

Q&A 251.3

Management of depression in breastfeeding mothers – are tricyclic antidepressants safe?

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Background

Tricyclic antidepressants (TCA) are effective for the treatment of moderate to severe depression, anxiety disorders and neuropathic pain (1).

Although tricyclic antidepressants have been prescribed for longer, most recent clinical data on use of antidepressants in lactation has been for selective serotonin reuptake inhibitors (SSRIs). Because of concerns about toxicity, tricyclics have been prescribed less often than SSRIs for post natal depression (2). Most tricyclic antidepressants have a higher fatal toxicity index than SSRIs (3). There is no clinically significant difference in effectiveness between SSRIs and TCAs in the management of depression (1,4). Choice of therapy should be based on individual patient requirements (1).

Answer

Tricyclics and related compounds (mianserin and trazodone)

All tricyclic antidepressants, except doxepin, can safely be given to a woman who is breastfeeding provided the infant is full term, healthy and his or her progress is monitored. The non-sedating agents imipramine and nortriptyline are preferred, if clinically appropriate (4).

The limited evidence available suggests there is no short-term toxicity to the infant after exposure to tricyclic antidepressants, except doxepin, via breast milk (5). Few long-term follow-up studies of breastfed infants whose mothers were treated with antidepressants have been published. However, no long-term developmental effects on the infant have been demonstrated in available data (6,7).

The ideal TCA for breastfeeding mothers is one that is non-sedating, has a short half-life, has reduced antimuscarinic effects, has no active metabolites, is highly protein-bound, and which has been studied clinically in pregnancy and in women who breastfeed (8). Imipramine and nortriptyline most closely meet these criteria. Lofepramine has a lower potential for antimuscarinic effects, but no quantitative studies on passage into breast milk have been conducted (8). Half lives of tricyclic antidepressants are given in Table 1. Sedating tricyclic antidepressants are listed by the British National Formulary as amitriptyline, clomipramine, dosulepin (dothiepin), doxepin, mianserin, trazodone, and trimipramine. Those with less sedative properties include imipramine, lofepramine, and nortriptyline (1).

The evidence base for the use of TCAs in lactation consists mainly of case studies which confirm that TCAs are excreted in higher concentrations in hindmilk than foremilk and the milk/maternal plasma ratio exceeds one (6).

Although data have been derived from single case reports or small studies, estimates of the amount of TCA ingested by an infant via breast milk are of the order of 0.2-4% of the weight adjusted maternal daily dose (9).

Quantitative studies of levels of tricyclic antidepressants in breast milk are available for amoxapine, amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline [8,10] and the related agent trazodone [11]. Some studies in which infant serum levels were also monitored generally showed levels below the limit of detection [8,10]. Tricyclic antidepressants undergo substantial first-pass metabolism. Thus, even though the ingested daily dose of most TCAs is approximately 1% of the weight adjusted maternal dose, the amount absorbed into the infant's systemic circulation is likely to be substantially less (12).

Data available for individual agents are summarised below:

Amitriptyline

Quantitative data on the passage of amitriptyline into human milk are limited to 6 mother-infant pairs. The maternal doses in these studies ranged from 25 – 175 mg daily (13-17). Milk levels were recorded up to 14 weeks postpartum. Amitriptyline levels ranged from 12 – 151 micrograms/l and that of the metabolite, nortriptyline, from 20 – 87 micrograms/l. In one case report, peak milk levels of amitriptyline were seen at 1.5 hours post dose (15). In the majority of cases where it was measured, infant serum levels of amitriptyline and nortriptyline were below the limit of detection (5 micrograms/l and 15 micrograms/l respectively). In one instance, the infant had a serum level of amitriptyline of 7.5 micrograms/l when the maternal dose was 100 mg daily (17). Estimated infant intakes via breast milk have been calculated as 35 - 50 micrograms/kg/day after maternal doses of 100 – 175mg a day (13,16). No adverse effects were noted in any of the exposed infants (13-17).

