Q&A 259.4

Malaria prophylaxis—what can be given to breastfeeding mothers?

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

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Background

The number of women travelling whilst breastfeeding is increasing globally (1). The incidence of malaria is also on the rise (2), hence adequate chemoprophylaxis is important for both a breastfeeding mother and her child when travelling to malarious areas. In making a choice of treatment, mother's health must be carefully balanced against any risk to her nursing infant (1).

This Q&A examines evidence on the potential risks to the infant when antimalarials are taken by the mother for malaria prophylaxis whilst breastfeeding. It does not include evidence for these and other antimalarials when used to treat malaria.

Answer

Chloroquine and hydroxychloroquine

The dose of chloroquine for malaria prophylaxis in adults and children aged over 13 years weighing greater than 45kg is 310mg chloroquine base for one week before, during and for four weeks after travel in a risk area (3). It can be used in neonates and children using an age and body-weight adjusted dose (3).

Hydroxychloroquine is not licensed or routinely recommended for malaria prophylaxis, except when a patient is already taking it as treatment for a medical condition (eg rheumatoid arthritis or lupus erythematosus) and who also requires chloroquine for malaria prophylaxis. In this case hydroxychloroquine can be substituted, although dose changes may be required (4).

Several studies have reported the levels of chloroquine and hydroxychloroquine in human breast milk—see Table 1 (5-18). While the consensus is that the calculated infant dose is too small to be harmful, most studies involved either a single maternal dose, or were performed early during treatment. Due to the long half-life of chloroquine and hydroxychloroquine (60 and 40 days, respectively) (19), repeated administration is likely to result in higher plasma and milk levels than those reported in Table 1. Doses used for malaria prophylaxis are substantially lower (3)

The amounts consumed by a breastfed infant via milk are considered insufficient for both adverse effects and protection, and the full recommended dose of chloroquine—where this agent provides appropriate protection—must be given to the infant regardless of maternal prophylaxis (20-22). There has been a single report of a 5 month old breastfed child suffering from Kawasaki disease, whose mother was taking hydroxychloroquine, the infant recovered after 1 week. No details supporting a causative link were reported. (23). No other reports of adverse effects due to chloroquine or hydroxychloroquine after exposure of breastfed infants via milk were found in the literature. (1, 5-18).

Ocular toxicity is a well documented side effect of both chloroquine and hydroxychloroquine (3). The risk is thought to be related to the cumulative dose (21, 24). A total dose of 1g/kg body weight of chloroquine base is associated with retinal damage (21), but this amount is unlikely to be achieved after short term administration to mother or infant for malaria prophylaxis. Ocular toxicity after *in utero* exposure to chloroquine has been reported on a few occasions, associated with high-dose maternal therapy for auto-immune conditions (21, 24, 25). In contrast, four studies in which 16, 8, 13 and 5 infants were exposed to hydroxychloroquine *in utero* and subsequently via milk, reported no adverse ocular effects during the first year of life, One woman breastfeed her infant for 30 months whilst taking hydroxychloroquine (200mg daily), electroretinography performed on the infant at the end of this time was completely normal. (26) The mothers were treated for auto-immune conditions throughout pregnancy and the breast-feeding period, and it can therefore be expected that steady-state levels were achieved (23, 27, 28).

