Q&A 97.5

Can mothers breastfeed while taking azathioprine?

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

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Background

Azathioprine is a cytotoxic immunosuppressant drug. It is used either alone or in combination (usually with corticosteroids) in the treatment of many conditions including suppression of organ transplant rejection, autoimmune disease and rheumatoid arthritis [1,2].

Azathioprine is metabolised to mercaptopurine (6-MP), a purine analogue, which inhibits DNA synthesis [1,3]. 6-MP is further metabolised to active metabolites, including 6-thioguanine nucleoside (6-TGN) and 6-methylmercaptopurine nucleosides (6-MMPN). The metabolism of 6-TGN is undertaken by the enzyme thiopurine methyltransferase (TPMT), deficiencies of which can lead to excessive toxicity [3]. Immune responses become suppressed following administration of azathioprine due to its cytotoxic action on dividing immune cells.

Patients receiving azathioprine alone, or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections. Azathioprine is associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leucopenia, but also occasionally as anaemia and thrombocytopenia. Nausea, vomiting and diarrhoea can also occur [1,2].

Azathioprine is, therefore, used in a variety of clinical situations in which treatment is essential and in all age groups, including women who may wish to breastfeed their infants. This raises the question of the compatibility of azathioprine with breastfeeding.

Answer

The following information relates to full term and healthy infants. 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.

Pharmacodynamic data can give a theoretical indication of transfer of a drug into breast milk. Passage of azathioprine/6-MP into the breast milk should be expected due to low molecular weights (277 and 170 respectively) and low protein binding (30% and 19% respectively) [4,5]. The mean oral bioavailability of azathioprine is 44% and that of 6-MP is 50% [4, 5]. Therefore, infant absorption of azathioprine/6-MP from breast milk should be expected.

Evidence of the secretion of azathioprine/6-MP into breast milk, and its safety in breastfed infants, is limited to relatively small studies with limited numbers of mothers and infants [6–24].

Breast milk and infant levels

In a study of two lactating women taking azathioprine (75 mg and 25 mg/day respectively) following renal allograph, small quantities of 6-MP in milk were identified. Only one mother, taking 75 mg/day, was breastfeeding her infant. Milk levels peaked at around 2 hours (3.4 nanograms/mL) and again at 8 hours (4.5 nanograms/mL) after administration of 75 mg. In the mother not breastfeeding her infant, the peak level at 2 hours after a 25 mg dose was 18 nanograms/mL [6]. No effect on IgA levels in the milk of the mother taking 75mg were noted. Based on the one mother-infant pair who breastfed, it was estimated that the infant would ingest a maximum of 0.1% of the maternal weight-adjusted dose of azathioprine (based on the 6-MP levels) [3, 4]. Infant plasma levels were not measured [6].

In a further study of two mother-infant pairs, the mothers received azathioprine, 100 mg/day, for systemic lupus erythematosus (SLE). No 6-MP was detected in milk samples (limit of detection 5 nanograms/mL) from which the authors calculated that the infant would ingest less than 0.09% of a weight-adjusted maternal dose [7].

In another study, 10 infant-mother pairs were receiving azathioprine, 75–150 mg/day as a single daily dose, for SLE, lupus nephritis, Crohn's disease or post transplantation. Milk samples were collected before the daily dose was taken and at each breastfeed for 12–18 hours on days 3, 7,10, and 28 postpartum. Of the 31 total samples, 6-MP was detected in only two, although assay sensitivity limits were not stated. These were in one mother at 3 hours and 6 hours (1.2 and 7.6 nanograms/mL respectively) after maternal azathioprine ingestion on day 28. 6-MP and 6-TGN were not detected in the blood of 7 infants in whom it was measured [8].

In a study with eight infant-mother pairs, mothers were taking azathioprine, 75–200 mg daily, for inflammatory bowel disease (IBD). Mothers were 1.5 to 7 months postpartum and all had normal TPMT phenotypes. Peak milk 6-MP levels of 2–50 nanograms/mL occurred within 4 hours of the maternal dose, dropping significantly by 5 hours. It was estimated that, at peak milk levels, the infants would ingest a maximum of 0.0075 mg/kg/day, equivalent to less than 1% of the weight-adjusted maternal dose. However, in practice, exposure will only be approximately 10% of the maximum levels due to lower levels in the remaining samples [9].

