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SAFETY OF AZATHIOPRINE, CICLOSPORIN & PREDNISONE IN BREASTFEEDING

Question:
What is the safety of azathioprine, ciclosporin and prednisone during breastfeeding? These have been taken throughout pregnancy.

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 (e.g. 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].

Azathioprine is metabolised to 6-mercaptopurine (6-MP) which is subsequently metabolised to several active metabolites including 6-thioguanine nucleotides which are responsible for cytotoxicity and 6-methylmercaptopurine which may contribute to reactions such as pancreatitis[3].
There are limited data describing the distribution of azathioprine or its metabolites into milk[1,4-6]. In one study, the dose that a suckling infant would ingest in a day was a maximum of 0.1% of the weight-adjusted maternal daily dose[1]. This dose was calculated as azathioprine equivalents from measured 6-MP concentrations. Another study suggested the infant would ingest 1.2% of the maternal dose (weight-adjusted)[7]. Short-term observations in three infants exposed via breast milk did not reveal any adverse effects[1]. Failure to measure the concentrations of the active metabolites renders assessment of azathioprine's safety in lactation extremely difficult because considerable interindividual variability in metabolite concentrations will exist secondary to inherited differences in enzymes that metabolise 6-MP[3].

Azathioprine has been ingested by other women during breastfeeding without measurement of drug concentrations in milk. Two women opted to breastfeed while receiving azathioprine 75 and 100 mg/day. The infants were reported to have normal blood counts and growth rates, and no increase in infections[1]. Six other women breastfed their infants while receiving azathioprine (and ciclosporin) and were reported to have infants that developed as expected at a 12-36 month follow-up[8].

Prednisone is metabolised in the liver to the active metabolite, prednisolone. In one study, the amount of prednisolone a suckling infant would ingest in a day was an average of 1.9% (maximum 3.6%) of the weight-adjusted maternal daily dose [1]. Many authors consider that short courses of relatively low doses of prednisone (e.g. < 20mg/day) are compatible with breastfeeding[1,2,9]. With higher doses or prolonged courses, there may be the potential for adrenal suppression in the infant, particularly in the case of prematurity.

Ciclosporin: Several groups have advocated that ciclosporin should be avoided during breastfeeding because of its inherent toxicity [1,4]. One woman ingesting ciclosporin 6mg/kg/day breastfed her child without evidence of adverse outcomes. At five weeks of age, the infant's ciclosporin concentration was < 3 mcg/L while the simultaneous maternal trough concentration was

85-fold higher at 260 mcg/L[10]. On average, the infant received approximately 1.5% of the maternal dose, weight-adjusted.

Milk to plasma concentration ratios of 0.31, 0.40 and 0.17 have been reported in mothers who were lactating but not breastfeeding their infants[4]. The approximate dose of ciclosporin that an infant would ingest via breast milk would be approximately 0.018mg/kg/day if the following assumptions were made:
a) infant milk ingestion of 0.15L/kg/day
b) the M/P ratio = 0.4 ('worst-case' scenario)
c) the maximum therapeutic plasma concentration was 300mcg/L for a 5mg/kg/day maternal dose
Assuming a maternal weight of 60kg, the amount of drug ingested by the infant would be less than 0.01% of the maternal dose (weight-adjusted). If a paediatric dose of 3mg/kg/day is assumed (being at the minimum end of the dose range for maintenance doses), the comparative amount ingested by the infant through breast milk would be 0.6% of the paediatric treatment dose.

Nyberg *et al.,* [8] prospectively followed 7 mother:child pairs exposed to ciclosporin throughout pregnancy and breast feeding. Although the data available in the paper is limited, they found the maximum dose that the infant ingested was 0.65% of the maternal dose (weight-adjusted), while the average exposure was around 0.15% (assuming maternal dose of 200mg/day). None of the infants had detectable ciclosporin concentrations from random blood samples (limit of detection = 30mcg/L). There were no apparent side effects in the infants[8].

Thiagarajan *et al.,* [11] described a woman who ingested ciclosporin, prednisone and azathioprine during pregnancy and commenced breastfeeding soon after delivering a 1.8kg baby at 34 weeks' gestation. The infant was exclusively breastfed for the first 10.5 months of life. Ciclosporin was not detected in random infant blood samples taken on five occasions between 23 days and 10.5 months post-partum (limit of detection < 25mg/L). The infant dose (calculated from the highest of three breast milk concentrations taken at an unknown time in the dosing interval) was around 0.4%. No adverse effects were detected in the breastfed infant.

Conclusions:

Infant exposure to azathioprine and 6-MP appears to be low via breast milk. Unfortunately, studies have not addressed the transfer of 6-mercaptopurine's active metabolites. Infant exposure to ciclosporin also appears to be very low. If the infant has been exposed to these agents in utero, then exposure via breast milk is likely to be neglible by comparison. However, the relative risks must be considered with respect to the benefits of breastfeeding and the potential unknown risks of ongoing exposure to low doses of these agents e.g. growth retardation, carcinogenicity.
Prednisone is usually considered safe in breastfeeding when maternal doses are less than 20mg/day. The half-life of prednisolone is around 3 hours suggesting that infant exposure may be approximately halved if maternal drug ingestion occurs just after a feed, and breastfeeding is withheld for approximately 3-4 hours post ingestion.

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