Q&A 395.1

Are first-generation antipsychotics safe during breast feeding?

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Background

The first-generation antipsychotic drugs (FGAs) act predominantly by blocking dopamine D_2 receptors in the brain. First-generation antipsychotic drugs are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin (1). The British National Formulary (1) classifies the phenothiazine derivatives into three groups:

- chlorpromazine, levomepromazine, and promazine, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.
- pericyazine and pipotiazine, generally characterised by moderate sedative effects, but fewer extrapyramidal side-effects than groups 1 or 3.
- fluphenazine, perphenazine, prochlorperazine, and trifluoperazine, generally characterised by fewer sedative and antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Butyrophenones (benperidol and haloperidol) resemble the group *3* phenothiazines in their clinical properties. Thioxanthenes (flupentixol and zuclopentixol) have moderate sedative, antimuscarinic effects, and extrapyramidal effects. Diphenylbutylpiperidines (pimozide) and the substituted benzamides (sulpiride) have reduced sedative, antimuscarinic, and extrapyramidal effects.

The Maudsley Prescribing Guidelines state that FGAs still play an important role in schizophrenia and offer a valid alternative to second generation antipsychotics where these are poorly tolerated or where FGAs are preferred by patients (2).

The BNF lists 13 FGAs as being available in the UK (1). Data on their use in lactation is limited and, for some agents, absent.

Answer

Chlorpromazine, haloperidol, perphenazine, sulpiride, trifluoperazine, flupentixol and zuclopenthixol have all been detected in breast milk (3). Infant intake of FGAs via breast milk has been estimated between 0.1% (perphenazine) (4) and 20.7% (sulpiride) (5) of the maternal weight adjusted daily dose. FGAs have relatively long half-lives (see Table 1). Long half-lives and reduced drug clearance, especially in neonates and premature infants, can lead to drug accumulation and an increased risk of adverse effects following chronic exposure to drugs via breast milk (6).When selecting a FGA for use in a breast feeding mother, a less sedating agent with a shorter half-life and data to support use in lactation is preferred. In the absence of clinical data for the use of FGAs in lactation, pharmacokinetic parameters may influence the choice of agent. These are summarised in Table 1.

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 (9). Prolactin levels in mothers with established lactation may not affect the ability to breastfeed (10). A prolonged and elevated prolactin level above baseline non-lactational levels is required for sustained milk production. However, sensitive and active lactocytes in the breast are also required for milk synthesis and insufficient milk production may be seen even in the presence of high prolactin levels (10).

TABLE 1. Pharmacokinetic properties of First Generation Antipsychotics (5,7,8,11,12)

Agent	Half life	Protein Binding	Oral bioavailability
Benperidol	7.65 hours		30-72%
Chlorpromazine	30 hours	90-95%	32-100%
Flupenthixol	35 hours	>95%	40%
Haloperidol	12-38 hours	92%	60%
Levomepromazine	15-30 hours		50%
Pericyazine	12 hours		
Perphenazine	9-12 hours	90-93%	60-80%
Pimozide	55 hours		>50%
Prochlorperazine	6-10 hours (single dose) 14 – 22 hours (repeated doses)	90%	12.5%
Promazine		"Extensive"	
Sulpiride	6 – 9 hours	40%	27 – 34%
Trifluoperazine	24 hours	90 – 99%	
Zuclopenthixol	20 hours	98%	49%

Neonates exposed to antipsychotics near term may exhibit withdrawal symptoms including agitation, hypertonia, tremor, somnolence, respiratory distress or feeding disorders (13).

Chlorpromazine

Chlorpromazine is detectable in the milk of some mothers during therapy, but levels appear not to correlate well with the maternal dose or serum level (10).Quantitative data for the passage of the drug into breast milk are available for 29 mother-infant pairs. Milk levels between < 5 mcg/L and 568 mcg/L have been recorded after maternal doses of chlorpromazine ranging from 50 – 1200mg daily (10). One older study from 1964 reported milk levels of 10-14 mg/L in a mother after a dose of 200 mg chlorpromazine. Different assay methods may affect the results obtained. One reviewer commented that older assay methods were insensitive and non-specific (10).

Metabolites may contribute to higher values obtained with non-specific methods (14).Chlorpromazine and its metabolites have also been detected in the urine of two breastfed infants whose mothers were taking the drug (14).Drowsiness and sedation has been reported in breastfed infants exposed to chlorpromazine via breast milk (15, 16), although co-medication with dichloralphenazone may have contributed to the symptoms in one case. Very limited long-term follow-up data indicate no adverse developmental effects when the drug is used alone (10). However, using it in combination with haloperidol can negatively affect development (14).

Flupentixol

Data on the use of flupentixol in lactation are limited to 7 mother-infant pairs (17, 18, 19,). Maternal doses ranged from 2 mg daily of flupentixol to 60 mg every 3 weeks of the decanoate salt. Milk levels of between 0.8 and 6.8 ng/ml were recorded between 4 and 48 days postpartum (17, 18, 19). One small study comparing data for chlorprothixene, flupentixol and zuclopenthixol noted that there was some relationship between lipophilicity and excretion into breast milk (19). Infant intake via milk has been estimated at 0.4 mcg/kg/day or 0.6% of the weight adjusted maternal dose (18). Serum levels

measured in one infant on days 6 &7 postpartum were recorded as <0.2 and < 0.3 mcg/l. No adverse effects in breastfed infants have been reported to date (20).

