Antigout Drugs

This chapter deals with the treatment of gout and hyperuricaemia and the drugs used mainly for these disorders.

Gout and hyperuricaemia

Uric acid is the final product of the metabolism of endogenous and exogenous purine in man. An excess of uric acid, measured in the plasma as sodium urate, constitutes **hyperuricaemia**. This excess may be caused by an overproduction or underexcretion of urate. It is influenced by genetic and environmental factors and may be classified as primary (mainly idiopathic) or secondary. An increase in urate production may be caused by excessive dietary purine intake, certain cancers or their treatment, or, more rarely, enzyme defects of purine metabolism. Reduced urate excretion may be caused by renal disease, hypertension, or the intake of certain drugs such as thiazide diuretics. Other factors contributing to hyperuricaemia include hyperlipidaemia, obesity, alcohol consumption, and lead exposure.

A patient is usually considered to be hyperuricaemic when plasma-urate concentrations exceed 0.42 mmol/litre (7 mg per 100 mL) in men and postmenopausal women or 0.36 mmol/litre (6 mg per 100 mL) in premenopausal women. At these high concentrations there is a risk of crystals of monosodium urate monohydrate being formed and deposited in synovial fluid and various tissues. However, some subjects may have supersaturated plasma-urate concentrations without any crystal deposits, while others may suffer from deposits in the absence of apparent hyperuricaemia.

The presence of urate crystals in the synovial fluid leads to an inflammatory response in the affected joint, commonly at the base of the big toe (podagra). The ensuing exquisite pain, tenderness, erythema, and swelling constitute the clinical manifestations of **acute inflammatory gouty arthritis**. Repeated acute attacks may be associated with a visible or palpable build up of crystal deposits (**tophi**) at various sites including in and around the affected joint. Tophi release urate crystals into the synovial fluid after various stimuli and so cause further acute attacks, leading to **chronic tophaceous gout**. Intra-articular and peri-articular tophi may cause gradual joint erosion, which, without treatment, results in disabling **chronic gouty arthritis**. Rarely, the kidney can be affected by urate deposits producing a gouty nephropathy or by uric acid calculi or stones (uric acid nephrolithiasis or urolithiasis).

Treatment aims to alleviate the acute attack, prevent future attacks, and lower plasma-urate concentration.

Plasma-urate concentrations may be reduced by control of obesity and modification of diet and alcohol intake. Drug treatment can relieve the pain of acute attacks but more prolonged therapy for hyperuricaemia is generally only considered if there are recurrent attacks of gout or there is renal involvement (see under Chronic Gout, below).

Acute gout. An attack of acute inflammatory gouty arthritis is best treated as soon as possible with an NSAID. Aspirin or other salicylates are not suitable since they may increase plasma-urate concentrations. Treatment is started with high doses of an NSAID, the doses being reduced as the patient responds. Usually treatment can be withdrawn within 1 to 2 weeks. Colchicine is an effective alternative; it may be used alone, or with an NSAID. Patients who do not respond to NSAIDs or colchicine, or for whom these drugs are contra-indicated, may be treated with a systemic corticosteroid. Intra-articular corticosteroids are effective in acute monoarticular gout, or when used adjunctively in patients with polyarticular gout; infection of joints should be excluded prior to injection. Intravenous, intramuscular, or subcutaneous corticotropin has been reported to alleviate pain and inflammation in acute gout. It may be used alone or adjunctively, and may be a useful alternative in patients with renal and gastrointestinal contra-indications to other therapies. Other therapies for acute gout include adjunctive analgesics and topical ice. Drugs used for chronic gout (allopurinol or the uricosurics) should not be started during an acute attack since they can exacerbate and prolong it (see below).

Chronic gout. If the patient suffers frequent acute attacks or develops tophaceous gout, or has renal complications as a result of urate overproduction, then long-term treatment of hyperuricaemia may be needed. Such **urate-lowering therapy** should not be started during an acute attack, or for 2 to 3 weeks thereafter, as fluctuations in urate concentration may prolong the existing attack or initiate a new one. Treatment involves inhibiting the production of uric acid or enhancing its urinary excretion, in order to maintain a serum urate concentration at or below 0.3 or 0.36 mmol/litre. Hyperuricaemia due to overproduction of urate is treated with allopurinol which inhibits the enzyme xanthine oxidase, involved in purine metabolism. Hyperuricaemia associated with underexcretion of uric acid can be treated with either allopurinol or a uricosuric such as benzbromarone, probenecid or sulfinpyrazone. Allopurinol is most commonly given as first-line therapy, but may be combined with or replaced by uricosurics if treatment fails. Allopurinol should also be used for patients with renal urate deposits or with uric acid renal calculi as it reduces urolithiasis. Febuxostat is an alternative xanthine oxidase inhibitor under investigation.

