Is breastfeeding safe with azathioprine?

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Summary

Background: Azathioprine is commonly used as an immunosuppressant during pregnancy in the management of various conditions such as connective tissue disorders, inflammatory bowel disease and pregnant women with organ transplant. Continuation of azathioprine through pregnancy and postpartum is vital for maternal reasons. However, there is limited evidence regarding safety of use of azathioprine with breastfeeding.

Methods and results: We report an observational case series of 10 mother–baby pairs managed at a tertiary teaching hospital. Mothers on azathioprine who were keen to breastfeed were counselled antenatally regarding limited short-term and long-term safety data for the babies. Mothers participating in this study completed a questionnaire at every visit. At follow-up visits, babies were examined by a neonatologist for clinical signs of infection and checked for adverse effects on haematological profile.

Conclusion: There was no clinically significant adverse effect on haematological profile or immunosuppression in these babies. Our case series supports safety of azathioprine in the short term. However, large numbers are needed to determine long-term safety of azathioprine and breastfeeding.

Keywords: azathioprine, breastfeeding, maternal–fetal medicine

INTRODUCTION

Azathioprine is an antimetabolite used as an immunosuppressant in the treatment of conditions such as connective tissue disorders, inflammatory bowel disease and renal transplant. The incidence of inflammatory bowel disease (Crohn's disease, ulcerative colitis) is increasing in the reproductive age group and does not significantly affect fertility particularly once remission is achieved.¹ The use of azathioprine in pregnancy is advised to achieve optimal outcome and prevent maternal and fetal complications of inadequately treated disease.² All women on azathioprine should ideally have preconception counselling to discuss the safety of its continued use in pregnancy. Women keen on breastfeeding should be provided with balanced and evidence-based information regarding its safety during breastfeeding.³ Azathioprine is readily absorbed orally and rapidly metabolized to 6-mercaptopurine (6-MP), its active metabolite.

Both azathioprine and 6-MP cross the placenta, although only low concentrations have been detected in the fetus.⁴ Its major toxic effects include increased susceptibility to chest infections, bone-marrow depression and hepatotoxicity. Most of the published experience of azathioprine in pregnant

women has been in those with renal transplants and no specific teratogenicity related to azathioprine has been reported.⁵ The World Health Organization (WHO) and Food and Drugs Administration advises against the use of azathioprine in breastfeeding women due to its immunosuppressive effect on babies.^{3,6} Recent studies suggest that azathioprine in doses (1.2–2.1 mg/kg) may be safe in breastfeeding women.¹ The advice to avoid breastfeeding while on azathioprine is based on limited data.^{4,7}

The aim of this observational case series was to clinically monitor breastfed infants of mothers taking azathioprine, and to assess the effects of azathioprine on the haematological profiles of these infants. This was in response to considerable interest from women taking azathioprine who expressed a desire to breastfeed their infants.

METHODS

This study was conducted in a teaching hospital in the UK. Women on azathioprine were seen in the joint maternal medicine clinic and were counselled by a consultant obstetrician and maternity pharmacist regarding the limited data and lack of long-term follow-up available regarding the effects of azathioprine on the infant. Those who expressed a desire to breastfeed while on azathioprine were recruited into this study. Only clinically well infants greater than 35 weeks of gestational age, born to mothers taking azathioprine 2 mg/kg or less per day who wished to breastfeed, were considered eligible. Consent to monitor infants was obtained from the

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Note: This paper is dedicated to the memory of Mr Edmund Howarth who worked tirelessly for the wellbeing of pregnant women. He sadly passed away on 6 August 2010.

mothers. During the period of breastfeeding, infants were seen by a paediatrician. All women were asked to report any illness such as diarrhoea or chest infections in their baby. Full blood counts were performed at intermittent intervals during this time to monitor the potential effects of azathioprine on bone marrow function. Mothers were also asked to complete a questionnaire each time the baby was brought for review, covering their medications as well as frequency of breastfeeding.

The Local Research Ethics committee was consulted and agreed that as this was a part of the clinical monitoring offered to the infants no formal ethics approval was needed.

RESULTS

There were 10 mother–baby pairs included in this study. Clinical indications and dose of azathioprine taken antenatally and while breastfeeding are shown in Table 1. Five mothers required other medications as shown in the table. The neonatal demographics, including gestational age, birth weight and sex are also included.

Table 2 illustrates the haematological profiles of the babies at follow-up. One of the women (Case 2) chose not to take azathioprine during her pregnancy, but commenced azathioprine once the infant was four weeks of age and continued to breastfeed while taking it until the infant was 15 weeks of age when breastfeeding stopped. All the mothers were taking less than 2 mg/kg/day of azathioprine.

It can be seen from the tables that for the majority of observations, the total white cell and neutrophil counts remained within normal reference levels. Baby 1 at six weeks of age showed a neutrophil count of 0.9 (normal lower limit being 1.0), which subsequently recovered, while baby 6 at five weeks of age showed a total white cell count of 4.9 (normal lower limit being 6.0). Other babies demonstrated neutrophil

counts at the lower end of the range on some occasions. Total white cell counts were all in the normal range apart from the one mentioned above. All the infants remained clinically well with no signs of increased rates of infection during this period.

