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Mercaptopurine

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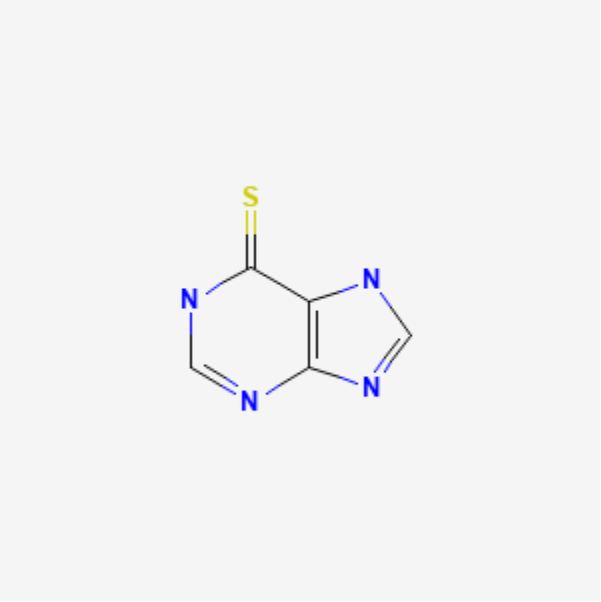

Drug Levels and Effects

Summary of Use during Lactation

In the treatment of conditions such as ulcerative colitis and Crohn's disease, most professional guidelines and other experts consider breastfeeding to be acceptable during mercaptopurine therapy.[1-9] Azathioprine is rapidly converted to mercaptopurine, so data from mothers taking azathioprine apply to mercaptopurine. No active metabolites of mercaptopurine were found in the blood of breastfed infants whose mothers were taking azathioprine and only poorly documented cases of mild, asymptomatic neutropenia and increased rates of infection have been reported occasionally. It might be desirable to monitor exclusively breastfed infants with a complete blood count with differential, and liver function tests if azathioprine is used during lactation, although some authors feel that such monitoring is unnecessary.[10]. 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.[11] Avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant in breastmilk.[12]

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.[13] 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.[14]

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.[15]

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).[16]

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.[17]

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 mothers and infants had the wild type TPMT *1/*1 genotype and all 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.[18]

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.[19]

In a multi-center study of women with inflammatory bowel disease in pregnancy (the PIANO registry), 102 women received a thiopurine (azathioprine or mercaptopurine) and another 67 received a thiopurine plus a biological agent (adalimumab, certolizumab, golimumab, infliximab, natalizumab, or ustekinumab) while breastfeeding their infants. Among those who received a thiopurine or combination therapy while breastfeeding,

infant growth, development or infection rate was no different from 208 breastfed infants whose mothers received no treatment.[20]

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 taken 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.[21] 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) Adalimumab, Azathioprine, Budesonide, Certolizumab Pegol, 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

Milk, Human

Antineoplastic Agents

Antimetabolites

Immunosuppressive Agents