Q&A 206.2

Which oral antihistamines are safe to use whilst breastfeeding?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Background

Oral antihistamines, which inhibit the effects of histamine at H1 receptors, have been classified as first generation (i.e. relatively sedating) or second generation (i.e. relatively non-sedating) (1). They are of potential value in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hay fever) and vasomotor rhinitis. They may also be of some value in preventing urticaria and are used to treat urticarial rashes, pruritus, insect bites and stings, and are used in the treatment of drug allergies (2).

First generation antihistamines cause sedation and this sedating activity is sometimes used to manage the pruritus associated with some allergies. There is little evidence that any one of the older, 'sedating' antihistamines is superior to another and patients vary widely in their response (2).

Second generation antihistamines cause less sedation and psychomotor impairment than the first generation antihistamines possibly because they penetrate the blood brain barrier only to a slight extent (1).

Table 1 summarises the licensed antihistamines available within the UK (2).

Table1

Non-Sedating Antihistamines	Sedating Antihistamines
Cetirizine, loratadine, levocetirizine, desloratadine, acrivastine, bilastine, fexofenadine, mizolastine	Alimemazine, chlorphenamine, clemastine, cyproheptadine, hydroxyzine, ketotifen, promethazine

Answer

According to the manufacturer's data antihistamines are generally not advised in breastfeeding. However, this is not based on good evidence, but usually due to the lack of data and the possibility of transfer into breast milk.

Non-Sedating Antihistamines

Cetirizine

In an unpublished open study 6 post partum women were administered bromocriptine to reduce milk secretion and were then administered a single dose of cetirizine 20mg (twice the normal recommended daily dose). The mean concentration in milk after 2 hours was 8 nanograms/mL. This demonstrates low transfer into milk (3).

A woman who was nursing her newborn infant was treated for pemphigus with oral prednisolone and a topical corticosteroid and was taking cetirizine 10mg daily. She continued breastfeeding throughout treatment and her infant was developing normally at 8 weeks of age and beyond (4).

The British Society for Allergy and Clinical Immunology recommends cetirizine at its lowest dose as one of the preferred choices if an antihistamine is required during breastfeeding (5).

Of note, the Summary of Product Characteristics for cetirizine states that it is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration (6). However, the manufacturer was unable to verify this data (7).

Levocetirizine

Levocetirizine is an enantiomer of cetirizine. Whilst there are no data regarding its use during breastfeeding, problems would not be anticipated based on the information which is known about cetirizine use during breastfeeding.

Loratadine

After a single oral dose of 40mg (four times the normal recommended daily dose) of loratadine in 6 women, average peak milk levels of 29.2 (range 20.4 to 39) micrograms/L occurred at two hours after the dose. In addition, average desloratadine peak milk levels of 16 (range 9 to 29.6) micrograms/L occurred at 5.3 hours after the dose. The total amount excreted in milk over 48 hours was 11.7 micrograms of loratadine and its metabolite, desloratadine. The calculated average and maximum expected doses of loratadine plus desloratadine in milk were 0.46 and 1.1% and of the maternal weight-adjusted dose, respectively, after the 40mg dose. The authors extrapolated that after a standard 10mg daily dose of loratadine approximately 3 micrograms of loratadine and its metabolite, desloratadine would be excreted into breast milk (8). The mothers did not breastfeed their infants during this study.

A survey of 51 mothers who took loratadine during breastfeeding between 1999 and 2001 was conducted by a teratogen information service. Most of the infants were over 2 months old and loratadine was generally taken for one week or less. Two mothers reported minor sedation in their infants, one at 3 days of age and one at 3 months of age. Both mothers were taking a dose of 10 mg daily. Weight gain and psychomotor development were similar to infants in a control group of breastfed infants unexposed to medications. In an extension of the study, no differences in sedation or any other side effects (p=0.606) in the infant were found between mothers who took loratadine during breastfeeding and those of the control group (9).

The British Society for Allergy and Clinical Immunology recommends loratadine at its lowest dose as one of the preferred choices if an antihistamine is required during breastfeeding (5).

Desloratadine

Although desloratadine has not been specifically studied in breastfeeding it is the active metabolite of loratadine and the data show that low levels of both loratadine and desloratadine are excreted in breast milk (8). Based on the evidence which is available for loratadine, no problems would be anticipated with the use of desloratadine whilst breastfeeding.

Fexofenadine

Fexofenadine is an active metabolite of terfenadine. Milk levels have not been measured after fexofenadine administration. However, after 60mg every 12 hours orally of its parent compound, terfenadine, peak steady-state fexofenadine milk levels in four adults averaged 41 micrograms/L (range 23 to 60 micrograms/L). Based on the data on drug passage into breast milk in this study and the typical serum levels found after terfenadine administration, the authors calculated that an exclusively breastfed infant would receive less than 0.45% of the weight-adjusted maternal dosage of fexofenadine and would not be expected to cause any adverse effects in the infant (10).

In a prospective telephone follow up study terfenadine was used by 25 breastfeeding mothers (doses not reported) and irritability was reported in 3 breastfed infants (11).

There are no breastfeeding studies for acrivastine, bilastine, or mizolastine.

Sedating Antihistamines

Clemastine
A single report describes a 10 week old, previously well fully breastfed infant, admitted with a 2 day history of drowsiness, irritability, refusal to feed and crying. The mother was taking phenytoin, carbamazepine and clemastine 1mg twice daily, which was started 3 days before the baby was admitted. The infant became drowsy and irritable 12 hours after taking clemastine. When the evening dose of clemastine was omitted the infant was behaving normally and feeding well. The clemastine level 20 hours after administration was 20 micrograms/L in the mother's plasma, 5-10 micrograms/L in breast milk but undetectable in the infant's plasma. The concentrations of phenytoin and carbamazepine did not vary in the breast milk (12).