POPULATION	TREATMENT	SAMPLING TIMES	MILK LEVELS	CALCULATED INFANT DOSE	REF
27 women	450mg chloroquine base p.o daily for 3 days (n=27); same + 225mg IV daily (n=8), all from day 3 post delivery	Times not stated, from 24 hours after first to 24 hours after last dose	<2 micrograms/ml	Not stated	5
18 women	20–45mg chloroquine base daily for 7 days	273 samples taken over 14 days starting 3 days prior to treatment	Traces in 17 samples from 7 patients. ,All below quantification limit *	Not stated	6
3 women	Single dose of 300mg chloroquine base (plus dapsone 100mg, pyrimethamine 12.5mg)	6 samples per patient, collected over a 9 day period	9.49, 18.1 and 13.93 micrograms/ml/hour (CQ) 1.87, 3.62 and 2.42 micrograms/ml/hour (DECQ) #	190 micrograms/kg cumulative dose (4.2% of weight-adjusted maternal dose) over 9 days; metabolites not included; based on 1litre milk/day	7
11 women	Single dose of 600mg chloroquine base	0, 3, and 24 hours (n=5) or 0, 3, 6, 9, 24, 48h and then for up to 7 days (n=6)	Average 4.4 micrograms/ml (at average peak time of 14.4 hours)	660 micrograms/kg/day based on 150ml milk/kg/day	8
5 women	Single dose of 300mg chloroquine base	12 times in 168 hours	Mean 3.97 micrograms/ml (at mean peak time of 3.06 hours)	1.65mg/day based on 1litre milk/day; equivalent to 0.55% of weight-adjusted maternal dose	9
6 women	Single dose of 3mg/kg chloroquine base (intramuscularly) 2 weeks post delivery	0 and 2 hours post dose	163-319 (mean 227) micrograms/l	Max. 47.9 micrograms/kg/day, assuming peak at 2 hours and 150ml milk/kg/day	10
16 women	465mg chloroquine base daily for 3 days after clinic visits (frequency not specified)	Times not stated, samples collected between days 3 and 21 post delivery	Median 226 (CQ) and 97 (DECQ) micrograms/l with wide intersubject variability #	Average 34 and 15 micrograms/kg/day (2.3 and 1% of maternal for CQ and DECQ); maximum 177 and 267 micrograms/kg/day (13.9 and 19.6% of weight-adjusted maternal dose, CQ and DECQ) #	11
1 woman	600mg chloroquine base daily for 2 days then 300mg daily for 3 days	Times not stated, 17 samples collected during treatment and for a further 4 days.	Mean 1.2mg/l (range 0.2 – 2.8mg/L)	Not stated	12
20 women	300mg weekly chloroquine base during pregnancy modified to 100mg daily during the last 10 days of pregnancy and first 10 days postpartum.	Times not stated. Daily sample collected over three consecutive days during first 10 days postpartum.	Median 352 micrograms/L.	Not stated	13
1 woman	310mg hydroxychloroquine base daily for 6 weeks for systemic lupus erythematosus	2, 9.5 and 14 hours after first dose; 17.7 hours after second dose	1.46, 1.09, 1.09 and 0.85 (mean 1.1) micrograms/ml at sequential sampling times.	0.11 mg/kg daily (2% of weight-adjusted maternal dose)	14
1 woman	155mg hydroxychloroquine base daily for rheumatoid arthritis	First sample between 15 and 24 hours, second sample between 39 and 48 hours after first dose	3.2 and 10.9 nanograms/ml; 480 and 2042 nanograms recovered during first and second 24 hours period.	Calculated as 0.48 to 1.64 micrograms/kg/day based on 150ml milk/kg/day	15
2 women	155mg hydroxychloroquine base once or twice daily, throughout pregnancy	Not stated, but presumably in steady state as given throughout pregnancy	0.34 and 1.42 micrograms/ml	0.06 and 0.2mg/kg/day based on 500ml milk/day	16
2 women	Hydroxychloroquine (dose not stated)	Not stated	1.13 and 1.39 micrograms/ml	No more than 0.2mg/kg.day.	17
6 women	Hydroxychloroquine 400mg daily (n=5) or 200mg daily (n=1)	Not stated, multiple samples	376 nanograms/ml [range 20-1463 nanograms/ml] HCQ and 36 nanograms/ml [range 11-111nanograms/ml] DECQ	Max dose 1mg/day HCQ and 0.066mg/day DECQ based on 150ml milk/kg/day	18

** fluorimetric analysis-possibly false positive results included, # CQ:chloroquine; DECQ: desethylchloroquine (principle metabolite of chloroquine)*

Table 1: Studies of chloroquine and hydroxychloroquine levels in breast milk

Avloclor® and Nivaquine® brands of chloroquine are not contraindicated in lactation, although product literature for both confirm that there is insufficient chloroquine in milk to protect the infant (29, 30).

