Azathioprine

SCG: For Transplant patients

The following guidelines are designed to provide information relating to azathioprine and to outline the responsibilities of the primary and secondary care teams and patients in the prescribing of azathioprine.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

Introduction:

Azathioprine is metabolised to mercaptopurine, a purine analogue, and inhibits DNA synthesis producing an antiproliferative effect on dividing cells.

RESPONSIBILITIES and ROLES

Specialist responsibilities (Transplant team):

1. Initially prescribe and stabilise the patient on the treatment regimen and monitor transplant graft function.
2. Monitor efficacy of the treatment and side effects.
3. Advise on action to be taken in the event of abnormal blood count.
4. Provide access to back up and support facilities.
5. Evaluate any adverse events reported by the GP.
6. Provide patients with a current medication record book ("blue book").
7. Educate patients in knowledge of drug therapy to maximise compliance and be aware of when to seek medical attention.

General Practitioner's responsibilities:

1. Prescribe azathioprine once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital.
2. Encourage patients to complete their daily medication record and document any changes to therapy in the "blue book".
3. Check for possible drug interactions when newly prescribing or stopping concurrent medication.
4. Report any suspected adverse events to the Transplant Unit. (All potential adverse events need to be reported).
5. Monitor blood counts and discuss any abnormalities with Transplant Unit.

Patient's role:

1. Complete daily medication record in their "blue book".
2. Notify the GP and Transplant Unit of any suspected adverse events.
3. Notify use or intended use of over the counter (OTC) and herbal medications.

BACK-UP ADVICE AND SUPPORT

Papworth Hospital Main Switchboard	01480 830541
Transplant Unit Reception	01480 364455
Transplant Coordinators (on-call)	01480 830541 (via Hospital Switchboard)
Pharmacy Medicines Information Service	01480 364179 Mon - Fri 9 am to 5 pm
Transplant Pharmacist	01480 830541 ext. 4179 (bleep 931)
Consultant Transplant Cardiologist:	Dr J Parameshwar
	Dr Clive Lewis
Consultant Transplant Pulmonary Physician:	Dr J Parmar

Consultant and medical staff are always available to
give advice and can be contacted through the main hospital switchboard on: 01480 830541

SUPPORTING INFORMATION

Licensed indications:

Azathioprine is licensed in many therapeutic areas including organ transplantation. These guidelines pertain to the indicated use of azathioprine in enhancing survival of heart, lung and heart/lung transplants and it's steroid sparing effect.

Dosage and Administration:

Doses employed in transplantation range from up to 5mg/kg initially reducing to 1 to 4mg/kg orally daily. The usual established maintenance dose at Papworth Hospital is 1-2mg/kg orally once daily.

Azathioprine should be taken with or immediately after food to minimise nausea.

Contraindications - in transplantation:

- Hypersensitivity to azathioprine or any excipients. Hypersensitivity to 6-mercaptopurine should alert prescriber to probable hypersensitivity to azathioprine.
- Breastfeeding

Cautions:

- Malignancy, especially lymphomas and skin tumours are more common in immunosuppressed patients - advise patient to limit exposure to sunlight by wearing light clothing and using a high factor sunscreen.
- Susceptibility to opportunistic infections is increased in patients receiving immunosuppression.
- Patients should be instructed to report any evidence of bone-marrow depression e.g. infection, bruising, bleeding.
- Patients who are pregnant or likely to become pregnant require careful assessment of risk versus benefit. Adequate contraceptive precautions should be advised when either partner is receiving azathioprine.

Therapeutic Use:

Azathioprine is prescribed as part of combination immunosuppressant therapy (most commonly with calcineurin inhibitors e.g. ciclosporin or tacrolimus and corticosteroids) for the prevention of rejection post solid organ transplantation.

Side Effects:

All immunosuppressive agents are powerful and potentially toxic drugs, and therefore adverse events may be observed. Any adverse effects detected should be reported directly to the Transplant Unit. The following is a summary of adverse reactions reported with azathioprine:

Infections	Increased susceptibility to viral, fungal and bacterial.
Haematological	Bone marrow depression (dose dependent, usually reversible), leucopenia, thrombocytopenia, anaemia, agranulocytosis, pancytopenia, aplastic anaemia. Patients should be warned to report sore throats, abnormal bruising/bleeding.
Gastrointestinal	Uncommonly, cholestasis and deterioration in LFTs (may be associated with a hypersensitivity reaction). Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described primarily in transplant patients. A minority of patients experience nausea when first given azathioprine - this may be relieved by administering the tablets after meals.
Hypersensitivity reactions	Uncommon, but clinical features include malaise, dizziness, nausea and vomiting, diarrhoea, fever, rigors, rash, vasculitis, myalgia, arthralgia, hypotension, renal/ hepatic dysfunction and cholestasis. IMMEDIATE withdrawal is indicated - liaise with Transplant Unit.
Neoplasms (benign and malignant)	Rarely, Non-Hodgkins lymphomas, skin cancers, sarcomas and uterine cervical cancer, acute myeloid leukemia and myelodysplasia.

The above list of adverse events is not exhaustive but does cover the most frequently reported events. A more comprehensive list can be found in the Imuran® SPC.

Monitoring:

FBC On initiation of therapy, weekly complete blood counts including platelets for the first weeks, fortnightly for the next month and three monthly thereafter. More frequent monitoring should be undertaken in the presence of severe hepatic/renal failure or if high doses are used. Subsequent blood counts should be done routinely monthly (or at least at intervals of not longer than 3 months). Maintain white cell count (WCC) 4 to 6×10^9/L.

LFTs at baseline and regular monitoring especially in hepatic impairment – suggest 3 monthly in hepatic impairment and 6 monthly otherwise.

Drug Interactions:

ALLOPURINOL Inhibits metabolism of mercaptopurine (the active metabolite of azathioprine) leading to accumulation and development of toxicity.

THE DOSE OF AZATHIOPRINE MUST BE REDUCED TO ONE QUARTER OF THE ORIGINAL DOSE WHEN ALLOPURINOL IS INTRODUCED.

Aminosalicylates Increased incidence of bone marrow toxicity possible. Use with caution.

Warfarin Concommitant use with azathioprine may lead to inhibition of anticoagulant response. Monitor INR and increase warfarin dose as required.

Live vaccines are contra-indicated and should not be given to immunocompromised individuals. Other vaccines may be less effective.

For advice on azathioprine interactions including herbal medicines please do not hesitate to contact the pharmacy Medicines Information Department.

Availability:

- Azathioprine is widely available from wholesalers as 25mg and 50mg tablets.

References:

- SPC Imuran® tablets accessed via emc.medicines.org.uk on 07/07/2011. Last updated 15/04/2011
- Stockley's Drug Interactions accessed via medicinescomplete.com on 07/07/2011. Last updated May 2011
- BNF 61 March 2011.

Guidelines:
Reviewed by: Transplant Pharmacist
Approved by: Papworth Hospital Drugs and Therapeutics Committee September 2006
Reviewed by: Transplant Pharmacist (H Chapman) – Approved by Transplant Steering Group 14/09/2011
Approved by: Papworth Hospital Drugs and Therapeutics Committee via Chairman's action 18/01/2012