Four women taking azathioprine 1.2–2.1 mg/kg/day and their infants were studied [10]. These were supplemented by two additional infant-mother pairs in a subsequent report [11]. All had the normal TPMT phenotype. Maternal 6-TGN and 6-MMPN concentrations were consistent with those associated with improved therapeutic outcomes. Neither 6-TGN nor 6-MMPN were detected in any of the infants (assay sensitivity 30 picomoles per 8 x 10^8 red blood cells). It was concluded that azathioprine may be 'safe' during breastfeeding in patients with the normal TPMT phenotype (~90% of caucasian patients) taking 'normal' doses [10,11].

In a study of three breastfeeding mothers taking azathioprine, 100–175 mg/day, for SLE or IBD, infant blood samples were taken at 3 days and at 3 weeks postpartum. In one infant, low (unspecified) levels of 6-TGN, but no 6-MMPN, were found in the infant's blood at 3 days postpartum, and neither could be detected at 3 weeks in this, and another, infant [12].

Effects on breastfeeding infants

Some studies have assessed whether exposure to azathioprine, through its metabolite 6-MP, in breast milk presents any apparent risk to the breastfed infant. In a study in which one infant was breastfed, follow-up at 3 months showed that the infant had remained in the 75th percentile for height and weight and there were no effects on haemoglobin levels, leucocyte or platelet counts, or infection rates [6]. In another study, two infants were breastfed while their mothers received azathioprine 75–100 mg daily after renal transplantation. Azathioprine/6-MP levels in maternal plasma, breast milk, and infant plasma were not determined. At follow up (time not specified), infants had normal blood cell counts and no significant increase in infection rates. Above average growth rates were noted [13].

In a single case study, a mother received azathioprine, 100 mg daily, as part of a post kidney and pancreas transplant regimen, including ciclosporin and prednisone, for 10.5 months after delivery. During this time her infant was exclusively breastfed, with partial breastfeeding up to 2 years. The infant grew and developed normally. The mother subsequently breastfed a second infant successfully [14]. In a similar study the infants of 6 mothers receiving azathioprine, ciclosporin and prednisone post-transplant showed no adverse effects related to growth, development or renal function, although the main focus of the study was on the ciclosporin [15].

In a prospective observational study seven infants who were breastfed while their mothers received azathioprine, 50-100 mg/day, were evaluated. Infants underwent routine blood tests to check for immunosuppression. One infant demonstrated a reduced neutrophil count at 6 weeks, which subsequently returned to normal with continued breastfeeding. A second infant experienced a reduced total white cell count at 5 weeks, which subsequently returned to normal, again with continued breastfeeding. All infants were developing normally at follow-ups (at 1–24 weeks) and none showed an increase in infection rate [16,17]. Feeding in one infant was subsequently discontinued due to effects on blood count (details are not given) [17].

In a study of 4 mother-infant pairs, the mothers were receiving azathioprine, 50–100 mg/day for SLE or post organ transplantation. Infants were breastfed for up to 12 months and followed-up for 1–15 months, after which no adverse effects were noted in any of the infants, who also had normal growth

and development [7]. In a further study, no signs of immunosuppression were detected in 10 infants, three of whom were born at 32–34 weeks gestation, whose mothers were taking 75–150mg/day azathioprine. The infants were followed-up for 28 days. One infant had a borderline low neutrophil count, but normal white cell count [8].

In a study of three infants whose mothers were taking azathioprine, 100–175 mg/day, the infants were found to be healthy, with normal growth and no history of recurring infections at 4–24 months postpartum after breastfeeding for 4–12 months [12]. No adverse effects were seen in six breastfed infants at 3 months postpartum whose mothers were taking azathioprine, 1.2–2.1 mg/kg/day [11].

In a questionnaire survey of 128 fertile women with autoimmune hepatitis, four women with eight infants were identified as having taken azathioprine (dose and duration unspecified). No adverse effects were reported in the infants exposed to azathioprine via breast milk [18].

In a prospective study, 15 breastfed infants of 11 mothers with Crohn's disease, who received azathiorpine at a median maternal dose of 150 mg daily (range 100–250 mg daily), were studied. Infants breastfed for a median of 6 months (range 1–18 months) and were followed for a median of 3.3 years (range 0.6–6 years). All infants were assessed to have adequate mental and physical development. No untoward clinical events in the infants, including infections, were attributable to azathioprine [19].

