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SAFETY OF THIAZIDE DIURETICS IN BREASTFEEDING

Question:
A patient requires treatment for Meniere's disease that is increasingly debilitating with frequent exacerbations. She takes prochlorperazine as required, but needs regular treatment. How safe are thiazide diuretics when breastfeeding a healthy 9 month old who feeds three or four times daily?

Answer:
Drug safety during breastfeeding can be assessed by determining the magnitude of infant exposure ie. the dose ingested via milk and infant pharmacokinetics, and the drug's inherent toxicity. The infant's dose (mg/kg) can be expressed as a percentage of the maternal dose (mg/kg). For drugs with relatively low toxicity, an infant dose that is less than 10% of the maternal dose (weight-adjusted) is probably compatible with breastfeeding. However, for drugs with greater inherent toxicity (eg. immunosuppressives), this cut-off is too high and even low drug exposure may be contraindicated. Higher exposure for a given dose may occur in premature infants and those with impaired renal or hepatic function due to reduced ability to eliminate drugs[1,2].

There are four single-ingredient thiazide (or thiazide-like) preparations in New Zealand: bendrofluazide, chlorthalidone, cyclopenthiazide and indapamide.
We are not aware of any data describing the transfer of bendrofluazide, cyclopenthiazide or indapamide into human breast milk[1,3,6]. There are some data for chlorthalidone and on average, it is suggested that a breastfeeding infant ingests approximately 6.7% (maximum 15.5%) of the maternal chlorthalidone dose, after correcting for the difference in body weight[1]. This indicates that the magnitude of infant exposure may be greater than our notional cut-off of 10%, that has been used to guide safety.
There has been some controversy regarding recommendations for the use of these agents in breastfeeding. For example, the American Academy of Paediatrics considers bendrofluazide and chlorthalidone to be 'safe' in breastfeeding, despite the lack of data for bendrofluazide and possible high infant exposure to chlorthalidone[7]. Other sources advise that chlorthalidone should not be used in lactation[8].

Bendrofluazide has higher protein-binding than chlorthalidone (94% and 74%, respectively)[8] which tends to mitigate against transfer into breast milk. Another feature suggesting that bendrofluazide may pose lower risk than chlorthalidone is that is has a shorter half-life of approximately 3 - 9 h compared with 50 - 90 h for chlorthalidone[8]. This suggests that chlorthalidone may accumulate in a breastfeeding infant, particularly in very young or premature babies.

Thiazide, thiazide-like and loop diuretics are suggested to suppress lactation[1]. It is not clear what risks this poses for a woman who is established in lactation. The study investigating the effect of bendrofluazide on lactation suppression used large doses of 15mg daily[9]. It is likely that the lower doses that are in current use eg. for hypertension (usually 2.5mg/day) carry substantially less risk.

Conclusions:
Where possible, all drugs should be avoided in breastfeeding unless the potential benefits outweigh the risks. This patient's Meniere's disease is debilitating suggesting that it may be reasonable to

initiate bendrofluazide, despite the lack of data supporting its use. While data is available for chlorthalidone, the infant dose may be above our notional cut-off of 10% that is often use to guide safety in lactation. Bendrofluazide is likely to offer a safety advantage over chlorthalidone because of higher plasma protein-binding and shorter plasma half-life. Infant exposure will be further reduced in this case as the baby is only feeding three to four times daily and is older so will have enhanced clearance compared with a younger baby.

In general, administering the dose just after a feed helps to minimise infant exposure. Any baby who is exposed to a drug in breast milk should be monitored for possible side effects such as poor suckling or irritability.

References:

1. Bennett PN. Drugs and human lactation (2nd ed), 1996
2. Gardiner SJ, Begg EJ. Prescriber update: May 2001 (www.medsafe.govt.nz).
3. Drugdex, Micromedex
4. Briggs GG *et al.* Drugs in pregnancy and lactation (6th ed), 2002
5. Medline 1966 - 2002
6. Embase 1988 - 2002
7. Ward RM *et al.* Pediatrics 2001; 108(3): 776-89
8. Dollery C. Therapeutic Drugs (2nd ed), 1999
9. De Gezelle H *et al.* Acta Obstetrica et Gynecologica Scandinavica 1979; 58(5): 469-72 [as per abstract].

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