

Managing Problem Gout

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Abstract

For the management of acute gouty arthritis, non-steroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice. In recent years, the use of colchicine has declined because of its frequent adverse reactions, and its reduced efficacy when administered more than 24 hours after onset of an acute attack. Intra-articular corticosteroid therapy (e.g. methylprednisolone acetate) is indicated for the treatment of acute mono or oligoarticular gouty arthritis in aged patients, and in those with co-morbid conditions contraindicating therapy with either NSAIDs or colchicine. Oral corticosteroids (e.g. prednisone), and both parenteral corticotrophin (ACTH) and corticosteroids (e.g. intramuscular triamcinolone acetonide) are valuable, relatively safe alternate treatment modalities in those with polyarticular attacks.

For the treatment of hyperuricaemia and chronic gouty arthritis, allopurinol is the preferred urate-lowering drug. Its toxicity in elderly individuals, those with renal impairment, and in cyclosporine-treated transplant patients can be minimised by adjusting the initial dose according to the patient's creatinine clearance. In those experiencing cutaneous reactions to allopurinol, cautious desensitisation to the drug can be achieved using a schedule of gradually increasing doses. The therapeutic usefulness of uricosuric drugs is limited by the presence of renal impairment, occurrence of intolerable side-effects, or concomitant intake of salicylates. They are particularly indicated in patients allergic to allopurinol and in those with massive tophi requiring combined therapy with both allopurinol and a uricosuric.

Ann Acad Med Singapore 1998; 27:93-9

Key words: Difficult gouty arthritis, Treatment

Introduction

Gout occurs in 3 overlapping phases: a long phase of asymptomatic hyperuricaemia, a period of recurrent acute gouty attacks separated by asymptomatic intervals (interval gout), followed in about 10% of patients by chronic tophaceous gouty arthritis.¹ Gout is one of the better understood of the arthritic disorders, and certainly one of the most satisfactory to treat. However, every so often, difficulties are encountered regarding some aspects of its treatment² (Table I).

When gout is diagnosed, the patient usually requires some form of long-term therapy. It is important therefore to establish a firm diagnosis at the outset. This can be secured by demonstration of intra- or extracellular, needle-shaped, negatively-birefringent monosodium urate crystals in joint fluids, bursal effusions or in aspirates from tophi, using compensated polarised light microscopy (Fig. 1).^{1,2} However, this may not be possible in all patients for a number of reasons: absence of a detectable joint effusion or visible tophaceous deposits, an inaccessible joint, inexperience with joint aspiration or evaluation of synovial fluids for crystals, or presence

of a few urate crystals or crystals too small ($<1\ \mu\text{m}$) to be seen by light microscopy.^{1,2}

Under these circumstances, the diagnosis of gout can be made on the basis of a typical clinical history (middle aged or elderly man, or post-menopausal woman, presenting with recurrent attacks of acute monoarticular or

TABLE I: SPECIFIC PROBLEMS IN THE TREATMENT OF GOUT

Acute Gouty Arthritis

- Acute gout in patients with co-morbid conditions contraindicating NSAIDs
- Postoperative state
- NSAIDs hypersensitivity
- Severe attacks refractory to both NSAIDs and colchicine

Chronic Gouty Arthritis

- Massive tophaceous deposits
- Gout in patients with renal impairment
- Gout in the elderly
- Cutaneous reactions to allopurinol
- Gout in the transplant patient
- Refractory gout

NSAIDs: Non-steroidal anti-inflammatory drugs

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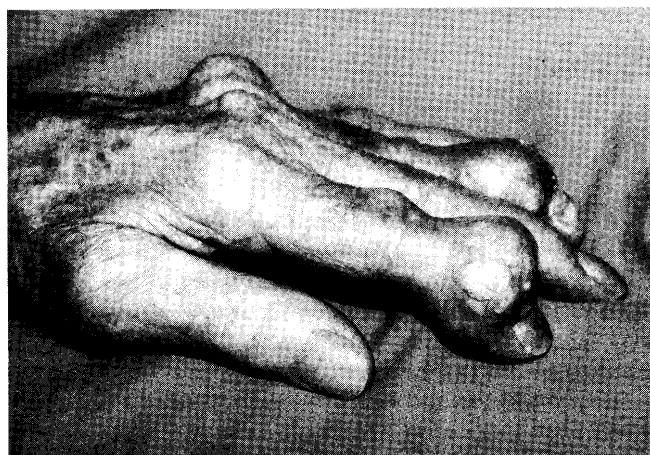