Haloperidol

Data from 15 mother-infant pairs shows that haloperidol is present in breast milk and has been found in serum and urine of infants exposed to the drug via breast milk (21).Limited information indicates that maternal doses of haloperidol up to 10 mg daily produce low levels in milk and do not affect the breastfed infant (21). Fore-milk levels ranging from < 1 mcg/L to 24.0 mcg/L were seen after maternal doses of 1 – 40 mg daily. (14) Correlation between breast milk levels and maternal serum levels was better than with maternal dose (14). Haloperidol has been found in the urine of breastfed infants (14, 22) and the serum of 4 breastfed infants after maternal doses of 5 – 20 mg daily (14).Three case reports (22, 23, 24) and one small study (14) involving 9 infants exposed to haloperidol via breast milk did not show any adverse effects on development in periods up to 18 months, and, in one case, at 8 years. A decline in developmental scores was found at 12 to 18 months of age in 2 infants of mothers taking both chlorpromazine and haloperidol (14).

Perphenazine

A single case study reported infant exposure to perphenazine via breast milk as 0.1 % of the maternal daily dose (16 - 24 mg). No adverse effects were seen in the infant over a 3.5 month period during which it was breast fed (4).

Sulpiride

Sulpiride is an antipsychotic drug used in doses of 400 – 800 mg daily for schizophrenia, however, several studies using smaller doses of 100 – 200 mg daily have found it to significantly increase prolactin levels and breast milk production in doses that do not produce overt neuroleptic effects on the mother (25).Sulpiride increases serum prolactin, but its clinical value in increasing milk supply is questionable. (26).Postpartum mothers are at a relatively high risk for postpartum depression and sulpiride can cause depression as a side effect. Therefore, sulpiride should probably be avoided in women with a history of major depression and not used for prolonged periods in any mothers during this time of high susceptibility (27).

Sulpiride is excreted into breast milk in rather large amounts (18% of the maternal weight-adjusted dosage in some cases) but blood concentrations in breastfed infants have not been evaluated (27). In one study, 20 women took sulpiride 50 mg twice daily by mouth to enhance milk production. Based on a single milk sample from each woman taken at 2 hours after the morning dose between the 3rd to the 7th day of therapy, the average milk level 970 mcg/L. This equates to an average maximum infant dosage of 146 mcg/kg/day or 8.7% (range 2 to 18%) of the weight-adjusted maternal dosage (27,28). No adverse effects have been reported to date in breastfed infants exposed to the drug via milk (27).

Trifluoperazine

A study in two nursing mothers taking oral trifluoperazine 5 and 10 mg daily respectively found that levels of the drug in milk were undetectable (< 1 mcg/L) (14). However, trifluoperazine was found to be present in infant serum of a breast fed infant aged 1.9 weeks whose mother was taking a daily dose of 10 mg. The authors stated that use of the drug during pregnancy may have contributed to this finding (29). No adverse effects were noted in two breast fed infants when maternal therapy with trifluoperazine was combined with clonazepam and valproic acid (29) or olanzapine 10 mg daily, paroxetine and procyclidine (30).

Two mothers taking trifluoperazine 5 and 10 mg per day orally breastfed their infants from 1 week and 8 weeks of age, respectively. Mental and psychomotor development were measured at various times up to 30 months of age and were found to be normal (14).

Zuclopenthixol

Limited data from two studies involving 7 mother-infant pairs and maternal oral doses of up to 50 mg daily or depot injections of 72 mg every 2 weeks reported low levels in breast milk and no detectable short-term adverse effects in the breastfed infants (31,32). Infant exposure via breast milk was calculated as 0.8 to 3 mcg/kg daily with the maternal doses given (14 - 24 mg daily) or 0.3 to 0.8% of the maternal weight-adjusted dosage for one mother-infant pair (32). No data are available on long term effects on infant development (33).

Summary

- Only limited data are available on the use of FGAs during lactation.
- Estimates of infant ingestion of FGAs via breast milk vary between 0.1% and 20.7% of the weight adjusted maternal dose.
- When selecting a FGA for use in a breast feeding mother, a less sedating agent with a shorter half-life and data to support use in lactation is preferred.
- Adverse reactions (drowsiness and sedation) in breast fed infants have been reported after exposure to chlorpromazine via breast milk.
- Adverse effects on infant development have been seen only when chlorpromazine was used in combination with haloperidol
- 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 FGAs via breast milk.
- Infants exposed to FGAs via breast milk should be monitored for sedation, poor feeding, behavioural effects, extrapyramidal symptoms and achievement of developmental milestones

Limitations

Only limited data are available for the passage of first generation 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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Search strategy

- Embase (via NHS Evidence http://www.library.nhs.uk/hdas/search?databases=bnj.ovi.emez
- accessed online 27.7.12) NEUROLEPTIC AGENT AND (BREAST FEEDING OR BREAST MILK OR LACTATION)[Limit to: Human and (Languages English)]
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    - accessed online 25.7.12) : NEUROLEPTIC AGENT AND (BREAST FEEDINGOR BREAST MILK OR LACTATION)[Limit to: Human and (Languages English)
- Trent & West Midlands UK Drugs in Lactation Information & Advisory Service (UKDILAS) database
- US National Library of Medicine Drugs & Lactation (Lactmed) database. Accessed via http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
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