

Are atypical antipsychotics safe during breast feeding?

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Background

Unlike first-generation antipsychotic drugs which act predominantly by blocking dopamine D2 receptors, second-generation antipsychotics (SGAs - also known as atypical antipsychotics) act on a range of receptors (1). SGAs are less likely to cause extrapyramidal symptoms (EPS) and tardive dyskinesia but this may be balanced by a greater risk of metabolic effects. The main difference between the two groups is the size of the therapeutic index for acute EPS. This value is very narrow for haloperidol whereas it is wide for olanzapine (2).

In the UK, seven SGAs are licensed for the treatment of schizophrenia. Some are licensed for additional indications such as manic episodes, bipolar disorder, schizoaffective disorder, psychotic disorders associated with Parkinson's disease and aggression in moderate to severe Alzheimer's disease (1).

The NICE 2009 guideline for schizophrenia no longer recommends prescribing SGAs as first line treatment but suggests that benefits and side effect profiles of individual drugs should be discussed with the patient to inform choice (3).

Answer

Amisulpride, aripiprazole, clozapine, olanzapine, quetiapine and risperidone have all been detected in breast milk (4). Although no data are available for the use of paliperidone during breastfeeding, it is the active metabolite of risperidone. 9-hydroxyrisperidone has been detected in breast milk following maternal use of risperidone (5, 6). Infant intake of SGAs via milk has been estimated between 0.09% (quetiapine) (7) and 10.7% (amisulpride) of the weight adjusted maternal dose (8).

SGAs have relatively long half-lives: see Table 1 below. The long half-lives and reduced drug clearance, especially in neonates and young infants, can lead to drug accumulation and an increased risk of adverse reactions following chronic exposure to the drugs via breast milk (9).

Table 1.

Adult half-lives of atypical antipsychotics (10-16)

SGA	Half-life
Amisulpride	12 hours
Aripiprazole	75 - 146 hours
Clozapine	12 hours
Olanzapine	32 - 52 hours
Paliperidone	23 hours
Quetiapine	7 hours
Risperidone	3 hours (active metabolite - 24 hours)

Adverse effects have been reported in breastfed infants exposed to clozapine (17) and olanzapine (18, 19). Infant sedation has been described when breastfeeding mothers were receiving co-therapy of SGAs with benzodiazepines (20,21).

Since dopamine inhibits prolactin release, all antipsychotics acting as dopamine antagonists can cause measurable changes in serum prolactin but in some cases, levels do not exceed the normal range. The increase in serum prolactin is probably dose-related (2). Prolactin levels in mothers with established lactation may not affect the ability to breastfeed (22). A prolonged and elevated prolactin level above baseline non-lactational levels is required for sustained milk production. The volume of milk secreted is not directly related to the plasma prolactin level. (23). One possible case of failure to establish lactation has been reported in a woman taking aripiprazole (24).

Neonates exposed to antipsychotics near term may exhibit withdrawal symptoms including agitation, hypertonia, tremor, somnolence, respiratory distress or feeding disorders (10).

Amisulpride

Data on the use of amisulpride during lactation are limited to two mother-infant pairs (8,25,). Infant intake via breast milk has been estimated as 183 mcg/kg daily or 6.1% of the maternal weight-adjusted dosage after a maternal daily dose of 200 mg (25) and 534 mcg/kg daily or 10.7% of the maternal weight-adjusted dosage after a maternal daily dose of 400 mg (8). Infant serum amisulpride concentration 3.1 hours after the mother's daily dose of 200 mg was 4 mcg/L or 3.9% of the maternal serum concentration (25). No adverse effects in breastfed infants have been reported to date.

Aripiprazole

Only limited data are available from three mother-infant pairs (26, 27, 28). After maternal daily doses of 15 - 18 mg daily, milk levels for aripiprazole of 13 - 14 mcg/L (26) and 38.7 mcg/L (28) were recorded. Milk:plasma ratios have been estimated between 0.04 (27) and 0.2 (26). A case report noted that milk drug levels taken 30 minutes before the maternal dose and at 4 and 10 hours post dose were undetectable (< 10 mcg/L) 27 days post-delivery. The authors estimated that a fully breastfed infant would receive less than 0.7% of the maternal weight-adjusted dosage (27). There are anecdotal reports of somnolence breastfed infants (29).

Clozapine

Quantitative data on the passage of clozapine into breast milk is based on a single case report (30). A milk clozapine level of 63.5 mcg/L was noted one day postpartum. At 3 days postpartum her dose was increased from 50mg to 100 mg daily, and at 7 days postpartum clozapine in milk was 115.6 mcg/L with a corresponding maternal plasma level of 41.4ng/ml. Limited data suggest that clozapine may accumulate in breast milk. The infant did not breastfeed.