Chlorphenamine
There are no studies reporting levels of chlorphenamine in breast milk after maternal use. Chlorphenamine is licensed for infants over one year of age. Additionally, the BNF for Children provides a dose for infants over 1 month of age of 1mg twice daily (unlicensed) (13). This therefore represents experience of use in the paediatric population at much higher doses than those that would be transferred across into breast milk.

In a prospective telephone follow up study chlorphenamine was used by 5 breastfeeding mothers (doses not reported) with no adverse effects reported in their breastfed infants (11).

In a study, serum prolactin levels decreased significantly after a single dose of intravenous dexchlorpheniramine 20mg (n=6), however, this regimen given at the onset of suckling did not alter stimulation of prolactin release. These results suggest that histamine H1 receptors are involved in the regulation of basal prolactin secretion postpartum, but they do not participate in the mechanisms underlying suckling induced prolactin release (14).

Cyproheptadine
There are no studies on the safety of cyproheptadine in breastfeeding. The long term treatment with cyproheptadine, 16 to 24mg daily, in the management of galactorrhea-amenorrhea syndrome was studied in 15 women. This resulted in a significant decrease in serum prolactin at 8 and 16 weeks. Seven women had decreased galactorrhea and two had cessation of galactorrhea (15). Therefore, unless it is intentionally being used to lower maternal serum prolactin levels, cyproheptadine should be avoided during breastfeeding because it may interfere with breast milk production.

Ketotifen
In an unpublished case report a mother took ketotifen 1mg daily whilst breastfeeding. The breastfed infant became somnolent 4−7 days after the mother started therapy. Analysis of the mother's milk revealed 5.4 nanograms/mL of ketotifen (16).

Hydroxyzine
Spontaneous reports of adverse drug reactions in breastfed infants were compiled by the French Pharmacovigilance Network between January 1985 and June 2011. There were 276 adverse drug reactions reported in 174 breastfed children. Hydroxyzine was reported to cause adverse reactions in 8 infants and to be one of the drugs most often suspected in serious adverse reactions, primarily sedation (17).

Promethazine
A study evaluated the effect of various factors on the time between delivery and lactogenesis time (LT). LT was defined as the umber of hours between delivery and the time that each mother first observed the signs of a surge in milk production. The mean LT for the entire sample (n=127) was 50+/-15 hours. Of the sedative and analgesic medications given in labour, only promethazine was associated with a significant increase in the mean LT of 68+/-16 hours (n=6). In contrast, the mean LT was 56+/-7 hours (n=5) when other medication, without promethazine, was received during labour (18).

There are no breastfeeding studies for alimemazine.

Summary

- There are very limited studies or case reports for the use of antihistamines in breastfeeding.
- Studies of the non-sedating antihistamines, loratadine and cetirizine, show low levels of transfer into breast milk and these would be considered the preferred choice antihistamines for a breastfeeding mother.
- Limited data suggests the transfer of fexofenadine into breast milk is low and could be considered acceptable where loratadine and cetirizine are either ineffective or contraindicated.
- Although there is no specific evidence for the use of the other non-sedating antihistamines during breastfeeding, based on pharmacology and the evidence available for other non-sedating antihistamines, problems would not be anticipated. Therefore, their use would be considered acceptable during breastfeeding, with caution.
- The use of sedating antihistamines may cause adverse effects in the breastfed infant such as drowsiness and irritability.
- If treatment with a sedating antihistamine is required then occasional doses of chlorphenamine may be used with infant monitoring for drowsiness and irritability.
- Data on the use of other sedating antihistamines is lacking and cannot be confirmed as safe.
- Where an antihistamine is prescribed, co-therapy with other sedating agents is best avoided.
- Antihistamines may cause a reduction in serum prolactin but this probably has no effect on breast milk production where lactation is established, and when the doses used are low. However, cyproheptadine should be avoided because of the evidence that is available for interference with breast milk production.
- There are no data on antihistamine use when breastfeeding a premature infant.

Limitations

- Evidence of the secretion of antihistamines in breast milk, and their safety in breastfed infants, is limited to relatively small studies with limited numbers of mothers and infants. Evidence for long-term safety is lacking.
- There are no data for most antihistamines.
- The information relates to full-term and healthy infants. Evidence in pre-term infants is lacking. If the infant is pre-term, of low birth weight or has other concomitant pathology or medical problems, then specialist advice should be sought as this answer may not apply. Contact the UK Drugs in Lactation Advisory Service (UKDILAS) provided by the Trent and West Midlands Medicines Information Services
- For the purpose of this Q&A cyclizine and cinnarizine, which are used for nausea, vomiting and labyrinthine disorders have not been included.

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Search strategy

- Summary of Product Characteristics Accessed via www.emc.medicines.org.uk
- BNF for Children September 2015–2016: Available from https://www.medicinescomplete.com/mc/bnfc/current/
- BNF Online (British National Formulary) 70th edition Available from https://www.medicinescomplete.com/mc/bnf/current/
- LactMed* Edition: Available at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
- Medication and Mothers Milk*Edition: Thomas Hale Publishing. Available from http://www.medsmilk.com/
- UKDILAS Drugs in Breast Milk In-house Database
- Martindale The Complete Drug Reference. Accessed via www.medicinescomplete.com
- Embase (Standard Search Patterns) [link]