milk had not yet been achieved. The authors suggested that to reduce infant exposure, mothers could breastfeed one to two hours after a dose in contrast to nursing towards the end of the 12 hour dosing interval when the largest milk to serum ratio was observed (4).

Another study looked at the excretion of ranitidine into the breast milk of 6 women following a single oral 150 mg dose. Milk and blood samples were obtained at 2, 4 and 8 hours post dose. Drug concentrations in breast milk varied between subjects and were higher than plasma concentrations. There were also wide variations in milk to plasma drug concentration ratios between subjects which was attributed to differences in composition of the milk. The median milk to plasma ratio was 1.92 at 2 hours, 2.78 at 4 hours and 6.70 at 8 hours. The ratio increased with time after dosing as the drug appears to be cleared more rapidly from plasma than milk. The authors comment that the milk to plasma ratios seen in this study may not be applicable to chronic dosing when steady state concentrations have been achieved (5).

Ranitidine is used in neonates although the oral preparation is not licensed for use in children under 3 years and the injection is not licensed for infants under 6 months. Oral absorption in neonates is unreliable (6).

Cimetidine

In a case study a mother took a 400 mg dose and over the following 10 hours, five milk and blood samples were taken. For the following 3 days the mother took 200 mg three times a day and 400 mg at night. On day 4 further milk and blood samples were taken. After the single 400 mg dose the drug concentration in plasma was highest in the first sample taken 1 hour post dose but in milk the peak concentration occurred between 1 and 3 hours post dose. The last three sample pairs gave milk to plasma ratios of 3.04, 3.57 and 3.53. Over the 10 hour collection time 325 micrograms of cimetidine was excreted into 130mL of milk. After chronic

dosing, milk concentrations at times of minimum maternal plasma levels were found to be high and similar, at 6, 5.8 and 4.88 micrograms/mL. This resulted in highly variable milk to plasma ratios. The chronic dosing study suggests that an active transport mechanism exists as plasma levels were in the range expected whereas milk levels remained elevated. The authors commented that the clinical significance of the findings is unclear. They calculated that the maximum amount of cimetidine that an infant could ingest if they consumed one litre of milk a day and fed when milk levels were highest would be approximately 6 mg. They advised that caution may be warranted with cimetidine in lactation (7).

A randomised study provides further evidence that cimetidine accumulates in breast milk by an active transport mechanism. 12 lactating women received single oral doses of 100 mg, 600 mg and 1200 mg of cimetidine in a crossover design study on 3 different days. The authors predicted a mean milk to serum ratio 1.05 ± 0.18 for a diffusion model. The observed overall mean milk to serum ratio (5.77 ± 1.24) was 5.5 times greater than predicted and did not differ significantly for the different doses. Mean peak concentration (t_{max}) in milk showed a delay and was 3.3 ± 0.7 hours compared to a mean serum t_{max} of 1.7 ± 0.6 hours post dose. The dose of cimetidine ingested by the breastfed infant was estimated to be 6.7% of the maternal dose, based on mean milk to serum ratios. Despite the concentration mechanism, infant exposure via breast milk still appears to be low and the authors comment that this should be safe under normal conditions. Neonatal therapeutic doses of cimetidine quoted in this paper are 10-20 mg/kg/day which would be much higher than the amounts received via breast milk. Exposure of the breastfed infant to cimetidine could potentially be reduced by avoiding breastfeeding when the drug peaks in milk at 3 hours post dose (8).

Cimetidine, in general, is not widely used due to its hepatic enzyme inhibition effects and associated drug interactions. This could potentially pose a problem during breastfeeding if the infant is taking any interacting medication.

Famotidine

A study found that famotidine is secreted into human breast milk but appears to be less extensive than with either cimetidine or ranitidine. Eight women who did not breastfeed their infants were given a single 40 mg dose of famotidine. Milk to plasma ratios were 0.41, 1.78 and 1.33 at 2, 6 and 24 hours respectively. The concentration of famotidine in milk was found to lag behind the concentration measured in plasma by 2-4 hours. The mean observed peak breast milk concentration, 72 ± 21 nanograms/ml at 6 hours post dose, was not significantly different from the mean peak plasma concentration, 75 ± 22 nanograms/ml, measured at 2 hours post dose (9).

In a second study seven women were given oral famotidine 40 mg daily in 2 or 4 divided doses for 3 days at 12 to 16 weeks postpartum. Mean concentrations of famotidine in breastmilk were 53 ± 20 and 55 ± 23 nanograms/ml at 3 and 6 hours after a dose, respectively. *Detail in this study, presented as a conference abstract, is lacking* (10)

Nizatidine

In a study, in 3 women 150 mg was administered as a single dose and then once every 12 hours for a total of 5 doses. On average, 96 micrograms, less than 0.1% of the maternal dose, was secreted into milk during a 12 hour time period after either single or multiple dosing. The half life of nizatidine in serum and breast milk was less than 2 hours which suggests that drug accumulation would not occur. The authors also used a 'worst-case' analysis, assuming that the maximum rate of secretion of nizatidine into breast milk would continue through a 24 hour dosing interval. They calculated that no more than 1.1 mg of nizatidine would be secreted into milk during this period and the infant would consume less than 1% of the maternal dose of nizatidine. The authors suggest that to minimise infant exposure to nizatidine the mother could avoid nursing when the concentrations of nizatidine would be greatest, for 6-8 hours after a dose, and discard all breast milk during this interval (11)

Summary

- ◆ Although data is lacking, the use of any H₂-receptor antagonist in breastfeeding mothers does not appear to pose a significant risk to the infant and no adverse effects have been reported.
- ◆ Ranitidine is used in neonates in the UK and the therapeutic doses given in these circumstances are likely to be much larger than the amounts received via breast milk.
- ◆ Ranitidine and cimetidine appear to accumulate in breast milk and there is evidence that cimetidine is actively transported into breast milk.
- ◆ Famotidine and nizatidine appear in breast milk in lower amounts.
- ◆ All of the H₂-receptor antagonist have short half lives which reduces the risk of drug accumulation in the infant.
- ◆ Cimetidine, in general, is not widely used due to its hepatic enzyme inhibition effects and associated drug interactions. This could potentially cause problems for the infant if they are taking any interacting medication.
- ◆ If an H₂-receptor antagonist is required during lactation, treatment should be limited to the lowest dose and shortest course length required to control symptoms.
- ◆ Ranitidine is the first choice agent in breastfeeding mothers due to greater experience of its use during lactation.
- ◆ If a mother is to breastfeed whilst taking an H₂-receptor antagonists the infant should be monitored for normal growth and any unusual adverse effects but these would not be expected.

Limitations

- There is a lack of data about transfer of H₂-receptor antagonists into human breast milk.
- The information relates to full-term and healthy infants. Evidence in pre-term infants is largely lacking. 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. *Contact the UK Drugs in Lactation Advisory Service (UKDILAS) provided by the Trent and West Midlands Medicines Information Services.*

References

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