Chloramphenicol: is it safe in breastfeeding?

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Background

Chloramphenicol is a potent broad-spectrum antibiotic. It is available in the UK in several formulations—oral capsules, IV injection/infusion, ear drops, and eye drops and ointment [1]. However, as it is associated with serious haematological side-effects when administered systemically, it is recommended that systemic use should be reserved for the treatment of life-threatening infections, particularly those caused by Haemophilus influenzae, and also for typhoid fever [1].

An additional concern with chloramphenicol use is “grey baby syndrome” due to toxicity in premature and young infants associated with the lack of liver enzymes to metabolize the drug [1]. Therefore, oral or parenteral chloramphenicol is normally considered to be incompatible with breastfeeding [2, 3, 4] due to its potential toxicity, including aplastic anaemia.

The most common use of chloramphenicol is for superficial eye infections, for which it is considered to be the drug of choice [1]. Chloramphenicol ophthalmic products are frequently prescribed, and bought over the counter, for eye infections in adults and children. Chloramphenicol is also occasionally used in the ear for the treatment of otitis externa in adults and children [1, 5].

The low systemic absorption of chloramphenicol from topical formulations frequently raises questions on the safety of using topical chloramphenicol in mothers who are breastfeeding their infants.

Answer

Systemic chloramphenicol and breastfeeding

Variable milk levels have been found in breast milk of mothers taking oral chloramphenicol after single doses or multiple doses [6-9]. In a study of 50 breastfed infants whose mothers were given oral chloramphenicol 1 g (n=20), 2 g (n=20), or 3 g (n=10) daily, several side effects were noted in the infants—poor sucking (100%), somnolence (50-60%), vomiting (10–90% depending on dose), and excessive abdominal gas and abdominal distension (100%) [10]. No other studies have reported infant side effects after ingesting chloramphenicol through breast milk.

Systemic chloramphenicol is licensed for administration directly to neonates and premature infants, however its use is only advocated for life-threatening infection [1, 4]. Systemic use has been associated with a 13-fold increase in the risk of aplastic anaemia (compared to idiopathic aplastic anaemia) and this effect is considered not to be dose-related [11]. It is therefore possible that aplastic anaemia might occur as a result of exposure via breastfeeding, however this has not been reported [2]. This risk is likely to be lower than the risk of exposure via direct administration to an infant.

In light of the reported side-effects in breastfed infants exposed to oral chloramphenicol [10], and due to the theoretical risk of small amounts of chloramphenicol in breast milk precipitating aplastic anaemia in the infant, systemic chloramphenicol is contra-indicated where possible during breastfeeding.

Toxicity of topical chloramphenicol

Due to this risk of non-dose-related aplastic anaemia there is also a theoretical risk that low amounts of chloramphenicol absorbed from topical formulations (ophthalmic or administration into the ear) could precipitate aplastic anaemia as well. The evidence to support this is conflicting.

Chloramphenicol eye drops administered directly to children produced no detectable urine levels [12]. However, a review has identified 23 anecdotal case reports, including 10 deaths, which suggest a possible association between ophthalmic use of chloramphenicol and blood dyscrasias [13,12]. Analysis of these reports, supported by another analytical review [14], concludes that there is, however, only a theoretical risk of ophthalmic chloramphenicol-induced idiosyncratic aplastic anaemia. Retrospective studies have also supported this conclusion.

In a 4-year retrospective study in the Netherlands, it was found that there was no excess risk of developing aplastic anaemia after use of ophthalmic chloramphenicol [15]. Another study in Scotland concluded that
the epidemiology of acquired aplastic anaemia failed to make an association with ophthalmic chloramphenicol use [16].

A further analysis of the expected incidence of chloramphenicol-induced aplastic anaemia in the UK, based on the volume of prescribing relative to that in the USA, concludes that there is no increase in the incidence of aplastic anaemia when ophthalmic chloramphenicol is prescribed [15].

Overall, the balance of evidence suggests that the risk of blood dyscrasias with topical chloramphenicol has not been established. Chloramphenicol eye drops are well tolerated and the recommendation that they should be avoided because of an increased risk of aplastic anaemia is not well founded [1, 17].

Similarly, there is no evidence for the risk of aplastic anaemia associated with chloramphenicol use in the ear. Although this has not been specifically studied, there would be no pharmacological reason that this method of administration would represent any increased risk compared to ophthalmic administration.

