Metronidazole—is it safe to use during breastfeeding?

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

- The balance of current evidence and clinical experience, and the consensus of specialist opinion, is that there is no established mutagenic or carcinogenic risk to infants breastfeeding from mothers receiving routine short-course treatment with metronidazole by any route.
- Low-dose oral metronidazole, 200-400 mg three times daily, produces milk levels only slightly lower than corresponding levels in maternal plasma (76 to 99%). However, doses up to 500 mg three times daily for a 7 to 10 day course are considered to be compatible with breastfeeding.
- Single, 2 g high-dose oral metronidazole produces significantly higher levels in milk than low-dose oral therapy. However, the estimated total ingestion is still lower than the daily infant dose given directly. Daily 2 g oral doses, normally given for 3 days, are considered to be compatible with breastfeeding.
- Intravenous administration produces similar maternal plasma and milk levels to equivalent oral doses, although the data are limited. Short-course IV metronidazole is considered to be compatible with breastfeeding.
- Administration of metronidazole by rectal, vaginal, or topical routes produces significantly lower plasma levels, and would therefore be expected to produce correspondingly lower milk levels than after oral administration, and is considered to be compatible with breastfeeding.
- Adverse effects in breastfed infants whose mothers have been treated with metronidazole are rare and unsubstantiated, and include loose stools, candidiasis and lactose intolerance.
- Anecdotal reports of infants rejecting milk at the start of feeds may be due to a metallic/bitter taste imparted to foremilk by a water soluble metabolite, although this again has not been substantiated.
- If an infant is exposed to metronidazole via breast feeding they may experience alteration of the oral and gut flora, therefore monitor the infant for oral candida infections and diarrhoea. The infant should also be monitored for rash due to the theoretical concern of hypersensitivity.
- The concentrations of metronidazole seen in breast milk are too low to have a bactericidal effect in the infant; therefore an infant with an active infection needs independently treating in their own right.
- There are no data relating to the effects of metronidazole exposure in preterm breastfed infants. Special consideration should be given to the use of metronidazole by any route in preterm or low-birth-weight infants, or in infants with compromised renal or hepatic function.

Background

Metronidazole is a 5-nitroimidazole derivative with high activity against anaerobic bacteria and protozoa. It is used in the treatment and prophylaxis of anaerobic bacterial infections and in the treatment of susceptible protozoal infections (1,2,3).

It is available in oral, intravenous, rectal, vaginal (gel) and topical (gel/cream) formulations (2,3).

Given the range of conditions metronidazole is indicated for, it is frequently prescribed for women who may be breastfeeding. This Medicines Q&A reviews the evidence for the excretion of metronidazole into breastmilk, and where available, amounts reported in infants after exposure via breast milk. Advice on whether it is safe to breastfeed whilst taking metronidazole is given.

Answer

Mutagenic and carcinogenic risks

The balance of current evidence and clinical experience, and the consensus of specialist opinion, is that there is no established mutagenic or carcinogenic risk to infants breastfeeding from mothers receiving routine short-course treatment with metronidazole by any route (4,5,6).

Historically, metronidazole has been contraindicated with breastfeeding because it has been shown to be genotoxic and mutagenic in bacteria, carcinogenic in some animals and possibly mutagenic in humans. This concern has been reflected in authoritative US reviews of drug excretion in breast milk, which recommend withholding breastfeeding for 12–24 hours following a single oral dose regimen (7,8). However, extensive reviews have indicated that there is no substantive evidence from both in vitro and in vivo studies of a mutagenic or carcinogenic effect in humans (9,10). The author of another critical review of antibiotics in breast milk concludes that, whilst the potential for any long-term effects remain unknown, and will most likely never be available, evidence from the routine clinical use of metronidazole suggests that the previous concerns are largely overstated and that short-course maternal metronidazole therapy during breastfeeding should be well tolerated without interruption to the normal breastfeeding routine (6).

Pharmacokinetics

Metronidazole shows almost complete absorption after oral administration (98–100%), which means that the infant will also absorb the majority they are exposed to via breast milk (4, 11). Other routes of administration have differing absorption and bioavailabilities which influence the amount of drug available to pass across into breast milk, generally resulting in lower exposure (12-15).

It has very low protein binding (less than 20%), therefore more metronidazole is freely available to pass across into breastmilk (4, 12). Despite this, the amount received by the breast feeding infant is still considerably less than the therapeutic paediatric dose (16).

Metronidazole is extensively metabolised; it has two metabolites, one of which is active, the hydroxyl metabolite possesses 30% to 65% of the biological activity of metronidazole (11).
It has a relatively short half-life (8.5 hours for metronidazole and 9.7 hours for the hydroxymetabolite (11, 16), therefore drug accumulation in the exposed breastfed infant is unlikely, reducing the risk of adverse effects.

