

Which antidepressants are safe to use in breast-feeding mothers?

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As postpartum depression can occur in up to 10% of mothers, antidepressants will often be required in mothers who are breast-feeding. The judicious use of antidepressants is important since all psychotropic drugs cross into the breast milk. Drug excretion into breast milk occurs primarily by passive diffusion. Small, highly lipid soluble, unionised drugs diffuse more rapidly than other drugs. It must be remembered, however, that for those drugs with a high volume of distribution, such as the highly lipid soluble drugs, most of the drug is outside the plasma compartment, leaving only a small proportion free to transport from plasma to milk. Also, most lipophilic drugs are concentrated in hind milk which is richer in fat than fore milk. All of the antidepressants are highly lipid soluble with large volumes of distribution.

Studies have shown that imipramine and its metabolite desipramine produce breast milk concentrations similar to those found in plasma (Sovner & Orsulak, 1979). However, assays of samples of infants' serum taken after steady state has been achieved in the mother failed to detect the parent compound or its metabolite (Stancer & Read, 1986). This could indicate many things including an increased volume of distribution in the infant or it may simply reflect that the assay method was not sensitive enough. Whatever the reason blood levels appear to be too low to cause problems: a separate cohort of imipramine breast-fed babies was observed for a period of up to 28 months without any adverse effects being noticed (Misri & Sivertz, 1991).

Amitriptyline and its metabolite nortriptyline have also been examined. Both drugs have been found in higher concentrations in milk than in the plasma of lactating mothers. It has been estimated that the baby of one patient received approximately 1% of the mother's dose (Brixen-Rasmussen *et al.*, 1982). The

infant showed no clinical signs of drug activity and amitriptyline and nortriptyline could not be detected in the infant's serum.

There are little data on the use of clomipramine in breast-feeding. In one case report it was suggested that the infant received as much as 3.7% of the mother's dose (Pons *et al.*, 1994). The active metabolite was not included in this calculation. A small prospective study of four nursing mother-infant pairs (Wisner *et al.*, 1995) found extremely low levels of clomipramine and its metabolites in the infants' serum and no adverse effects were detected in the infants.

A metabolite of doxepin, n-desmethyldoxepin, appears to accumulate in infants. Although the amount in breast milk is small there is a risk that severe drowsiness and respiratory depression can occur (Matheson *et al.*, 1985). It has been suggested that if this is extrapolated to other tricyclic antidepressants, tricyclics with short half-lives (including active metabolites) are a better option: accumulation is less likely to occur.

If we consider the new antidepressants, it appears that only 0.06% of a single 300 mg dose of moclobemide is excreted unchanged in the milk over a 24 hour period (Pons *et al.*, 1990). The authors concluded that an average 3.5 kg breast-fed neonate would be exposed to approximately 1% of the maternal dose on a mg/kg basis. It seems unlikely that this would be hazardous to suckling infants, but this was only a single dose study and infants were not followed up.

The selective serotonin reuptake inhibitors (SSRIs) are all lipophilic and so likely to be excreted into breast milk. For fluoxetine the milk to plasma concentration is about 0.3 and, for its active metabolite norfluoxetine, it is 0.2 (Pons *et al.*, 1994). The dose that is ingested by the infant is expected to be 3.2% (includes active metabolite) of the maternal dose on a mg/kg basis. There is little clinical information available on the SSRIs but an infant whose

mother was started on fluoxetine suffered no untoward effects, gained weight and met the usual developmental milestones (Isenberg, 1990). An infant whose mother was taking fluvoxamine also showed no adverse effects (Wright *et al*, 1991). For fluvoxamine the milk to plasma ratio is 0.3 and it has been suggested that the baby would ingest only about 0.5% of the maternal intake. Because of the long elimination half-life of fluoxetine and its metabolite, fluoxetine should perhaps be avoided in mothers who breast-feed.

Concentrations of paroxetine in breast milk, after a single 50 mg dose are similar to those found in plasma (Kaye *et al*, 1989). It might therefore be expected that less than 1% of the daily dose would be transferred to a breast-feeding infant when the drug is at steady state.

As most of the antidepressants pass into breast milk in approximately equal concentrations as that seen in maternal plasma, the infant will be exposed to considerably less drug (perhaps 0.001–0.01 times) than that to which the mother is exposed. Exposure to small doses over a long period of time could lead to accumulation as the baby's renal and liver function are not fully developed. The developmental behavioural effects of antidepressants have also not been studied widely and we still do not know what subtle effects take place on the newborn's neurotransmitter system and whether there could be substantial effects on central nervous system development.

There have been no systematic studies performed in breast-feeding mothers and most of the literature available relies on single case presentations. As there are more data available on the older tricyclics such as imipramine and amitriptyline, they remain the preferred drugs in mothers who breast-feed. The benefit of drug therapy must outweigh the potential risks to the infant and close, long-term monitoring of the infant is essential. Antidepressants should never be given to mothers breast-feeding infants who were born premature or who have any signs of hepatic or renal impairment.

Recommend in breast-feeding

Amitriptyline
Imipramine

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