Clomipramine

Limited data are available for 11 mother-infant pairs with maternal doses between 75 and 175 mg/day [17-21]. Considerable variation in milk levels was seen with values ranging from 32 – 624 micrograms/l. Infant plasma levels were measured in four of the five studies. In most cases, infant plasma levels were undetectable but reached 3.2 – 5.5 micrograms/l in two infants. The same study noted normal development using the Bayles Scale of Infant Development in the first 18 months of life (17). The risk of drug accumulation in neonates with immature excretory functions is underlined by the recording of a half-life of clomipramine of 92 hours in the first week of life compared with a maternal value of 25 hours (19). No adverse effects attributable to clomipramine via breast milk have been reported although neonatal withdrawal symptoms – jitteriness, respiratory distress and hypotonia - were seen in a neonate for 6 days after delivery. Breastfeeding was not started until day 7 (19). Calculated ingestion of clomipramine via breast milk was 0.4% of the maternal dose of 150mg (19). Infant exposure has also been calculated as 1.3 – 2.2% of the weight adjusted maternal dose (17,19).

The risk of drug accumulation in neonates with immature excretory functions is underlined by the prolongation of the half-life of clomipramine by two to three times the adult value in the first week of life (19).

Desipramine

Limited data are available for 4 mother-infant pairs (17,21,22). Milk levels of up to 328 micrograms/l. have been reported (22). Infant serum levels were below the limit of detection (10 – 25 micrograms/l) (17,21,22). No adverse effects were reported in these infants.

Dosulepin (dothiepin)

Dothiepin appears in breast milk in concentrations ranging from 11 – 475 micrograms/l after maternal doses of 25 – 225 mg daily (23,24). Estimated infant intake via milk has been calculated as 7.8 micrograms/kg/day or 4.4% of the weight adjusted maternal dose (9). Serum levels of dothiepin measured in 5 infants were less than 10 micrograms/l (24).

A study involving 15 mother-infant pairs assessed measures of cognitive and social development at 3 and 5 years in infants exposed to dothiepin via breast milk. No adverse effects were seen in comparison to a control group of 36 non-depressed mothers and their infants (25). Similarly, no adverse effects were seen in 8 breastfed infants following chronic maternal use of dothiepin (24).

Doxepin

Small, but significant amounts of doxepin and its metabolite, desmethyldoxepin, are excreted into breast milk (9). Limited data from 3 mother-infant pairs indicate that milk levels range from 7 – 60 micrograms/l for the parent drug (26,27,28). An infant ingestion of doxepin plus metabolite of 2.2% of the maternal dose of 2.4 mg/kg/day would therefore be expected (26).

Poor sucking and swallowing, muscle hypotonia, drowsiness and vomiting were reported in a 9 day old breastfed infant whose mother was taking doxepin 35mg daily (28). The amount of doxepin and

N-desmethyldoxepin ingested via breast milk was estimated to be 10-20 micrograms/kg/day or 2.5% of the weight-adjusted maternal dose. Infant-serum level of doxepin was approximately 10micrograms/l. Adverse effects subsided within 48 hours of cessation of breastfeeding.

A single case report has described an 8 week old infant who developed profound respiratory depression following an increase in maternal dose of doxepin from 10mg daily to 25mg three times daily (27). The infant was hospitalised but recovered after cessation of breastfeeding. Symptoms developed 4 days after increase of the maternal doxepin dose.

Imipramine

Published data are available for 10 mother-infant pairs (17,21,29,30,). Milk levels ranged from "a trace" to 622 micrograms/l with maternal doses of 50 – 200 mg daily. In four breastfed infants, no detectable drug or metabolite (desipramine) were found in infant serum (21). No adverse effects were reported in any of the breastfed infants (17,21,29,30,).

Lofepramine

No data are available on the passage of lofepramine into human milk. The drug has theoretical advantages for use in lactation of reduced anticholinergic effects, a short half life of 5 hours and high protein binding (99%) (31,32). An alternative agent for which clinical data in lactation exist is preferred.

Mianserin

Because of the need to perform regular blood counts for patients on mianserin (1), its use in breastfeeding mothers is not advised. A single case report describes milk levels of 20 – 80 micrograms/l after maternal doses of mianserin of 40 – 60 mg daily in two breastfeeding mothers. Neither mianserin nor its major metabolite were detectable in infant serum in the one infant where this was measured. Estimated infant intake of mianserin via milk was calculated as 0.5 – 1.4% of the maternal dose (33).

