Q&A 253.3

Management of depression in breastfeeding mothers – Are reboxetine, venlafaxine, duloxetine, mirtazapine, agomelatine and MAOIs safe?

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Background

The British National Formulary lists the major classes of antidepressants as tricyclics, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors (MAOIs) (1). A number of antidepressants do not fit readily into these categories:

- Duloxetine – a serotonin and noradrenaline reuptake inhibitor (SNRI)
- Mirtazapine – a presynaptic alpha 2 adrenoreceptor antagonist
- Reboxetine – a selective inhibitor of noradrenaline uptake
- Venlafaxine – a serotonin and noradrenaline reuptake inhibitor
- Agomelatine – melatonin receptor agonist and selective serotonin-receptor antagonist

Monoamine oxidase inhibitors may be classified as having a reversible action (moclobemide) or an irreversible action (phenelzine, tranylcypromine).

The drugs listed above are not considered first line choices for the treatment of depression (2,3). If initial treatment with a selective serotonin reuptake inhibitor (SSRI) is ineffective or not tolerated, choices for an alternative include mirtazapine, moclobemide and reboxetine (2). Venlafaxine, duloxetine, reboxetine, agomelatine and moclobemide are licensed for use in major depressive illness (4-8). MAOIs have dangerous interactions with some foods and drugs and should be reserved for use by specialists (1).

Answer

Experience of the use of MAOIs, reboxetine, venlafaxine, mirtazapine, agomelatine and duloxetine in lactation is very limited and they are not considered as first line antidepressants in breastfeeding women. Clinical experience for the individual drugs is summarised below.

Reboxetine

In one small study in 4 mother-infant pairs, multiple samples were taken at steady state (9). The mothers were taking reboxetine 4-10 mg daily for postnatal depression. Infant intake via milk was calculated as 1.7 micrograms/kg/day which equated to 2% of the weight adjusted maternal dose. No adverse effects were seen in any of the infants. Three of the four infants met normal developmental milestones. The fourth infant had developmental problems but these were not considered to be associated with maternal reboxetine therapy. Reboxetine was detected in the sera of all 4 infants in amounts between 2.3 – 5 micrograms/l (9).

Venlafaxine

Several studies have identified venlafaxine and its active metabolite, desmethylvenlafaxine, in breast milk in a total of 39 mother-infant pairs (10 -16). Peak levels of venlafaxine in milk were seen 1 – 3 hours post dose after use of the standard formulation and 5.7 (venlafaxine) and 7.7 hours (metabolite) after the sustained release preparation (10). Estimated infant intake via milk ranged from 3.5 – 9.2% of the maternal weight adjusted dose for venlafaxine plus metabolite (10 – 13,16). In studies where infant sera was analysed, venlafaxine was generally undetectable (11,14) but was present in a concentration of 5 micrograms/l in one infant (11). Desmethylvenlafaxine was present in the majority of infant sera at values up to 38 micrograms/l (11,17,18).

In 21 cases of infants exposed to venlafaxine via breast milk, two infants had decreased weight gain but normal growth (11). No adverse effects on mental, psychomotor or behavioural development were noted in periods up to 13 months (11,14,16).

Venlafaxine via breast milk was thought to have ameliorated neonatal withdrawal symptoms in one infant whose mother had been taking the drug at a dose of 375 mg daily throughout pregnancy. At 2 days postpartum, the infant had symptoms of lethargy, poor suckling and dehydration. These resolved over one week with continued breastfeeding (13).

One mother who was nursing a 10.3 month old infant reported that her milk let down took longer after starting venlafaxine one month earlier (11).

Duloxetine

Quantitative data on the passage of duloxetine into breast milk are limited to a study in 6 lactating women who were taking 40 mg 12 hourly over the 3.5 day study period (19) and two case studies (20,21). The women stopped breastfeeding during and after the study (19). Estimated infant intake via milk was calculated as 2 micrograms/kg/day or 0.14% of the maternal dose. This amount may be even lower as duloxetine is unstable in the acid conditions of the infant's stomach (22). In two breastfeeding mothers taking duloxetine 60 mg daily, estimated infant intake via milk was calculated as 7.1 and 7.6 mcg/kg/day or 0.82% and 0.81% of the weight adjusted maternal dose respectively (20,21).