Fig. 1a. Chronic tophaceous gouty arthritis of the left hand.

oligoarticular arthritis in the lower extremities, especially the great toes, with severe local pain, tenderness, swelling and redness, followed by a return to normal joint function), in association with documented hyperuricaemia.^{1,2} The diagnosis can sometimes be confirmed in these patients by demonstrating urate crystals in fluid aspirates from previously affected, but asymptomatic knee or first metatarsophalangeal joints.⁴

Hyperuricaemia, elevated serum urate over $450 \mu\text{mol/L}$ (7.0 mg/dl) in men, and over $360 \mu\text{mol/L}$ (6.0 mg/dl) in women, is the biochemical hallmark of gout.^{1-3,5} Acute gouty episodes without hyperuricaemia are rare, and may occur during the early phases of gout, following alcoholic excesses, after withdrawal of diuretic therapy, and during initial therapy with allopurinol or a uricosuric drug.^{1-3,5}

Specific Problems in the Treatment of Acute Gouty Arthritis

Standard therapy for acute gouty arthritis includes non-salicylate non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids (Table II).^{1-3,6,7}

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are preferred by most clinicians as the drugs of first choice in the treatment of acute gout.^{1,3,6,7} They are generally better tolerated and more predictable in their



Fig. 1b. Aspirate from one of the tophi showing masses of needle-shaped, 5 to $15 \mu\text{m}$ long monosodium urate crystals, as viewed by polarised light microscopy.

therapeutic effects than is high-dose oral colchicine.^{6,7} There is no clear advantage of any one preparation, but a large dose of indomethacin (50 mg tid or qid), naproxen (500 mg bid or tid), or diclofenac sodium (50 mg tid) on the first 1 to 3 days, with a reduction thereafter, is generally effective. Whatever drug is used, it should be started as early as possible after the onset of an acute episode. It is important, therefore, to supply the patient with the appropriate NSAID (preferably kept in a convenient pocket, for all too often gout strikes when the patient is far from home), and instructions on how to self-treat acute flares at the first "twinge" of an attack.

Although adverse reactions (e.g. nausea, dyspepsia, diarrhoea, headache and confusion) can occur, the duration of NSAID therapy is usually short, and serious toxicity leading to drug withdrawal, e.g. gastrointestinal (GI) bleeding, is rare ($<10\%$ of patients).^{1,7}

However, NSAIDs are potentially hazardous, and are not recommended for the treatment of acute gouty events in aged patients, and in those with co-morbid medical conditions such as congestive heart failure, renal impairment, previous or current peptic ulcer disease, GI bleeding, hepatic insufficiency, and chronic alcoholism. Parenteral NSAIDs, such as intramuscular (IM) ketorolac, offer no safety advantage.^{1,6,7}

Colchicine

Although colchicine is traditionally rooted in the treatment of acute gouty arthritis, in recent years, its use has steadily declined. Drawbacks include:

- 1) slow onset of action,
- 2) narrow benefit-to-toxicity ratio, with about 80% of patients experiencing GI toxicity (nausea, diarrhoea and abdominal pain) after oral administration, and
- 3) reduced therapeutic efficacy when administered 24 hours or longer after the onset of acute gouty inflammation.^{1,3,6-8}

It is administered orally in a dose of 0.6 mg every 1 to

TABLE II: DRUGS IN THE TREATMENT OF ACUTE GOUTY ARTHRITIS

- Colchicine
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids and corticotrophin (ACTH):
 - Intra-articular corticosteroids
 - Systemic corticosteroids
 - ACTH

ACTH: Adrenocorticotrophic hormone

2 hours until acute joint pain is relieved, the patient develops GI toxicity, or a maximum of 4 to 6 mg/day has been administered. Most patients experience some pain relief by 18 hours and diarrhoea by 24 hours, with gouty inflammation subsiding in 80% of patients in 48 hours.* Colchicine is more effective when given within 12 to 24 hours of onset of an attack, and is particularly useful for persons without renal or hepatic disease, who are intolerant or hypersensitive to NSAIDs.