In a group of 4 breastfed infants exposed to clozapine via breast milk, one infant experienced drowsiness and one infant experienced agranulocytosis possibly caused by clozapine (17). One female infant exposed to clozapine throughout pregnancy and lactation (up to 1 year) had a delay in speech development which was not normal until 5 years of age. The authors stated that this may have been due to exposure to the drug in lactation or pregnancy or may have been unrelated to maternal therapy (31). Women taking clozapine should not breastfeed (32).

Olanzapine

Limited information indicates that maternal doses of olanzapine up to 20 mg daily produce low levels in milk and undetectable levels in the serum of breastfed infants. Median infant intake of olanzapine has been estimated at 1.02% (33) in one study and 4% of the weight adjusted maternal dose in a single case report (34). A median peak milk level of 16 mcg/L occurred 5.2 hours (range 0.7 to 13.2 hours) after the dose in one study (33). A median milk:plasma ratio of 0.38 was noted in the same study (33). Olanzapine has been detected in the serum of breastfed infants whose mothers were taking olanzapine in some studies (35, 36). Isolated reports of adverse effects in breastfed infants exposed to olanzapine via milk have been reported (37). Somnolence, diarrhoea and nappy rash were reported in 1 infant and lethargy, poor sucking and shaking in a second (38).

Paliperidone

Although no data are available for the use of paliperidone during breastfeeding, it is the active metabolite of risperidone. Risperidone data indicate that the concentrations of paliperidone (9-hydroxyrisperidone) in breast milk are low, and amounts ingested by the infant are small (see below) (39).

Quetiapine

Published experience of the use of quetiapine in lactation is limited to 22 mother-infant pairs (40). Peak drug levels in milk have been recorded one hour post dose (7,41). Infant intake via milk has been estimated between 0.09% (7,41) and less than 0.5% (42) of the maternal weight-adjusted dosage. Very few adverse effects have been reported in breastfed infants. One case of infant sedation was noted but was attributed to co-therapy with mirtazapine and a benzodiazepine (20). In a group of six nursing mothers taking quetiapine in doses of 25 to 400 mg daily in addition to an antidepressant (usually paroxetine) for major depression postpartum, infants' development were tested at 9 to 18 months. Measurements were slightly low on the mental and psychomotor development scale in one infant and on the mental development scale in another. All other scores were within normal limits. The authors concluded that the low scores of the 2 infants were probably not caused by the drugs received by the infants in breast milk (43).

Risperidone

Limited information indicates that maternal risperidone doses of up to 6 mg daily produce low levels in milk (39). Estimated infant intake via milk has been estimated between 2.2 and 4.7% of the weight adjusted dose (5,6,44). No adverse effects have been reported in breast fed infants where the mother was receiving monotherapy with risperidone (39). Sedation was reported in one breastfed infant whose mother was taking risperidone in combination with flurazepam, clonazepam and bupropion (21).

Summary

- ◆ Only limited data are available on the use of SGAs during lactation.
- ◆ SGAs with the greatest evidence of safety for mother and infant should be considered first.
- ◆ Mothers receiving therapy with clozapine should not breastfeed.
- ◆ Estimates of infant ingestion of SGAs via breast milk vary between 0.09% and 10.7% of the weight adjusted maternal dose.
- ◆ Adverse reactions in breast fed infants have been reported after exposure to clozapine and olanzapine via breast milk. Sedation has been noted only when the mother was receiving co-therapy with benzodiazepines and some antidepressants.
- ◆ Risks can be minimised by using single daily doses and administering before the infant's longest sleep period. When necessary (e.g. with high dose therapy) for very young infants feeding frequently, one bottle feed can be substituted to avoid exposure to peak milk levels, where time to peak levels are known.
- ◆ Infants exposed to SGAs via breast milk should be monitored for sedation, poor feeding, behavioural effects, extrapyramidal symptoms and achievement of developmental milestones.
- ◆ Combined use with other sedating agents is best avoided as this increases the risks of drowsiness and poor feeding in the infant.
- ◆ Premature infants should not be exposed to antipsychotic medication via breast milk.

Limitations

Only limited data are available for the passage of atypical antipsychotics into breast milk. The majority of studies are single case reports or studies in small numbers of breast feeding mothers. Infant serum levels (as a more accurate measure of infant drug exposure) are often lacking. The above outline is provided for general guidance. Many decisions as to the safety of antipsychotic 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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