Use in breastfeeding women

Evidence relating to excretion of metronidazole in breast milk is relatively old and of poor quality. Nonetheless, metronidazole has been used widely in breastfeeding women for many years with few reports of adverse effects. The following provides a summary of the available evidence by route of administration.

Oral metronidazole: low dose

Low-dose oral metronidazole, 200-400 mg three times daily, produces milk levels only slightly lower than corresponding levels in maternal plasma (76 to 99%). However, doses up to 500 mg three times daily for a 7 to 10 day course are considered to be compatible with breastfeeding.

In a study with ten infant-mother pairs, mothers were given a single 200 mg oral dose of metronidazole 5 days postpartum. Mean milk levels at 4, 8 and 12 hours (measured in all 10 subjects) were comparable to mean maternal plasma levels. Infant plasma levels were 0.28 and 0.4 micrograms/mL at 8 hours in two infants and 0.2 micrograms/mL in another two infants at 12 hours. Levels were undetectable (<0.05 micrograms/mL) in the remaining 6 infants at each time. No infants were reported to have developed any oral or gastrointestinal side-effects. The authors calculated infant ingestion of metronidazole as 0.3 mg 4 hours after the dose, and 0.17 mg 8 hours after the dose, with a maximum of 0.41 mg by any infant (17).

In six mothers, 500 mg metronidazole orally daily, started on day 4 post-partum, produced peak milk levels after approximately 4 hours with a half-life in milk of 6.6 hours (18).

In a randomised study, 17 mothers were given oral metronidazole, 200 mg three times daily for 7 days postpartum. Mean milk levels on day 6 were 4.7 (range 1.1–15.2) micrograms/mL (19).

Fifteen women received 200 mg (n=11) or 400 mg (n=4) of metronidazole orally 3 times a day for postpartum endometritis starting 0 to 22 days postpartum. Single milk samples taken after a 200 mg or 400mg dose, contained a mean of 5.7 micrograms/mL and 14.4 micrograms/mL respectively of metronidazole and a mean of 2.1 micrograms/mL and 3.5 micrograms/mL respectively of hydroxymetronidazole, the active metabolite. Maternal levels of metronidazole were similar to those in breast milk but higher in milk than maternal plasma for the hydroxy metabolite. Mean infant plasma levels after 200 and 400 mg doses were 0.8 and 2.4 micrograms/mL of metronidazole and 0.4 and 1.1 micrograms/mL of hydroxymetronidazole. No adverse reactions were seen in any infants. The maximum infant ingestion of metronidazole was calculated as 3.0 mg/kg/day, which is below the therapeutic dose in infants (3, 20).

Twelve women taking oral metronidazole**,** 400 mg 3 times daily, had milk samples taken on days 3 and 4 postpartum. Mean milk levels of metronidazole at steady state over 2 days were 15.5 micrograms/mL two hours after a dose, reducing to 9.0 micrograms/mL at 8 hours. Mean milk levels of hydroxymetronidazole were 5.7 micrograms/mL two hours after a dose. Mean plasma levels measured in seven of the infants 4 to 8 hours after a maternal dose (and 30-90 minutes after breastfeeding) were 1.6 micrograms/mL for metronidazole and 1.4 micrograms/mL for hydroxymetronidazole. The authors estimated that a breastfed neonate ingesting 500 mL of milk daily with this maternal dosage would receive less than 10% of the recommended newborn therapeutic dosage of metronidazole (21).

One review concluded that short-term use of metronidazole or a low-dose regimen should not interrupt breastfeeding (22). Another review advised that depending on the dose used in the mother, potential infant daily dose via the breast milk would appear to just approach the lower end of a normal daily infant dose given directly, suggesting that short-course maternal metronidazole can be commenced without interruption to the normal breastfeeding routine (6).

Oral metronidazole: high dose, short course

Single, 2 g high-dose oral metronidazole produces significantly higher levels in milk than low-dose oral therapy. However the estimated total ingestion of metronidazole by the infant is still lower than

the daily infant dose given directly. Daily 2 g oral doses, normally given for 3 days, are considered to be compatible with breastfeeding.

Three mothers were given a single 2 g oral dose of metronidazole for trichomoniasis 6–14 weeks postpartum. The average metronidazole levels in breast milk were 45.8, 27.9, 19.1, 12.6 and 3.5 micrograms/mL at 2, 8, 12, 12–24, and 24–48 hours respectively after the dose. The half-life of metronidazole in milk in two of the mothers was 8.7–9.9 hours. The authors estimated that, if breastfeeding were to continue without interruption after administration of a 2 g dose of metronidazole, the infant would receive 21.8 mg via breast milk during the first 24 hours and a total of 25.3 mg over 48 hours. With a 12-hour interruption of breastfeeding the 48 hour infant dose would be 9.8 mg, reducing to 3.5 mg if breastfeeding was interrupted for 24 hours (23). However, although delayed feeding reduces exposure, this is not considered necessary (5).

