

Q&A 39.4

Metronidazole—is it safe to use during breastfeeding

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

Metronidazole is a 5-nitroimidazole derivative with high activity against anaerobic bacteria and protozoa. It is used in the treatment of susceptible protozoal infections such as amoebiasis, balantidiasis, *Blastocystis hominis* infections, giardiasis, and trichomoniasis. Metronidazole is also used in the treatment and prophylaxis of anaerobic bacterial infections, especially acute necrotising ulcerative gingivitis, bacterial vaginosis, pelvic inflammatory disease, nongonococcal urethritis, tetanus, and antibiotic-associated colitis. It is used for surgical and gynaecological sepsis because of its activity against colonic anaerobes, especially *Bacteroides fragilis*. Metronidazole is also active against *Clostridium difficile*. It is also used, in conjunction with other antimicrobials and anti-ulcer agents, to eradicate *Helicobacter pylori* in peptic ulcer disease (1,2,3). It is available in oral, intravenous, rectal, vaginal (gel) and topical (gel/cream) formulations (2,3).

Answer

Mutagenic and carcinogenic risks

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 reviews of drug excretion in breast milk, which recommends withholding breastfeeding for 12–24 hours following a single oral dose regimen (4,5). However, an extensive review has indicated that there is no substantive evidence from both *in vitro* and *in vivo* studies of a mutagenic or carcinogenic effect in humans (6). 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 (7).

Therefore, 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 (8,9,10).

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 3.4, 2.2 and 1.3 micrograms/mL respectively, which were comparable to mean maternal plasma levels of 3.9, 2.3 and 1.8 micrograms/mL respectively. 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 at the first feed, 4 hours after the dose, and 0.17 mg at the second feed, at 8 hours, with a maximum of 0.41 mg by any infant. This was, however, only a single-dose study (11).

In six mothers, 500 mg metronidazole orally daily, started on day 4 post-partum, produced peak milk levels after approximately 4 hours (compared to 2 hours in maternal plasma) with a half-life in milk of 6.6 hours (compared to 5.4 hours in maternal plasma) (12). 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 (13).

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 1 to 9 days of therapy, and from 30 minutes to 4 hours after a 200 mg dose, contained 1.6 to 12.2 (mean 5.7) micrograms/mL of metronidazole and 1.1 to 3.8 (mean 2.1) micrograms/mL of hydroxymetronidazole, the active metabolite. Milk samples taken 2 to 3 hours after a 400 mg dose contained 11.6 to 18.0 (mean 14.4) micrograms/mL of metronidazole and 2.4 to 6.3 (mean 3.5) micrograms/mL of hydroxymetronidazole. Maternal levels of metronidazole were similar to those in breast milk (milk/plasma (M/P) ratio 0.99 for 200 mg and 0.98 for 400 mg) but higher in milk than maternal plasma for the hydroxy metabolite (M/P 1.17 and 1.20 respectively). 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 with milk ingestion of 500 mL/day which is below the therapeutic dose in infants (14).

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. Corresponding maternal plasma levels were not measured. The half-life of metronidazole in milk in two of the mothers was 8.7–9.9 hours. It was 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 25.3 mg over 48 hours. With a 12-hour discontinuation of breastfeeding the 48 hour infant dose would be 9.8 mg, reducing to 3.5 mg if breastfeeding was discontinued for 24 hours (15)

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 (days 3 and 4 of treatment) 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 to 90 minutes after breastfeeding were 1.6 micrograms/mL for metronidazole and 1.4 micrograms/mL for hydroxymetronidazole. The mean milk/plasma (M/P) ratio was 0.91 for metronidazole and 0.77 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 dosage of metronidazole (16).

In a separate component of the study, 35 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 antimicrobials. Dosages and routes of administration were not stated, but some mothers received the drugs intravenously initially and then were switched to oral therapy. More infants exposed to metronidazole and ampicillin had very loose stools compared to those exposed to ampicillin alone or no therapy (n = 5, 3, 1 respectively), especially when the drugs were given intravenously. Stools normalised when intravenous metronidazole and ampicillin were changed to oral therapy (n=2) and when concurrent therapy was changed from ampicillin to erythromycin (n=1). More frequent and heavier growth of *Candida* species was found in the oral and perianal swabs of metronidazole-exposed infants (7:5:3 respectively). 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 (16).

A case of diarrhoea and lactose intolerance, possible related to maternal metronidazole treatment, has also been reported. However, there was no information of dose, route of administration, and no confirmation of the association with metronidazole (17).

