Focus on Allopurinol

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Introduction

Urate saturation of extracellular fluids results in hyperuricaemia.[1] The deposition of this monosodium urate (MSU) in joints, soft tissues and bones, triggers an inflammatory arthritis and can manifest in many forms including acute gout flare, chronic gouty arthritis and tophaceous gout (formation of tophi).[1] Factors that lead to changes in the extracellular urate concentration have the potential to trigger a gout flare-up and include stress (mainly due to medical conditions), dietary choices and drugs, including aspirin, diuretics and even allopurinol.

Indications

Allopurinol is used to reduce urate concentrations in body fluids and/or urine to prevent or reverse the deposition of urate/uric acid and is indicated in the management of the main clinical manifestations of urate deposition which include chronic gouty arthritis, idiopathic gout and skin tophi.[2]

Mechanism of action

Allopurinol, and its active metabolite oxypurinol, both inhibit xanthine oxidase, an enzyme that converts hypoxanthine to xanthine, and xanthine to uric acid, thus decreasing the production of uric acid.[3] By lowering both serum and urine concentrations of uric acid below its solubility limits, allopurinol prevents or decreases urate deposition in the joints, thereby preventing the occurrence or progression of gouty arthritis.[4]

Pharmacokinetics

Around 80 to 90% of allopurinol is absorbed from the gastrointestinal tract following oral administration.[4] Seventy percent of allopurinol is metabolised in the liver and converted to oxypurinol by oxidative metabolism.[4] The half-life of allopurinol is one to three hours and for oxypurinol the half-life is around 15 hours (12–30 hours), and is prolonged in patients with impaired kidney function.[3,5] Oxypurinol, and up to 10% of unchanged allopurinol, is excreted in the urine.[5]

Dosing (adults)

Allopurinol treatment should be introduced at a low dosage of 100 mg/day to reduce the risk of adverse reactions such as nausea, vomiting and diarrhoea.[2] If needed, the dose may be increased by 100 mg/day every two to five weeks until the target serum uric acid level is achieved.[3] The usual maintenance dose is 300 mg/day. However, doses of up to 900 mg/day have been used.[2]

It is recommended that allopurinol be taken after meals for better gastrointestinal tolerability.[2,6]

Renal impairment

Allopurinol is excreted in the kidney and reduced renal function may lead to accumulation of the medicine and its metabolites. The dose and the frequency of dosing may therefore require reduction in these patients. The following schedule is recommended as guidance in adult patients with impaired renal function:[2]

Creatinine clearance > 20 ml/minute	give standard dose
Creatinine clearance between 10 and 20 ml/minute	give 100 to 200 mg/day
Creatinine clearance < 10 ml/minute	give 100 mg/day or at longer intervals.

If plasma monitoring facilities are available, plasma oxypurinol levels should be maintained below 100 micromol/litre (15,2 micrograms/mL).[2]

Allopurinol and its metabolites are removed by renal dialysis and dosages should be adjusted accordingly.[2]

Hepatic impairment

Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.[2]

Efficacy

A 2014 Cochrane review reported that allopurinol 300 mg daily increases the proportion of patients achieving a target serum urate concentration (25/26 patients achieved target serum urate concentrations with allopurinol 300 mg daily compared to 0/26 with placebo).[7] A summary of two Cochrane reviews in 2014, concluded that there is moderate quality data supporting the efficacy and safety of allopurinol in gout.[8] Significantly more (38%) participants taking allopurinol, achieved a serum urate level of < 6.0 mg/dl when compared to placebo.[8]

Safety

Contraindications

Allopurinol is contraindicated in patients with hypersensitivity to allopurinol or any excipients in the product, in patients with severe hepatic or renal disorders and in patients with an acute gout attack.[2]

Special warnings and precautions

Allopurinol should not be started until an acute attack of gout has completely subsided as further attacks may be precipitated by allopurinol.[2] Due to the destabilisation of intra-articular uric acid microtophi when initiating any urate-lowering therapy, there is an increased incidence of acute gouty flares, especially during the initial few months of allopurinol therapy.[3] Thus it is advisable to give a nonsteroidal anti-inflammatory drug (NSAID) or colchicine for at least one month when starting treatment with allopurinol.[2,6] If acute attacks occur in patients receiving allopurinol, treatment with allopurinol should continue at the same dose while the acute attack is treated with a NSAID or colchicine.[2]

If a skin rash or other signs of hypersensitivity occur, treatment with allopurinol should be withdrawn immediately as this could result in more serious hypersensitivity reactions including Stevens-Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). After recovery from mild symptoms, allopurinol may be reintroduced at a low dose (e.g. 50 mg per day) and gradually increased. If the rash recurs, allopurinol should be permanently withdrawn.[2]

Certain populations (including people of Han Chinese, African and Indian ancestry) carry the HLAB-B*5801 allele which is considered a genetic risk factor for serious hypersensitivity reactions (e.g. SJS/TEN) with allopurinol use. Screening of these high-risk patients should be considered before starting treatment with allopurinol. Those individuals who test positive should not start treatment with allopurinol unless there are no other reasonable therapeutic options and the benefits of use outweigh the potential associated risk. Those who test negative may still be at risk of SJS/TEN.[2]

Drug interactions

Allopurinol may increase the activity of certain medications. When using 6-mercaptopurine or azathioprine with allopurinol, the dose of 6-mercaptopurine or azathioprine should be reduced to a quarter of the usual dose.[2,6] Theophylline metabolism may be inhibited, and theophylline levels should be monitored in patients starting or increasing allopurinol therapy. Plasma concentration of ciclosporin may be increased and ciclosporin toxicity should be considered if used with allopurinol.

Medicines with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxypurinol which may reduce the efficacy of allopurinol.[6]

Concomitant use of allopurinol and ampicillin or amoxicillin may increase the risk of developing a skin rash. When possible, an alternative to ampicillin or amoxicillin should be considered in patients using allopurinol.[6]

Please refer to the manufacturer's professional information for further information on possible drug-drug interactions.

Adverse effects

The most common adverse effects associated with the use of allopurinol include maculopapular pruritic rash, nausea and vomiting.[3] Gastrointestinal side effects can be reduced by taking allopurinol with plenty of liquids and by having frequent small meals.[9] Other adverse effects include altered taste, drowsiness and diarrhoea.

Less commonly, allopurinol can cause a rash or flaking of the skin. Patients should stop treatment if a rash develops, especially if it is a severe skin rash or, in rare instances, if mouth ulceration occurs.[9] Other less common and rare side-effects include liver necrosis, granulomatous hepatitis, cholestatic jaundice, interstitial nephritis, and vasculitis.

Important prescribing points

- Allopurinol should not be initiated until an acute attack of gout has completely subsided. There is an increased incidence of acute gouty flares, especially during the initial few months when starting treatment.[3] Thus, it is advisable to give an NSAID or colchicine concurrently with allopurinol for at least one to six months when starting treatment.[2,9]
- A high fluid intake and frequent small meals may reduce the incidence of nausea and vomiting associated with allopurinol therapy.[9]
- Patients should be warned that drowsiness, vertigo and ataxia may occur and should exercise caution when driving, using machinery or participating in dangerous activities.[5,6]
- A doctor should be consulted if a skin rash or any other sign of hypersensitivity occurs.[2,5]

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