Topical chloramphenicol and breastfeeding

No evidence has been published relating to the levels of chloramphenicol in breast milk after topical administration of chloramphenicol to a breastfeeding mother, although levels would be predicted to be very low. Also, there have been no reported side effects in breastfed infants whose mothers have been treated with topical chloramphenicol.

Despite the negligible serum levels that may be expected in a breastfed infant after maternal use of ophthalmic chloramphenicol or chloramphenicol ear drops, there is still a theoretical risk, not supported by clinical evidence, of dose-unrelated aplastic anaemia [8, 16].

The manufacturers of ophthalmic and ear preparations of chloramphenicol marketed in the UK advise against or caution their use in breastfeeding, as safety has not been specifically established [18–21].

Because evidence for the safety of topical chloramphenicol in breastfeeding mothers is lacking, the use of chloramphenicol via these routes should proceed with caution. However, it should not be used in mothers where there is a past or family history of blood dyscrasias [2, 16, 18, 20]. Alternative microbiologically appropriate agents such as fusidic acid or gentamicin are preferred during breastfeeding, to eliminate the theoretical concerns about topical chloramphenicol-induced blood dyscrasias, especially in new-born and preterm infants [2, 25].

If chloramphenicol eye drops are used during breastfeeding the mother can reduce potential systemic absorption further by naso-lachrymal occlusion (squeezing tear ducts in the corner of the eye for a few minutes after application). A link to the technique can be accessed here [18, 23].

Summary

- Systemic chloramphenicol is normally contra-indicated in breastfeeding mothers due to the theoretical risk of aplastic anaemia, and reported adverse effects in breastfeeding infants, although the quality of this evidence is poor.
- Although there are concerns around “grey baby syndrome” and chloramphenicol use, milk concentrations as a result of systemic exposure are likely to be too low to cause this effect. It is therefore extremely unlikely with ophthalmic and ear preparations.
- Ophthalmic chloramphenicol products are routinely used, and considered to be the treatment of choice for superficial eye infections, including in children.
- There is no evidence on the safety of topical chloramphenicol in infants exposed via breastfeeding after maternal use; risks of toxicity in the infant are theoretical and not supported by direct clinical evidence. Therefore, the use of chloramphenicol via the ear or eye can proceed with caution.
- If microbiologically appropriate, preparations containing fusidic acid or gentamicin are preferred.
- Topical chloramphenicol should be avoided during breastfeeding if there is a past or family history of blood dyscrasias.
- If chloramphenicol eye drops are considered appropriate during breastfeeding, systemic absorption can be minimised by naso-lachrymal occlusion immediately after administration.
- As a precaution monitor the infant for abdominal distension, difficulty breathing, vomiting, diarrhoea, anaemia, rash, and ashen grey skin colour, following maternal exposure to chloramphenicol via any route.
**Limitations**

- Evidence relating to excretion of chloramphenicol in breast milk is relatively poor and old, although it is not a drug used commonly enough to expect new evidence.
- The only evidence relating to chloramphenicol side effects in breastfeeding infants is old (1972) and from a foreign language source.
- There is no evidence relating to excretion of chloramphenicol into breast milk after ophthalmic administration.
- There is inconclusive evidence relating to the risks of non-dose related haematological toxicity of chloramphenicol, which may be relevant to levels that may be expected to be found in breast milk after ophthalmic administration to the mother.

The above information applies to maternal monotherapy and a full-term, fit and healthy infant only. Should the infant be premature, unwell, or the mother taking multiple medication, an individual risk assessment is required. Please contact the UK Drugs in Lactation Advisory Service for advice on 0116 258 6491 or ukdilas.enquiries@nhs.net.

**References**


From the NHS Evidence website www.evidence.nhs.uk
Quality Assurance

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Search strategy
For chloramphenicol in breast milk:

- Embase and Medline (Standard Search Pattern)
- UKDILAS in-house databases and resources:
- Manufacturers (eMC)

For ophthalmic toxicity of chloramphenicol

- Embase
  1. Chloramphenicol /ae
  2. Chloramphenicol /io/tp
  3. 1 and 2

Available through Specialist Pharmacy Service at www.sps.nhs.uk