Twenty mothers were given a single intravenous infusion of 500 mg metronidazole. The mean concentration of metronidazole in breast milk, measured 1 to 12 hours after the infusion, was 7.6 micrograms/mL, which compared to 7.7 micrograms/mL in maternal plasma (measured at 3 and 8 hours). In 5 mothers the mean milk levels at one hour were 7.85 micrograms/mL, falling to 1.67 micrograms/mL at 12 hours. The authors suggest that the high levels of metronidazole in milk may cause milk to taste bitter which could lead to poor infant feeding (18). The suggestion of metronidazole imparting a bitter taste to milk is largely anecdotal and not supported by published evidence. It does, however, appear as a statement from authoritative sources (19) and may be related to the common side-effect of 'metallic taste' found with normal therapeutic use (1, 2).

The initial results of a study of rectal metronidazole, 1 g every 8 hours for seven doses for prophylaxis after caesarean section 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 (20).

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 (21).

Authors of reviews have concluded that short-term use of metronidazole or a low-dose regimen should not interrupt breastfeeding (22). 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 (10).

Use in infants and children

Metronidazole is used in infants and young children. In the treatment of anaerobic infections the recommended doses are: (3)

- Orally = 7.5 mg/kg every 12 hours in infants aged 1 to 2 months.
- Rectally = 125 mg 3 times daily for 3 days, then twice daily, for infants aged 1 month to 1 year.
- Intravenous infusion: 15mg/kg as a loading dose, followed by 7.5 mg/kg every 24 hours thereafter in neonates (including pre-term) and infants aged up to two months.

It can also be used intravenously for surgical prophylaxis in neonates, and orally or intravenously in infants aged one month and over. It can also be used orally for protozoal infections (amoebiasis, trichomoniasis and giardiasis) in children aged one year and over (3).

Similar doses in neonates, based on body weights from below 1.2 kg, are recommended by the American Academy of Pediatrics (1).

Pharmacokinetics

After oral administration, peak plasma levels of 6, 12, and 40 micrograms/mL following 250 mg, 500 mg, and 2 g single doses respectively, occur after 1 to 2 hours. Oral bioavailability is approximately 98-100%. (1, 23, 24).

After an intravenous loading dose of 15 mg/kg followed by 7.5 mg/kg every 6 hours peak steady-state plasma concentrations of about 25 micrograms/mL with trough concentrations of about 18 micrograms/mL have been found (23). A number of studies have demonstrated similar plasma levels after comparable oral and intravenous doses of metronidazole, with only a small delay in peak plasma levels after oral administration (8, 24).

The bioavailability of metronidazole from rectal suppositories is 60 to 80%; peak plasma levels are half those achieved with equivalent oral doses and occur after 4 to 12 hours (24).

Absorption from vaginal pessaries is poor with bioavailability of about 20 to 25%; absorption is gradual producing peak plasma concentrations of 1.1 to 1.9 micrograms/mL after a dose of 500 mg (23). An intravaginal gel formulation providing a dose of 37.5 mg metronidazole produced peak plasma levels of 300 nanograms/mL at 8 hours, with a bioavailability of 56% (1, 23). Administration of a single 5 g dose of a 0.75% vaginal gel in 12 normal subjects showed a mean maximum serum concentration of 237 nanograms/mL, or about 2% of the mean maximum serum level of a 500 mg oral tablet (25).

Bioavailability studies with a topical 7.5 g application of a 0.75% cream to the face of normal subjects resulted in mean maximum serum concentrations of 66 nanograms/mL which is approximately 1% of those attained after a single oral dose of 250 mg. (26).

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%). 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. The estimated total ingestion is 25.3 mg of metronidazole by the infant after feeding for 48 hours, although this is still lower than the daily infant dose given directly. If feeding is delayed for 12 hours after each dose, total infant exposure is reduced. Daily 2 g oral doses, normally given for 3 days, are considered to be compatible with breastfeeding, and in practice, delaying breastfeeding for 12 hours is not considered necessary.
- ◆ 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.
- ◆ Side-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.
- ◆ 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.

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.

- Set against these limitations is the broad consensus of expert opinion and the widespread, long-term use of metronidazole without confirmed evidence of risk when used in mothers who are breastfeeding their infants.
- There is no evidence, and limited experience, for assessing risks of exposure of preterm infants to levels of metronidazole found in breast milk. If there are unusual circumstances e.g. premature infants or infant morbidity, further expert advice can be sought. *Contact the UK Drugs in Lactation Advisory Service (UKDILAS) provided by the Trent and West Midlands Medicines Information Services.*

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Search strategy

For lactation evidence:

- Embase and Medline (Standard UKDILAS Search Patterns) [\[link\]](#)
- In-house UKDILAS database
- Medications and Mothers' Milk Online (Medilact): Metronidazole
- Drugs and Lactation Database (LactMed). Toxnet Toxicology Data Network, United States National Library of Medicine. Available from <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. Metronidazole monograph
- Manufacturers (eMC) of metronidazole products

For mutagenic/carcinogenic evidence:

- Medline/Embase: Metronidazole and (genotox*3 or mutagen*5 or carcinogen*5)