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SAFETY OF PETHIDINE IN BREASTFEEDING

Question:
A woman has been taking pethidine 300-400mg daily long-term while fully breast-feeding a 12 month old infant. Is this safe?

Answer:
There has been some controversy surrounding the safety of pethidine in breastfeeding with some authors advising against its use[1,2] and other suggesting that it may be compatible with breastfeeding[3].

It has been estimated that on average, a breastfed infant will receive <3.5% of a maternal pethidine dose, after adjusting for the difference in body weight[4,5]. Using the maximum breast milk concentrations reported in these studies, and assuming a maternal weight of 60kg and infant milk ingestion of 0.15L/kg/day, we calculated the maximum weight-adjusted maternal dose to be 3.7%[4] and 13.5%[5] (worse-case scenario).
Under most circumstances, a drug is considered relatively 'safe' in breastfeeding if the weight-adjusted infant dose is less than 10% of the weight-adjusted maternal dose. This implies that on average, pethidine should not be problematical in breastfeeding. However, it should be noted that these estimations of infant exposure do not account for exposure to the pharmacologically active metabolite, norpethidine.
It is assumed that in both studies outlined above, the maternal dose of pethidine was administered parenterally. The oral availability of pethidine is approximately 0.5 (50% of an oral dose will reach the systemic circulation) indicating that infant exposure (described relative to the maternal dose) will appear lower when the maternal dose is administered orally.
No comment was made regarding adverse events in the breastfed infant[5]. However, greater neurobehavioural depression was reported to occur in neonates receiving breast milk from mothers on pethidine patient-controlled analgesia (PCA) compared with morphine PCA[6].

In general, we consider that administration of a standard single dose of pethidine to a breastfeeding woman is not likely to be problematical due to relatively low infant exposure. However, with repeated dose administration, there is the possibility of accumulation of the active metabolite of pethidine, norpethidine (half-life = 15-20 h in adults; 63 h in neonates)[4,7]. This is more likely to occur in the presence of renal impairment, or immature kidneys (e.g. in neonates)[7].
Accumulation of norpethidine may result in excitatory neurological side effects including termor, myoclonus and seizures[1]. These adverse effects have most commonly been documented in individuals with renal impairment, or those on PCA [1]. Other factors that are suggested to predispose to neurotoxicity are high pethidine doses, co-administration with phenothiazines or with drugs that induce hepatic metabolism (e.g. carbamazepine) which may increase conversion of pethidine to norpethidine[7].

Discussion:
Short-term administration (e.g. single dose) of pethidine would not be expected to be problematical due to low transfer into breast milk. However, repeated dose administration may be associated with accumulation of the neurotoxic metabolite in both the mother and her breastfed infant. Therefore we

would advise that this agent is not used long-term during breastfeeding. Indeed, we would not recommend against its long-term use in any individual, lactating or otherwise.

References:

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