The World Health Organization recommends against the use of chloroquine during breastfeeding where the infant is Glucose-6-phosphate dehydrogenase (G6PD) deficient, and advises monitoring premature infants and neonates for side effects such as haemolysis and jaundice. (31)

Doxycycline

The dose of doxycycline for malaria prophylaxis in adults and children aged over 12 years is 100mg daily started 1–2 days before entering endemic areas and continued for 4 weeks after leaving (3). There are five studies of doxycycline excretion in breast milk, none of which relate to its use for malaria prophylaxis.

After administration of doxycycline (200mg followed by 100mg 24 hours later) to 15 mothers between days 15 and 30 post delivery, milk levels were on average 0.77 and 0.38 micrograms/ml at 3 and 24 hours respectively (equivalent to 32 and 36% of maternal serum concentrations, respectively). The highest observed level was 1.4 microgram/ml (32). Based on the highest level, and an infant's milk consumption of 150ml/kg/day, the theoretical maximum infant dose would be 210 micrograms/kg/day. The authors concluded that these amounts were unlikely to affect a breastfeeding infant (32).

The same dosing regimen and sampling times were used in 10 patients in a subsequent study. Milk levels were on average 0.82 and 0.46 micrograms/ml, respectively, with almost identical milk: plasma ratios to those found previously. No further information on the infants is included (33).

In another study of 13 women, a maximum infant dose of 450 micrograms/day was calculated, after maternal administration of 100 to 200mg doxycycline daily for one or two days. Sampling times are not stated, nor is it clear on what amount of milk the calculated infant dose is based. The authors considered their findings to be consistent with those of the two previous studies (34).

After a single oral dose of 100 mg in 3 women and 200 mg in 3 women, peak milk levels occurred between 2 and 4 hours after the dose. Average peak milk concentrations were 0.96 mg/L after 100 mg and 1.8 mg/L after 200 mg. Milk levels accumulated to about 3.6 mg/L with doses of 100 mg twice daily for 5 days (35).

After a single 200 mg dose of doxycycline to 2 women, average milk levels were 0.8 mg/L 2 hours after the dose, 0.7 mg/L 4 hours after the dose, and 0.4 mg/L 6 hours after the dose (36).

Tetracyclines can cause permanent discolouration of the teeth in children when given directly (37), and there is also the risk of bone deposition which may interfere with growth (19). However, the available literature indicates that there is unlikely to be harm with short-term use of doxycycline during lactation because milk levels are low and absorption by the infant is likely to be further inhibited by the calcium in the breast milk (38). No harmful effects have been reported to date in breastfed infants (38, 39). The World Health Organization recommends doxycycline as compatible with breastfeeding when prescribed for malaria prophylaxis. (31)

Mefloquine

The dose of mefloquine for malaria prophylaxis in adults and children aged over 45kg body weight is 250mg weekly for 2-3 weeks before, during, and for 4 weeks after travel in a risk area (3). It can be used in infants from 5kg body weight with a dose adjustment (3).

Only one study has been published which reported milk concentrations after administration of a single 250mg dose of mefloquine to two mothers. Samples were taken at various times up to 4 days in one mother, and up to 56 days in the other. Milk levels declined from 53 to 32 nanograms/ml, and a

steeper decline from 624 to 33 nanograms/ml was seen in maternal plasma. An infant would ingest approximately 80 micrograms/day (equivalent to 3.8% of the weight-adjusted maternal dose), based on a milk consumption of 1 litre daily (40). Although this amount is unlikely to be harmful, repeated administration during prophylaxis or treatment would most likely result in higher plasma and milk levels. No information about the infants was included in this publication (40).

The manufacturer of Lariam® advises against its use during lactation (41).

Proguanil

Proguanil is commonly used for malaria prophylaxis in conjunction with chloroquine and in combination with atovaquone (Malarone®) (4).