Nortriptyline

Measurements of nortriptyline in human milk are limited to a single case report (34). Milk levels ranged from 90 – 404 micrograms/l in a mother receiving nortriptyline 75 mg daily and studied between 4 and 48 days postpartum. Infant serum levels were not measurable (35,36). No adverse effects were observed in any of the breastfed infants followed for periods of up to 120 days postpartum (21,34-36).

Trazodone

A peak milk level of trazodone of 100 micrograms/l was seen in 6 lactating mothers given a single oral dose of 50 mg (11). The estimated infant dose via milk was calculated as < 5micrograms/kg in a 12 hour period or 0.36% of the weight adjusted maternal single dose of trazodone.

Trimipramine

No data are available on the passage of trimipramine in breast milk. An alternative agent for which clinical data in lactation exist is preferred.

Table 1. Adult half-lives of some tricyclic antidepressants (9)

| TRICYCLICS | Half-life |
|---------------|-----------------|
| Amitriptyline | 31-46 hours |
| Clomipramine | 19-37 hours |
| Doxepin | 8-24 hours |
| Dosulepin | 14.4-23.9 hours |
| Imipramine | 8-16 hours |
| Nortriptyline | 16-90 hours |
| Trimipramine | 23 hours (37) |

Summary

- ◆ Estimates of the amount of TCA ingested by an infant via breast milk are of the order of 0.2 - 4% of the weight adjusted maternal daily dose.
- ◆ With the exception of doxepin, no adverse effects have been noted in breastfed infants exposed to tricyclic antidepressants via breast milk.
- ◆ All tricyclic antidepressants, except doxepin, can safely be given to a woman who is breastfeeding, provided the infant is full term, healthy and his or her progress is monitored.
- ◆ The non-sedating agents imipramine and nortriptyline are preferred, if clinically appropriate.
- ◆ Risks can further be minimised by using a single daily dose of a TCA and breastfeeding immediately before drug administration. For very young infants feeding frequently, one bottle feed can be substituted to avoid drug peak milk levels at 1-3 hours post dose.
- ◆ Use of other sedating agents in the mother should be avoided since sedation can be additive.
- ◆ Infants should be monitored for drowsiness or other behavioural changes.

Limitations

Only limited data are available for the passage of tricyclic antidepressants into breast milk. The majority of studies are single case reports and many were conducted before 1990. The above outline is provided for general guidance. Many decisions as to the safety of antidepressant regimens in breastfeeding mothers will need to be taken on a case-by-case basis, particularly if there are unusual circumstances e.g. infant morbidity, requirement for high doses, concurrent medication etc. In these instances, further advice can be sought from the UK Drugs in Lactation Advisory Service provided by the Trent Medicines Information Service or the West Midlands Medicines Information Service.

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Search strategy

Please specify which of these are used if appropriate, (whether or not all of them yielded useful information) and add others if necessary:

- UK Drugs in Lactation Advisory Service – in-house data-base
- Medline and Embase: Standard UKDILAS search pattern found at <http://www.ukmi.nhs.uk/activities/specialistServices/default.asp?pageRef=2>
Drug names: :amitriptyline: clomipramine: desipramine: dothiepin: doxepin: imipramine: lofepramine: mianserin: nortriptyline :trazodone :trimipramine.
antidepressive agents-tricyclic (Medline;), tricyclic antidepressant agent (Embase)
- Medications and Mothers' Milk Online (Medilact) amitriptyline, lomipramine, dothiepin, doxepin, imipramine & nortriptyline monographs)
- Clinical Knowledge Service (antenatal and postnatal depression)
- SIGN website (postnatal depression and puerperal psychosis)
- Electronic Medicines Compendium (lofepramine)
- US National Library of Medicine Lactmed (amitriptyline, clomipramine, dothiepin, doxepin, imipramine & nortriptyline monographs)
- National Institute for Health and Clinical Excellence website (antenatal and postnatal mental health)