The infants of 23 women with inflammatory bowel disease were followed in a nonrandomized, prospective study. No differences were found in mental or physical development between 15 breastfed infants whose mothers received azathioprine (median dose 150 mg/day, breastfed for a median of 6 months, with follow-up at a median of 3.3 years) and 15 infants whose mothers did not take azathioprine (breastfed for a median of 8 months, with follow-up at a median of 4.7 years). There was greater incidence of common cold (>2 colds annually) and conjunctivitis in infants not exposed to azathioprine [20].

The infants of four mothers who took azathioprine (100–150 mg/day) and tacrolimus (4.5–15 mg/day) during pregnancy for organ transplantation were breastfed for 60–180 days and followed for periods of 7–20 months. None of the infants had any clear azathioprine-related side effects, although one had transient thrombocytosis that resolved despite continued breastfeeding. Developmental milestones were normal and no pattern of infections was noted [21].

In a prospective cohort study pregnant women with inflammatory bowel disease were followed throughout pregnancy and for 12 months postpartum. They were assigned to one of four groups including one group with azathioprine or mercaptopurine alone (n=265) and one with both azathioprine/mercaptopurine and an anti-TNF (n=59). 72% of 1052 women enrolled in the study breastfed their infants, although the proportion within each group is not stated. The use of azathioprine or mercaptopurine alone was not associated with any complication in the infants. Infants exposed to both azathioprin/mercaptopurine and an anti-TNF had a 50% increase in the number of infections between 9 and 12 months of age, although the relationship with breastfeeding could not be determined. Infants in all groups showed normal growth and development [22].

Thirty infants whose mothers were taking either azathioprine (n=28) or mercaptopurine (n=2) for inflammatory bowel disease during pregnancy and postpartum were prosepctively followed at 1 to 6 years of age and assessed using a quality of life questionnaire. Nine infants were breastfed for a mean of 7 months (range 3–13 months) and no significant differences were found between breastfed and formula-fed infants in the survey results. The authors conclude that mothers using azathioprine or mercaptopurine should be encouraged to breastfeed their infants [23].

Thirty infants of 29 mothers took azathioprine, 50–175 mg daily during pregnancy and breastfed for at least 1 month (range 1–17 months). Eleven babies were born prematurely (27–36 weeks). Three infants had low white blood cell (WBC) counts at birth that normalised during breastfeeding. Twenty infants had later WBC counts, one of whom had mild, asymptomatic neutropenia during 1.5 months of breastfeeding that persisted for 15 days following breastfeeding discontinuation. No other adverse effects were seen during a median of 9.5 months (range 1.5–30 months) of follow-up [24].

Summary

- Azathioprine passes into breast milk in small quantities. At the highest recorded level of 6-MP in breast milk (50 nanograms/mL) an infant consuming 150 mL/kg breast milk each day (international standard [4]) would ingest 7.5 micrograms/kg bodyweight of 6-MP (equivalent to 12.2 micrograms/kg bodyweight azathioprine). The recommended daily dose of azathioprine for a 1 month old infant is 1–3 mg/kg bodyweight daily [1, 25].

- The evidence available suggests that azathioprine, in normal therapeutic doses in the mother, is compatible with breastfeeding in infants who are full-term and healthy and with no compromised immune system.

- It would, however, be advisable to monitor the infant for signs of infection and immunosupression. If high dose azathioprine therapy is used, monitor infant blood counts. The frequency and duration of blood monitoring should be a clinical decision based on several factors including dose of azathioprine, frequency of breast feeding, age and health of the infant.

