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Mercaptopurine

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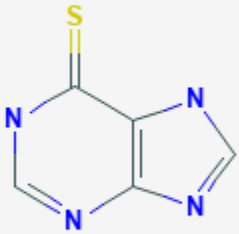

Drug Levels and Effects

Summary of Use during Lactation

Most sources consider breastfeeding to be contraindicated during maternal antineoplastic drug therapy, although antimetabolites such as mercaptopurine appear to pose the least risk to breastfed infants.[1] After high-dose chemotherapy, it might be possible to breastfeed safely during intermittent therapy with an appropriate period of breastfeeding abstinence. Although no data are available to determine an appropriate period to withhold breastfeeding, the drug's terminal half-life suggests that withholding breastfeeding for 1 to 2 days may be sufficient. Chemotherapy may adversely affect the normal microbiome and chemical makeup of breastmilk.[2]

In the treatment of conditions such as ulcerative colitis and Crohn's disease, low doses of mercaptopurine (6-MP) for immunosuppression appear to be acceptable.[3-8] No active metabolites of mercaptopurine were found in the blood of breastfed infants whose mothers were taking azathioprine and no adverse effects attributable to

mercaptopurine or azathioprine have been noted. See the Azathioprine record for details. Mothers with decreased activity of the enzyme that detoxifies mercaptopurine metabolites may transmit higher levels of drug to their infants in breastmilk. It might be desirable to monitor exclusively breastfed infants with a complete blood count with differential, and liver function tests if mercaptopurine is used during lactation, although some authors feel that monitoring is unnecessary.[9] Avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant in breastmilk.[10]

Drug Levels

Mercaptopurine is the active metabolite of azathioprine. It is further metabolized to active metabolites including 6-methylmercaptopurine, thioguanine, 6-thioguanine nucleosides (6-TGNs) and 6-methylmercaptopurine nucleosides (6-MMPN). The enzyme thiopurine methyltransferase (TPMT) is responsible for metabolism of 6-TGNs. Deficiencies in this enzyme can lead to excessive toxicity.

Maternal Levels. Mercaptopurine milk levels were measured in 2 patients receiving azathioprine following renal transplantation. In one, peak milk levels occurred 2 and 8 hours after a 75 mg oral dose and were 3.4 and 4.5 mcg/L respectively. In the other, a peak milk level of 18 mcg/L occurred 2 hours after a 25 mg oral dose. Serum levels were not measured.[11]

Four women receiving an immunomodulator to treat inflammatory bowel disease had metabolite levels measured in milk during the first 6 weeks postpartum. The abstract does not mention the specific drug and dose being taken, but the azathioprine metabolites 6-methylmercaptopurine (6-MMP) and 6-thioguanine nucleosides (6-TGNs) were measured. Although therapeutic levels were found in maternal serum, 6-MMP (<650 mcg/L) and 6-TGNs were undetectable (<123 mcg/L) in milk (time of collection not stated).[12]

A woman was taking 50 mg daily of mercaptopurine for Crohn's disease during pregnancy and postpartum. A milk sample taken on the first day postpartum 4 hours after ingestion of the dose had no detectable levels (<25 pmol/L) of mercaptopurine or its metabolites, 6-thioguanine and 6-methylmercaptopurine.[13]

Infant Levels. Four infants were breastfed (3 exclusively, 1 rarely received formula) during maternal use of azathioprine orally in dosages of 1.2 to 2.1 mg/kg daily. All of the mothers and infants had the wild type TPMT *1/*1 genotype and all of the mothers had normal enzyme activity. At 3 to 3.5 months of age, all of the infants' had undetectable blood levels of 6-TGNs and 6-MMPN.[14]

Effects in Breastfed Infants

In The Netherlands, 30 infants of mothers taking either azathioprine (n = 28) or mercaptopurine (n = 2) for inflammatory bowel disease during pregnancy and postpartum were followed at 1 to 6 years of age using a 43-item quality of life questionnaire. Of this cohort, 9 infants were breastfed for a mean of 7 months (range 3 to 13 months) No statistically significant differences were found between breastfed and formula-fed infants in any of the 12 domains of the survey.[15]

A prospective cohort study followed pregnant women with inflammatory bowel disease throughout pregnancy and for 12 months postpartum. Women were assigned to one of the following groups: unexposed (no thiopurines or anti-TNF agents); group A (azathioprine or mercaptopurine); group B (infliximab, adalimumab or certolizumab pegol) and group AB (both a thiopurine and an anti-TNF agent). Of 1052 women enrolled in the study, 72% breastfed their infants, although the extent and duration were not stated in the abstract. A total of 264 women were exposed to a thiopurine and 59 were exposed to a thiopurine plus an anti-TNF agent. The use of a thiopurine alone was not associated with any complication in the infants and their growth and development were normal throughout the 12 months. Infants exposed to both a thiopurine and an anti-TNF agent had a 50% increase in the number of infections between 9 and 12 months of age. The relationship of this increase with breastfeeding could not be determined from the available data.[16]

A national survey of gastroenterologists in Australia identified 21 infants who were breastfed by mothers taking a combination of allopurinol and a thiopurine (e.g. azathioprine, mercaptopurine) to treat inflammatory bowel disease. All had taked the combination during pregnancy also. Two postpartum infant deaths occurred, both at 3 months of age. One was a twin (premature birth-related) and the other from SIDS. The authors did not believe the deaths were medication related.[17] No information was provided on the extent of breastfeeding, drug dosages or the outcomes of the other infants.

Effects on Lactation and Breastmilk

Relevant published information was not found as of the revision date.

Alternate Drugs to Consider

(Immunosuppression) Cyclosporine, Tacrolimus; (Inflammatory Bowel Disease) Budesonide, Infliximab, Mesalamine, Prednisone; (Systemic Lupus Erythematosus) Hydroxychloroquine, Prednisone

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Substance Identification

Substance Name

Mercaptopurine

CAS Registry Number

50-44-2

Drug Class

Breast Feeding

Lactation

Antineoplastic Agents

Antimetabolites

Immunosuppressive Agents