The role of intravenous (IV) colchicine in the treatment of acute gout has recently come under closer scrutiny in light of growing concerns about its safety. A major concern is the drug's potential for serious toxicity (bone marrow suppression, oliguric renal failure, hepatic necrosis, severe diarrhoea, seizures and death), particularly in elderly patients with renal and/or hepatic impairment.^{1,6,7,9,10} This controversy has led to the publication of a set of guidelines for the IV administration of colchicine.^{9,10} However, inappropriate use of the drug is relatively common, and many clinicians have advocated restriction or outright ban on the use of IV colchicine.^{7,9,10}

Corticosteroids Including Corticotrophin (ACTH)

Intra-articular (IA) corticosteroid therapy and both systemic corticosteroids and ACTH are indicated for the treatment of acute gouty episodes in patients with coexisting medical illnesses, contraindicating the use of NSAIDs (Table III).^{1,3,6,7,11-14} Such treatment is also efficacious in the management of acute gout occurring during the postoperative period, for those with NSAID hypersensitivity, and for severe gouty attacks refractory to both NSAIDs and colchicine.^{1,6,7,11-14}

IA corticosteroid injections, such as methylprednisolone acetate 5 to 40 mg IA, are particularly useful for the treatment of acute mono- and oligoarticular gouty episodes in these patients. However, such therapy is not practical for those patients with polyarticular gouty attacks. Concern about coexistent joint infection, concomitant anticoagulant therapy and fear of needle injection may also preclude IA corticosteroid administration.^{7,12}

In these clinical situations, systemic corticosteroids are valuable, relatively safe, alternate treatment mo-

ality.^{1,3,6,7,11,12,14} IM corticosteroid preparations, such as triamcinolone acetonide 60 mg daily or methylprednisolone acetate 40 mg IM daily, repeated every 1 to 4 days as required, can be used to provide rapid control of acute polyarticular gouty attacks, thereby circumventing delayed absorption after oral administration.^{7,11,12} Intravenous methylprednisolone sodium succinate 40 to 160 mg daily, repeated every 1 to 4 days as required, is indicated for those receiving anticoagulant therapy.^{7,12}

Oral prednisone, 20 to 40 mg daily followed by gradual tapering over 4 to 8 days, is particularly useful for the ambulatory treatment of acute gouty flares in outpatients with co-morbid conditions contraindicating the use of NSAIDs.^{7,12}

Although the efficacy and safety of IM corticotrophin (ACTH), 40 units daily repeated as required, in the treatment of acute gout have been demonstrated in a number of studies,^{1,3,13,14} there is no compelling evidence that such therapy is superior to corticosteroids.⁷ Potential drawbacks of ACTH include: dependence of therapeutic effects on sensitivity of the adrenal cortex (drug may be ineffective in subjects previously treated with corticosteroids), failure to deliver a precise dose, increased release of adrenal androgens and mineralocorticoids which can lead to fluid overload, and a relatively short duration of action with a greater potential for rebound attacks and treatment failures compared to IM corticosteroids.^{7,14}

Specific Problems in the Treatment of Chronic Gouty Arthritis

The ultimate treatment of gout and its complications requires long-term control of hyperuricaemia.^{1,3,6} Two types of urate lowering drugs are available: allopurinol, a xanthine oxidase inhibitor which decreases uric acid synthesis; and uricosuric agents, including probenecid, and sulphapyrazone, which act by competitive inhibition of post-secretory renal tubular reabsorption of urate, thus increasing urate excretion and lowering serum urate.^{1,3,6}

Laboratory evaluation of a patient with gout includes determination of serum urate and creatinine, creatinine clearance, and a 24-hour urinary uric acid excretion in those with normal renal function. Purine enzyme studies, such as assays for hypoxanthine guanine phosphoribosyl transferase (HGPRTase) and phosphoribosyl pyrophosphate (PRPP) synthetase, are indicated in those presenting at a young age with severe hyperuricaemia, hyperuricosuria, and tophaceous gouty arthritis.