Intravenous metronidazole

Intravenous administration produces similar maternal plasma and milk levels to equivalent oral doses, although the data are limited. Short-course IV metronidazole is considered to be compatible with breastfeeding.

Twenty mothers were given a single intravenous infusion of 500 mg metronidazole. The mean concentration of metronidazole in breast milk was 7.6 micrograms/mL, which was comparable to maternal plasma levels. In 5 mothers the mean milk level at one hour was 7.85micrograms/mL, falling to 1.67 micrograms/mL at 12 hours (24).

Rectal, vaginal and topical metronidazole

Administration of metronidazole by rectal, vaginal, or topical routes produces significantly lower plasma levels, and would therefore be expected to produce correspondingly lower milk levels than after oral administration, and is considered to be compatible with breastfeeding.

The initial results of a study of rectal metronidazole, 1 g every 8 hours for seven doses in eight patients, showed a mean milk metronidazole concentration of 10 micrograms/mL (maximum 25 micrograms /mL) 30 minutes after completing treatment. The authors conclude that rectal metronidazole, at the dose used, is unlikely to have any harmful effects on the breastfed infant (25).

There have been no studies on the use of topical or vaginal metronidazole in breastfeeding mothers, although metronidazole administration by these routes during breastfeeding is considered unlikely to be of concern (5, 26).

Adverse effects

Thirty-five newborn infants whose mothers were receiving metronidazole in combination with other antibiotics (33 ampicillin, 1 erythromycin and 1 cefalexin) for postpartum infection or prophylaxis were monitored for adverse effects whilst breastfeeding. They were compared to 24 infants whose mothers received only ampicillin and 39 who received no antibiotics. Dosages and routes of administration were not stated, but some mothers received the drugs intravenously initially. More infants exposed to metronidazole had very loose stools and more frequent and heavier growth of *Candida* species. One infant exposed to metronidazole and ampicillin developed oral thrush. No differences were found between the groups in nappy rash, feeding problems, or weight gain up to the time of discharge (21).

In the previously described study where twenty mothers were given a single intravenous infusion of metronidazole, the authors suggest that the high levels of metronidazole in milk may cause milk to taste bitter which could lead to poor infant feeding (24). The suggestion of metronidazole imparting a bitter taste to milk is largely anecdotal and not supported by published evidence. It may, however, be related to the common side-effect of 'metallic taste' found with normal therapeutic use (1, 2).

A recent systematic assessment of clinical studies of antibiotics and lactation calculated an absolute infant dose as a percentage of the therapeutic daily dose for a wide range of antibiotics. The ingested dose for metronidazole, at 11% of the infant therapeutic dose, was one of the highest for all antibiotics. However the review notes that, based on these percentages alone, it is hard to predict any infant adverse effects (27).

Limitations

- Evidence relating to excretion of metronidazole in breast milk is relatively poor and old.
- The paucity of evidence is exacerbated when differences between dose regimens and routes of administration are compared.
- Inconclusive evidence relating to the mutagenic and carcinogenic potential of metronidazole.

The above information applies to maternal monotherapy and a healthy infant that was born at term. 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/ 0121 424 7298 or ukdilas.enquiries@nhs.net .

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Search strategy

For lactation evidence:

- Embase (Standard UKDILAS Search Patterns) (Available at https://hdas.nice.org.uk/, Accessed 28/5/20)
- Medline (Standard UKDILAS Search Patterns) (Available at https://hdas.nice.org.uk/, Accessed 28/5/20)
- In-house UKDILAS database. Accessed 28/5/20)
- Medication and Mothers Milk Online edition: Thomas Hale Publishing. Available from http://www.medsmilk.com/, Accessed 28/5/20
- Drugs and Lactation Database (LactMed). Toxnet Toxicology Data Network, United States National Library of Medicine. (Available from https://www.ncbi.nlm.nih.gov/books/NBK501922/?report=classic., accessed 28/5/20)
- Summary of Product Characteristics for metronidazole products (Available at https://www.medicines.org.uk/emc/, accessed 28/5/20)

For mutagenic/carcinogenic evidence:

- Medline/Embase: Metronidazole and (genotox* or mutagen* or carcinogen*) (Available at https://hdas.nice.org.uk/, Accessed 28/5/20)

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