Limitations

- Evidence of the secretion of azathioprine, and its metabolites, including 6-MP, into breast milk, and its safety in breastfed infants, is limited to relatively small studies with limited numbers of mothers and infants.
- Evidence for long-term safety is also scant.
- 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.*

References

1. Summary of Product Characteristics (SPC), Imuran tablets 25mg (Aspen Pharma Ltd). Available at www.emc.medicines.org.uk [Accessed on 12/01/2016] . Last updated on eMC 09/12/2014.
2. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. Available at www.evidence.nhs.uk/formulary/bnf/current. [Accessed on 12/01/2016.]
3. National Library of Medicine. "LactMed Database". Available at http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. [Accessed on 12/01/2016].
4. Hale TW. Medications and Mother's Milk. Online edition. Amarillo, TX. Pharmasoft Publishing. Available at www.medsmilk.com. [Accessed on 12/01/2016].
5. DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. [Accessed on 12/01/2016].
6. c CB , Moyer TP, Jiang NS et al. Breast-feeding after renal transplantation. Transplant Proc 1982;14:605-609.
7. Moretti ME, Verjee Z, Ito S et al. Breast-feeding during maternal use of azathioprine. Ann Pharmacother 2006;40:2269-2272.
8. Sau A, Clarke S, Bass J et al. Azathioprine and breastfeeding-is it safe? BJOG 2007;114:498-501.
9. Christensen LA, Dahlerup JF, Nielsen MJ et al. Azathioprine treatment during lactation. Aliment Pharmacol Ther 2008;28:1209-1213.
10. Gardiner SJ, Gearry RB, Roberts RL et al. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. Br J Clin Pharmacol 2006;62:453-456.
11. Gardiner SJ, Gearry RB, Roberts RL et al. Comment: breast-feeding during maternal use of azathioprine. Ann Pharmacother 2007;41:719-720.
12. Bernard N, Garayt C, Chol F et al. Prospective clinical and biological follow-up of three breastfed babies from azathioprine-treated mothers. Fundam Clin Pharmacol 2007;21 (Suppl. 1):62-63 (Abstract).
13. Grekas DM, Vasiliou SS, Lazarides AN. Immunosupressive therapy and breast-feeding after renal transplantation. Nephron 1984: 37: 68.
14. Thiagarajan KD, Easterling T, Davis C et al. Breast-feeding by a cyclosporine-treated mother. Obstet Gynecol 2001;97:816-818.
15. Nyberg G, Haljamae U, Frisenette-Fich C et al. Breast-feeding during treatment with cyclosporine. Transplantation 1998;65:253-255.
16. Khare MM, Qualie J, Currie A et al. Is breast feeding safe with azathioprine?, Leicester Royal Infirmary, Leicester, LE1 5WW. [Unpublished data 2004.
17. Khare MM, Lott J, Currie A et al. Is it safe to continue azathioprine in breast feeding mothers? J Obstet Gynaecol 2003;23 (Suppl 1):S48. Abstract 53.

18. Werner M, Bjornsson E, Prytz H et al. Autoimmune hepatitis among fertile women: strategies during pregnancy and breastfeeding? Scand J Gastroenterol. 2007;42:986-91.
19. Angelberger S, Reinisch W, Messerschmidt A et al. Breastfeeding during maintenance azathioprine treatment (AZA) in patients with Crohn's disease (CD). Gastroenterology 2008;134 (Suppl. 1): A657. Abstract.
20. Angelberger S, Reinisch W, Messerschmidt A et al. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. J Crohns Colitis 2011;5:95-100.
21. Gouraud A, Bernard N, Millaret A et al. Follow-up of tacrolimus breastfed babies. Transplantation 2012;94:e38-40.
22. Mahadevan U, Martin CF, Sandler RS et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology. 2012;142 (5 Suppl 1):S149. Abstract 865.
23. de Meij TG, Jharap B, Kneepkens CM et al. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:38–43.
24. Bernard N, Gouraud A, Paret N et al. Azathioprine and breastfeeding: long-term follow-up. Fundam Clin Pharmacol 2013;27 (Suppl 1):12. Abstract 05-03.
25. Paediatric Formulary Committee. *BNF for Children* (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. Available at www.evidence.nhs.uk/formulary/bnfc/current. [Accessed on 12/01/2016]

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Search strategy

- UK Drugs in Lactation Advisory Service – in-house data-base
- Medline and Embase: Standard UKDILAS search pattern found at http://www.ukmi.nhs.uk/activities/specialistServices/default.asp?pageRef=2
  Drug names: azathioprine; mercaptopurine
- Medications and Mothers' Milk Online (Medilact): azathioprine and mercaptopurine monographs)
- US National Library of Medicine Lactmed database: azathioprine and mercaptopurine monographs
- Electronic Medicines Compendium (Imuran SPC)