Baby 2 started breastfeeding at five weeks of age, and there were no concerns with haematological profile during follow-up. Limited follow-up was available on five of the seven babies. Baby 3 was discharged home at 12 days of age, having been admitted to the neonatal unit from birth with unexplained transient hypoglycaemia and hyponatremia. Breastfeeding was established at six weeks and stopped at 21 weeks of age.

Baby 4 required surgery for congenital bowel obstruction and hence was nil by mouth in the early neonatal period. The infant made an uneventful recovery and was discharged home at seven days fully breastfed. Breastfeeding was stopped at three weeks of age and the infant was discharged from hospital care at eight weeks of age.

In baby 5, monitoring was changed to a two-monthly schedule at the nine-week visit. Breastfeeding was stopped at 17 weeks of age. There have been no concerns with the baby's developmental milestones.

Baby 6 was admitted to the neonatal unit at two hours of age due to grunting and received antibiotics for seven days. She also had vomiting, which resolved by day 8 when she was discharged. There have been no concerns since.

Babies 7, 8, 9 and 10 were breastfed for three months and followed up until six months in the neonatal clinic. There were no concerns regarding their health or development.

DISCUSSION

It is universally accepted that breastfeeding is superior to formula feeding for the newborn. The use of potentially toxic drugs by breastfeeding mothers often causes concern. While

Table 1 Medications taken by mothers antenatally and neonatal outcomes

Mother and baby	Mother's indication for taking azathioprine	Dose of azathioprine	Other antenatal medications	Baby's gestation at delivery (weeks)	Birth weight (kg)	Sex of the baby
1	Ulcerative colitis	1.5 mg/kg/day	Nil	40	4.200	Male
2	Rheumatoid arthritis	100 mg o.d. postnatally. 1.3 mg/kg/day	Prednisolone 7.5 mg daily	35	2.260	Female
3	Ulcerative colitis	100 mg o.d. 1.4 mg/kg/day	Prednisolone 5 mg daily, mesalazine 800 mg t.d.s.	38	2.648	Female
4	Ulcerative colitis	100 mg o.d. 1.9 mg/kg/day	Nil	38	3.480	Male
5	Primary biliary cirrhosis, auto-immune hepatitis	75 mg o.d. 1.2 mg/kg/day.	Prednisolone 1 mg o.d., levothyroxine 100 µg o.d.	37	2.760	Male
6	Crohn's	75 mg o.d. 1.4 mg/kg/day	Codeine phosphate 90 mg daily, folic acid 5 mg o.d., Budesonide 6 mg o.d., omeprazole 20 mg o.d., vitamin B ₁₂	36	2.820	Female
7	Systemic lupus erythematosus	50 mg b.i.d. 1.65 mg/kg/day	Levothyroxine 25 µg o.d.	41	3.997	Male
8	Ulcerative colitis	50 mg b.i.d. 2 mg/kg/day	Nil	40	2.970	Female
9	Crohn's disease	100 mg 1.5 mg/kg/day	Nil	42	3.700	Female
10	Crohn's disease	50 mg b.i.d. 1.5 mg/kg/day	Nil	39	3.540	Male

o.d., once daily; b.i.d., twice daily; t.d.s., thrice daily

Table 2 Haematological profiles of babies 1–10 at follow-up

	Baby 1	Baby 2	Baby 3	Baby 4	Baby 5	Baby 6	Baby 7	Baby 8	Baby 9	Baby 10
Age in weeks	6 10	At birth 10 15	At birth 1 6 11 15 20 24	At birth 1 20	1 5 9	At birth 5 16	1 8 15	2 15 37	1 15 46	1 22
White cell count (WCC) (6.0 –17.5 x10 ⁹ / L)	7 10.2	12 10 8.2	13.3 10.6 13.9 11.6 12.8	21.3 12.9	11 12.2 7.7	15.6 4.9 7.5 7.9	20.8 10.4 11.7	15 11 11	25 9.3 11.1	27 9.2
Neutrophil count (1–8.5 X 10 ⁹)	0.9 4.1	6.7 2.1 1.3	9.04 4.13 1.2 2.09 1.2 1.8 2.8	15.12 6.9	3.96 3.78 1.4	13.57 1.0 2.2 1.9	15.59 1.10 2.5	10 4 2	3 2.6 2.9	3.5 3.3
Haemoglobin	12.1 11.2	18.2 9.7 9.9	15.6 16 11.1 10.8 10.7 11.1 10.6	17.7 16.9	14.6 9.2 9.4	15.3 12.2 11.6 11.7	16.6 11.4 11.4	18 17.9 13.3	14.7 12.1 10.4	17.2 13
Platelet count	599 585	305 624 534	160 215 657 582 608 532 472	296 302	405 545 472	282 480 603 533	236 627 600	397 681 513	290 790 920	278 368
Totally Breastfeeding (BF)	Yes Yes	No Yes Yes	see note 1	NBM Yes BF stopped at 3 weeks	Yes Yes Yes	Yes Yes Yes	Yes No No	Yes Yes Yes	Yes Yes Yes	Yes Yes
Dose of Azathioprine by mother (mg/kg/day)	1.5 1.5	1.3 1.3	1.4 throughout	1.9	1.2 1.2	1.4 1.4	1.65 1.65 1.4	2 2	1.5 1.5	1.5

