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Azathioprine – clinical implications of its use

Azathioprine (AZA) is probably the most common immunosupresive drug used in autoimmune diseases such as systemic lupus erythematosus (SLE) or Crohn's disease. It is not used specifically for acute treatment of active disease manifestations but as steroid sparing-agent, in patients who are steroid dependent or who have recurrent diseases exacerbations necessitating reinstitution of steroids. Maintenance treatment with azathioprine in doses of 1.5-2.5 mg/kg/day has been shown to be associated with a lower development rate of severe forms of SLE, such as nephritis, or central nervous system involvement. In doses 1.25-3.0 mg/kg/day it is clearly more effective than placebo in rheumatoid arthritis (RA), there appears to be a dose-response relationship. In RA probably it is not as effective as methotrexate, though data are inconsistent. In long term studies it is proved to be more effective than steroids alone in psoriatic arthritis, polymyositis/dermatomyositis, Behçet's syndrome, reactive arthritis (Reiter's syndrome). It is now a widely accepted opinion among rheumatologists and obstetricians that AZA can be safely continued during pregnancy, in women with lupus it may in fact help to preserve the pregnancy by preventing a disease exacerbation.

In rheumatoid arthritis AZA reduces the numbers of circulating B and T Lymphocytes (particularly suppresser, or $CD8^+$ cells) mixed lymphocyte reactivity, immunoglobulin M and IgG synthesis and interleukin-2 secretion.

Its immunosuppressive action appears to be derived from the suppression of DNA synthesis by interference with adenine and guanine ribonucleotides. Its main active metabolite 6-thioguanine (6-TGN), another metabolite of azathioprine's principal metabolic product 6-mercaptopurine (6-MP), inhibits the enzymatic conversion of inosinic acid to xanthylic acid, and of adenylsuccinic acid to adenylic acid.

The metylation of 6-MP to active 6-TGN is catalyzed by thiopurine methyltransferase (TPMT), an enzyme that exhibits interindividual variations as a result of a known genetic polymorphism of its alleles. 89% of subjects have a normal to high level of TMPT activity, 11% have intermediate activity and 0.3% have low or absent TPMT activity. This last group of subjects is at high risk of bone marrow immunosupression, whereas the rest have a lower frequency of toxicity. Patients with intermediate levels of activity have a relative risk of 3.1 for development of severe side effects (predominantly non-hematologic) compared to patients with high level of TMPT activity.

In toxicity more viral infections have been reported, although not all authors agree with this conclusion. A 50-fold increase in relative risk of malignant diseases has been documented in AZA treated renal transplant patients (particularly non-Hodgkin's lymphomas), probably there is a small additional risk of developing some malignancies when using AZA in RA and a relative risk of between 2.2 and 8.7 for developing lymphoproliferative disorders. In systemic lupus erythematosus (SLE) patients, large studies documenting a higher than expected rate of hematologic and lymphoproliferative malignancies concluded that none of the affected patients had received AZA or other immunosupressive agent. Hepatotoxicity appeared when AZA was given in doses higher than 2.5 mg/kg/day – generally reversible upon discontinuation of the drug. Most severe, potentially lethal but fortunately rather infrequent bone marrow toxicity has been associated with intermediate or reduced levels of TPMT.

Interactions with allopurinol, cyclophosphamide and neuromuscular blockers (e.g. succinyl choline) have been known to require decreasing of the azathioprine dose significantly (50-75% when using allopurinol).

Before using AZA it is appropriate to discuss about potential risks and treatment goals, to take a detailed history and to perform a physical examination and laboratory testing. Since secondary intracellular metabolites are the source of azathioprine's activity, measuring plasma levels of AZA is not useful. Measuring erythrocyte TPMT levels, suggested by Zdziarska et al. may provide a useful guide to how patients are likely to tolerate azathioprine and thus may help to choose appropriate dosing of the drug.

Today to test for possible acute AZA sensitivity, 25-50 mg doses are suggested for the first week followed by complete blood count. Thereafter doses are increased regularly by 0.5 mg/kg/day every month, aiming for 2-3 mg/kg/day. The dose may then be adjusted to the minimum effective dose. Monitoring includes hemoglobin, white blood cell and platelet counts every 2 weeks while dosing regimens are being changed, and every 4-6 weeks during stable regimens. Liver function tests can be performed every 6-8 weeks.

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