Only trace amounts of proguanil are stated to be found in human milk, (1) but there is no apparent supporting evidence for this. The WHO considers it safe for use during lactation. (31) Paludrine® (proguanil) is licensed for use by breastfeeding mothers (42).

Atovaquone

Atovaquone is used in combination with proguanil (Malarone®) for malaria prevention started 1–2 days before entering endemic areas and continued for 1 week after leaving. It is licensed for malaria prevention use in children weighing 11kg and above, and for the treatment of malaria in children weighing 5kg and above (unlicensed) (43).

There are no published studies of the passage of atovaquone into human milk (1, 20, 45). However, The Center for Disease Control and Prevention does recommend it for the prevention of malaria in women breastfeeding infants weighing at least 5 kg (1, 44).

The WHO makes no recommendations for the use of atovaquone during breastfeeding (20) and the manufacturers of Malarone® advise against its use (43).

Insect repellents

Malaria mosquitoes are particularly active from dusk to dawn. Using repellents, covering up with clothing from dusk, and the use of impregnated bed nets will help prevent bites (2).

The recommended insect repellent for travellers to malarial areas is N,N-diethyl-3-methylbenzamide (diethyltoluamide, DEET). There are many alternative products, the majority being less effective or shorter acting than DEET (4). The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. (3) Although there are no data on its transfer into human breast milk, DEET 20–50% in lotions, sprays, or roll-on formulations is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during breast-feeding where the mother is travelling to a malaria endemic country. (3, 4) For non-malaria endemic countries due to the lack of data, application to large body areas, and preparations containing more than 25% DEET, should be avoided (39).

Summary

- Wherever possible, travelling into endemic countries should be delayed until after the lactation period. If travelling is unavoidable, the appropriate malaria prophylaxis must be chosen, first and foremost, based on efficacy rather than safety during breastfeeding.
- Chloroquine, proguanil, and mefloquine are considered compatible with breastfeeding.
- The Center for Disease Control and Prevention indicates that atovaquone may be used during breastfeeding where the infant weighs at least 5kg.
- Short term use of doxycycline is unlikely to be harmful to a breastfed infant. However, for malaria prophylaxis doxycycline therapy is likely to be in excess of five weeks, and therefore doxycycline should be avoided during lactation for this indication if other suitable prophylactic

options are available. If no other options are available, breastfeeding can continue with caution.

- Hydroxychloroquine is not licensed or routinely recommended for malaria prophylaxis, except when a patient already taking it as treatment for a medical condition also requires chloroquine for malaria prophylaxis, in which case hydroxychloroquine can be substituted; dose changes may be required. In this situation, hydroxychloroquine would be considered compatible during breastfeeding.
- Although many of the drugs pass into breast milk in small amounts, prophylactic treatment, at the full recommended dose, must also be given to the infant.
- In addition to chemoprophylaxis, all usual measures to reduce the risk of insect bites, including the use of effective insect repellents, are strongly recommended.

Limitations

- Data for mefloquine are extremely limited, and there are no data at all for proguanil or atovaquone.
- There is no data on long-term use of doxycycline whilst breastfeeding.
- Studies of chloroquine or hydroxychloroquine transfer into breast milk are likely to underestimate infant exposure after repeated or prolonged maternal administration.
- None of the published studies are on the use of these drugs for malaria prophylaxis.
- The information relates to full term and healthy infants. Evidence in preterm infants is largely 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.

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Search strategy

- Embase and Medline (Standard UKDILAS Search Patterns)
- In-house UKDILAS database
- Midlands Medicines Lactation Website. Available from http://www.midlandsmedicines.nhs.uk/content.asp?section=6&subsection=17&pageIdx=1
- Medications and Mothers' Milk Online (Medilact)
- 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
- Centres for Disease Control and Prevention. Available from http://www.cdc.gov/
- National Travel Health Network & Centre (NaTHNaC), Hospital for Tropical Diseases, London. Available from www.nathnac.org
- Manufacturers Summary of Product Characteristics (SPC).
- World Health Organisation. Available from http://www.who.int/en/