Mirtazapine

Published data are limited to 10 mother-infant pairs where the maternal doses ranged from 22.5 to 120 mg mirtazapine daily (23-25). The concentrations of mirtazapine and its desmethyl metabolite were greater in hindmilk than in foremilk (23,24). Infant intake via milk was estimated as 8 micrograms/kg/day for mirtazapine and 3 micrograms/kg/day for the metabolite (24). In this study in 8 mother-infant pairs, it was calculated that infants would ingest an average 1.9% (0.7 – 3.1%) of the weight adjusted maternal dose (24). Mirtazapine has been detected in sera of breastfed infants in amounts up to 4 ng/ml (23, 24). A higher value of 10 ng/ml was seen in a single case report (25).The mother noted that the infant slept better through the night than its siblings. No adverse effects have been reported in infants exposed to mirtazapine via breast milk (23-26).

MAOIs

There are no data relating to the passage of first generation MAOIs (tranylcypromine and phenelzine) into breast milk and no data to support their safe use in lactation. Other antidepressants are preferred in breastfeeding mothers (3).

Unlike these drugs, moclobemide is a selective and reversible inhibitor of the MAO-A isoenzyme and does not have the same potential for food and drug interactions (8, 22).

Only very limited data are available on the use of moclobemide in lactation. Six lactating women received a single dose of moclobemide 300 mg. Peak milk levels of moclobemide and its major metabolite were seen 3 hours post dose and neither the parent drug not the metabolite were detectable in milk after 24 hours (27). The estimated infant exposure to moclobemide via breast milk for a neonate weighing 3.5 kg was calculated as 50 micrograms/kg/day - approximately 1% of the weight adjusted maternal dose. There are no data for steady state conditions. The infants of four breastfeeding women who took moclobemide in doses of 300 – 1200 mg/day achieved developmental milestones in the normal range at 12 months (28). Although an alternative drug for which more data exists is preferred, the short half life of 2 hours and apparent low passage into milk suggest that untoward effects in the breastfed infant are unlikely (22).

Agomelatine

Published data on the use of agomelatine in lactation are limited to a single case report (29). Agomelatine 25 mg daily was added to quetiapine 200 mg daily in a mother suffering from postpartum psychosis and depressive syndrome. Breast milk levels were measured pre-dose and up to 6 hours post dose on the first 3 days of treatment with agomelatine. A peak level of 2 mcg/l was seen 120

minutes post dose on day 1. Levels of the drug were below the limit of detection of < 0.1 mcg/l at 240 minutes on all 3 days. Peak levels in milk were seen between 1 and 2 hours post dose. Agomelatine has a short half-life of 1-2 hours and an absolute bioavailabilty of <5% at the therapeutic dose (7, 29). Further data are required to confirm the safety of the drug in lactation.

Summary

- Reboxetine, venlafaxine, duloxetine, mirtazapine, agomelatine and moclobemide are not considered first line antidepressants for use in breastfeeding mothers.
- Because of the absence of data on use in lactation and their potential to cause serious interactions with some foods and drugs, first generation MAOIs should be avoided in lactation.
- Limited data indicate that reboxetine, duloxetine and mirtazapine pass into milk in small amounts and estimated infant intake via milk has been calculated at values of up to 2% of the weight adjusted maternal dose. Values for venlafaxine are higher at 3.5 – 9.2%.
- Venlafaxine via breast milk may attenuate neonatal withdrawal symptoms where the drug is used close to term.
- Apart from two cases of reduced weight gain with venlafaxine, no adverse effects have been reported for infants exposed to reboxetine, duloxetine, mirtazapine,moclobemide or agomelatine.

Limitations

Data on the use of reboxetine, venlafaxine, duloxetine, mirtazapine, agomelatine and MAOIs in lactation are very limited.

The above outline is provided for general guidance only. 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, requirements 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 and the West Midlands Medicines Information Service.

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Search strategy

- 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:reboxetine, venlafaxine, duloxetine, mirtazapine,moclobemide, monoamine oxidase inhibitors (Medline), monoamine oxidase inhibitor (Embase), agomelatine

- Medications and Mothers' Milk Online (Medilact): venlafaxine, duloxetine, mirtazapine and moclobemide monographs)
- US National Library of Medicine Lactmed database: phenelzine, tranylcypromine, duloxetine and venlafaxine monographs
- SIGN website (postnatal depression and puerperal psychosis)
- Electronic Medicines Compendium (Cymbalat, Manerix, Edronax, Efexor and Valdoxan SPCs)
- National Institute for Health and Clinical Excellence website (antenatal and postnatal mental health and depression guidelines).