With either treatment there is mobilisation of urate crystals from established tophi, as the plasma-urate concentration falls, which can trigger further acute attacks of gout. Patients are thus also given **prophylaxis** with an NSAID or colchicine from the start of urate-lowering treatment until at least a month after the plasma-urate has been reduced to an acceptable concentration; up to 6 months of prophylactic cover has been recommended.

Once the hyperuricaemia is corrected, the patient continues to receive therapy with allopurinol or uricosurics indefinitely. If an acute attack occurs during such maintenance therapy, this therapy should be continued to avoid fluctuations in urate concentration, and the acute attack treated in its own right.

Surgery may have to be considered for patients severely affected by chronic tophaceous gout.

References[1-18] to gout and its management are given below.

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Allopurinol *(BAN, USAN, rINN)*

Allopürinol; Allopurinoli; Allopurinolum; Allopurynol; Alopurinol; Alopurinolis; BW-56-158; HPP; NSC-1390.

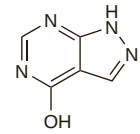
Аллопуринол

$C_5H_4N_4O$ = 136.1.

CAS — 315-30-0 (allopurinol); 17795-21-0 (allopurinol sodium).

ATC — M04AA01.

ATC Vet — QM04AA01.



Description. Allopurinol is a tautomeric mixture of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol and 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Allopurinol). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides.

USP 31 (Allopurinol). A fluffy white to off-white powder having only a slight odour. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of potassium and sodium hydroxides.

Incompatibility. Allopurinol sodium as a 3 mg/mL solution in 0.9% sodium chloride was visually incompatible with amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlormethine hydrochloride, chlorpromazine hydrochloride, cimetidine hydrochloride, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin hydrochloride, diphenhydramine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine hydrochloride, idarubicin hydrochloride, imipenem with cilastatin sodium, methylprednisolone sodium succinate, metoclopramide hydrochloride, minocycline hydrochloride, nalbuphine hydrochloride, netilmicin sulfate, ondansetron hydrochloride, pethidine hydrochloride, prochlorperazine edisilate, promethazine hydrochloride, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.[1]

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Adverse Effects

The most common adverse effect of allopurinol is skin rash. Rashes are generally maculopapular or pruritic, sometimes purpuric, but more serious hypersensitivity reactions may occur and include exfoliative rashes, the Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is therefore recommended that allopurinol be withdrawn immediately if a rash occurs (see Precautions, below). Further symptoms of hypersensitivity include fever and chills, lymphadenopathy, leucopenia or leucocytosis, eosinophilia, arthralgia, and vasculitis leading to renal and hepatic damage and, very rarely, seizures. These hypersensitivity reactions may be severe, even fatal, and patients with hepatic or renal impairment are at special risk.

Hepatotoxicity and signs of altered liver function may also be found in patients who are not hypersensitive. Haematological effects include thrombocytopenia, aplastic anaemia, agranulocytosis, and haemolytic anaemia.

Many other adverse effects have been noted rarely and include paraesthesia, peripheral neuropathy, alopecia, gynaecomastia, hypertension, taste disturbances, nausea, vomiting, abdominal pain, diarrhoea, headache, malaise, drowsiness, vertigo, and visual disturbances.

Patients with gout may have an increase in acute attacks on beginning treatment with allopurinol, although attacks usually subside after several months.

Incidence of adverse effects. A Boston Collaborative Drug Surveillance Program involving 29 524 hospitalised patients found that, with the exception of skin reactions, 33 of 1835 patients treated with allopurinol (1.8%) had adverse effects. These effects were dose-related and the most frequent were haematological (11 patients, 0.6%), diarrhoea (5 patients, 0.3%), and drug fever (5 patients, 0.3%). Hepatotoxicity was reported in 3 patients (0.2%). Two patients developed possible hypersensitivity reactions to allopurinol.[1]

A further analysis involving 1748 outpatients indicated no instances of acute blood disorders, skin diseases, or hypersensitivity that warranted hospital treatment. Liver disease, although found, was not considered to be associated with allopurinol.