THERAPEUTICS SNAPSHOT
PEER REVIEWED

Azathioprine

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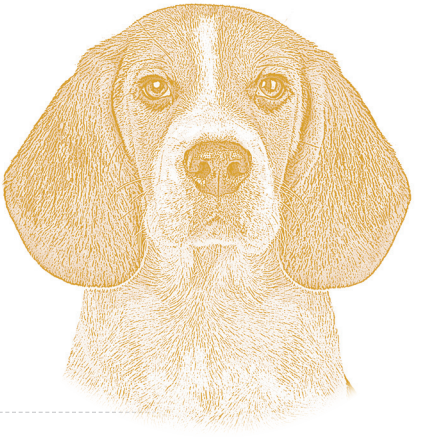

In dogs, azathioprine can be used as a steroid-sparing medication for immunosuppression.

Clinical Applications

Azathioprine works as an adjunctive and steroid-sparing medication during initial stages of immunosuppression.

- Clinical indications include immune-mediated hemolytic anemia or thrombocytopenia, immune-mediated polyarthropathy, inflammatory CNS disease, autoimmune dermatoses, acquired myasthenia gravis, and inflammatory bowel disease.

Azathioprine, a prodrug, is metabolized in the liver to 6-MP (also known as mercaptopurine), an antimetabolite that inhibits the enzyme responsible for purine synthesis, preventing DNA synthesis and, therefore, cell proliferation.

- 6-MP is subsequently metabolized by several enzymes, the most important being thiopurine methyltransferase (TPMT).
  - —Low TPMT activity correlates with increased myelosuppression in humans.
  - —TPMT activity in dogs is similar to that in humans and is significantly higher than that in cats and horses.
  - —Because low TPMT activity in cats correlates with a clinical finding of significant azathioprine-induced myelosuppression, use in cats is generally contraindicated.

Effects associated with azathioprine include

- Compromise of RNA synthesis through thioguanosine triphosphate incorporation
- Blocking of T-cell activation
- Increased apoptosis of activated T-cells by preventing upregulation of the pro-survival protein Bcl-xL
- Proliferating T- and B-lymphocytes lack nucleoside salvage pathways and are particularly sensitive to azathioprine

6-MP = mercaptopurine, TPMT = thiopurine methyltransferase

Protocol & Monitoring

Initial dosage is 1.0–2 mg/kg PO or 50 mg/m^2 q24h (may be ideal, particularly in large dogs) until remission is achieved and the overall dose of corticosteroids can be reduced (usually 2–4 weeks), followed by q48h administration.[1]

- For long-term maintenance, twice-weekly administration at half the initial dose, often on alternate days from corticosteroid administration, is recommended.
  —Tablets can be split, but owners should wear gloves or wash their hands after use, as azathioprine is mutagenic/teratogenic.[1]

Hemograms (with platelet counts) should be monitored q2wk during induction and periodically during maintenance.

- Based on author's clinical experience, dose should be reduced by 25% if WBCs drop below 7000 cells/mm^3 and discontinued if below 5000 cells/mm^3.

Serum liver enzymes should be monitored periodically within 1–4 weeks of starting the drug.[2]

Clinical response may occur after 1–6 weeks.[3]

- During this time, concurrent glucocorticoid use may be beneficial.

Owners should be instructed to monitor pets and immediately report to their veterinarian any signs of depression, fever, or inappetence, as these may signal an adverse effect.

Adverse Reactions

Bone marrow suppression is a dose-dependent side effect, with up to 90% of patients demonstrating changes in blood counts, but is often not severe enough to warrant discontinuation of the drug.[4]

- Most often seen as neutropenia and thrombocytopenia; nonregenerative anemia also possible[2]

Additional adverse reactions include GI upset (acute), increased ALT, demodicosis, dermatophytosis, and pyoderma with chronic use.

- Pancreatitis may occur but is more likely caused by concurrent use of glucocorticoids.
- Clinically significant hepatopathies have been reported.[2,5]

Adverse effects may be worse with coadministration of such drugs as ACE inhibitors or trimethoprim–sulfamethoxazole.[1]

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SUGGESTED READING

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