Note1: Baby 3 was initially mixed fed NG/BF. Breastfeeding was established at 6 weeks and at 20 weeks the baby was weaned to twice a day with formula feed in between. Breastfeeding was stopped at 21 weeks of age.

this is a balance of risk versus benefit, unfortunately there is often a paucity of data regarding breast milk excretion and effects on the newborn for many drugs.

At present, the WHO does not recommend azathioprine in breastfeeding mothers due to its immunosuppressive effects.⁶ Increasing numbers of women are using azathioprine in the antenatal and postnatal period for a range of disorders. There are limited data in the literature regarding safety of breastfeeding in women on azathioprine. This often leads to conflicting advice resulting in either mothers avoiding breastfeeding unnecessarily or discontinuing their medication, thus potentially causing harm to themselves.

After absorption, azathioprine is rapidly converted into 6-MP by the liver and subsequently undergoes further methylation by thiopurine-S-methyltransferase (TPMT) into 6-thioguaninenucleotides (6-TGN). TPMT has a trimodal variation in the general population. Deficiency is inherited in an

autosomal-recessive manner with one in 300 subjects having homozygous deficiency, and around 8–10% of the community having intermediate enzyme activities. Subjects with heterozygote deficiency will metabolize increased amounts of 6-MP through the pathway to 6-TGN. Although 6-TGN production underlies the therapeutic action of azathioprine, excessive amounts (as when TPMT is homozygous deficient) are extremely toxic and can result in myelosuppression, neutropenia and potentially death.

Although it is not possible to measure azathioprine in breast milk due to its short half-life of 10 minutes,⁸ 6-MP can be detected in breast milk. There is a theoretical possibility of cumulative toxicity of azathioprine metabolites due to repeated feeding at short intervals but there is no evidence to support this.⁸ Christensen *et al.* measured 6-MP levels in maternal plasma and breast milk of eight women taking azathioprine in doses of 75–200 mg once daily. Although the concentration

of 6-MP in maternal milk showed peak values within the first four hours of drug intake, there was a wide variation in levels. Further, the estimated maximum exposure of drug to infant was <1% of maternal dose per day.⁹ Moretti *et al.*¹⁰ in a series of four case reports on maternal use of azathioprine during breastfeeding found that the concentration of 6-MP in breast milk was too low to produce any clinical effects in infants. TPMT levels were not assessed in the current study as it is not local practice and most women were established on azathioprine without suffering any adverse effects. However, in infants with very low TPMT activity (1 in 300), breastfeeding should be avoided as accumulation of 6-MP could cause toxicity in higher doses. We did not measure 6-MP levels in the infants' blood or in breast milk and none of the infants showed signs of cytotoxicity or infection while being breast fed.

To the best of our knowledge, this is one of the largest case series in the literature regarding breastfeeding and azathioprine. There is emerging clinical and laboratory evidence pointing to the safety of breastfeeding in women on azathioprine though there are only a few small studies confirming this.⁸⁻¹⁰ Hence, until further evidence is obtained from larger studies, these infants will need to be monitored for white cell counts, neutrophil counts and evidence of infection. Infants of mothers on azathioprine should routinely be allowed to breast-feed and this information should be a part of prenatal counseling. There is also a need for long-term follow-up in these babies.

We would recommend the establishment of a national registry of all infants who are breastfed by mothers taking azathioprine and other immunosuppressant drugs. The feasibility and usefulness of such registers has been tested in the past, e.g. national epilepsy registry for pregnant women in UK. This would allow assessment of the safety of drugs such as azathioprine in breastfed infants in both the short and long term. These data would then be useful in counselling patients.

CONCLUSION

Our results suggest that in this case series there were no short-term adverse effects such as immunosuppression or infections in early infancy in babies breastfed by mothers taking

azathioprine. However, long-term effects are not known and further studies are required. Although several other small studies have confirmed the safety of azathioprine in breast-fed infants, it may be prudent to continue to monitor these infants clinically while they are breast fed. A multidisciplinary approach in the management of these women and their babies is likely to be beneficial to mother and baby. There is a need for increased awareness among health professionals caring for these women so that they can give the appropriate advice for breastfeeding. While we acknowledge the lack of information regarding long-term follow-up, data from this series will assist women in their decisions regarding breastfeeding.

DECLARATION

The authors have no conflict of interest to declare.

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