Not every patient with gout will require treatment with urate-lowering drugs (Table IV).^{1,6} Although synovial microtophi have been observed in joints of patients with gout, there is no convincing evidence that these intra-articular urate crystal deposits invariably lead to

TABLE III: INDICATIONS FOR CORTICOSTEROIDS IN THE TREATMENT OF ACUTE GOUTY ARTHRITIS

- Co-morbid medical illnesses: Cardiac failure, hypertension, renal insufficiency, peptic ulcer, gastrointestinal bleeding, hepatic insufficiency, chronic alcoholism, bleeding diathesis, anticoagulants
- Advanced age
- Postoperative state
- NSAIDs hypersensitivity
- Severe attacks refractory to both NSAIDs and colchicine

NSAIDs: Non-steroidal anti-inflammatory drugs

TABLE IV: URATE-LOWERING DRUGS

Indications for Allopurinol Therapy

- Severe or frequent (>4 attacks per year) gouty attacks despite corrective measures
- Major overproduction of uric acid with hyperuricosuria including HGPRTase deficiency and PRPP synthetase overactivity
- Chronic tophaceous gouty arthritis
- Gout complicated by urate nephropathy, uric acid nephrolithiasis or renal insufficiency
- Hyperuricaemia secondary to lymphoma, leukaemia and myeloproliferative disorders treated with cytotoxics or radiotherapy
- Failure of uricosuric drugs
- Recurrent calcium oxalate urinary calculi associated with hyperuricosuria

Indications for Uricosuric Drugs

- Patients under 50 years of age with primary gout, frequent gouty attacks, normal renal function and urinary uric acid excretion who have no history of urinary calculi
- Allergy or intolerance to allopurinol
- Combined allopurinol-uricosuric treatment for patients with massive tophaceous deposits

HGPRTase: Hypoxanthine-guanine-phosphoribosyl-transferase;

PRPP: Phosphoribosyl pyrophosphate

joint damage. Given the potential toxicity of long-term antihyperuricaemic drugs, current evidence does not support the view that all patients should be treated with these medications.

The administration of a drug to normalise serum urate is usually a lifelong commitment to regular daily therapy.^{1,6} Frequent measurement of serum urate concentrations is important in monitoring patient's compliance, and the effectiveness of urate-lowering treatment. The goal of therapy is to reduce and maintain serum urate not just to within the normal range, but into the mid to lower half of the normal range (to about 250 to 350 $\mu\text{mol/l}$ or 4 to 6 mg/dl), well below the concentration at which serum urate saturates the extracellular fluid (approximately 404 $\mu\text{mol/l}$ or 6.8 mg/dl at 37°C).^{1,5,6} This will prevent gouty attacks and promote resorption of tophaceous deposits.

Initiation of urate-lowering therapy during an acute attack of gout is generally not advisable; a major change in serum urate concentration, induced by starting allopurinol or a uricosuric drug, may prolong an attack already in progress.

The sharp reduction in serum urate level that takes place early in the course of urate-lowering treatment may be associated with flares of gout. These flares are often mistaken for a poor response to treatment. Some physicians advocate prophylactic colchicine 0.6 mg once or twice daily during the first 1 to 12 months after initiation of antihyperuricaemic therapy.^{6,15} However, this practice cannot be "routinely" recommended, given the potential toxicity of prolonged use of colchicine (neuropathy, myelotoxicity, alopecia and malabsorp-

tion syndrome), and the fact that only a minority (about 10% to 25%) of patients develop flares of gouty arthritis after initiation of allopurinol or uricosuric treatment.' Instead, many clinicians advocate the temporary use of a supplemental NSAID to control these attacks.^{1,16,17} Others prescribe prophylactic colchicine for those patients who are noncompliant with self-treatment of gouty flares.

Allopurinol

Allopurinol is the urate-lowering drug of choice.^{1,3,6,18} As a xanthine oxidase inhibitor, it interferes with the conversion of hypoxanthine to xanthine and of xanthine to uric acid leading to a reduction of serum and urinary urate concentrations, and a concomitant increase in serum and urinary hypoxanthine and xanthine concentrations.^{1,3,6,18}

Allopurinol is rapidly oxidised in the body to its principal metabolite oxipurinol, which is also a potent xanthine oxidase inhibitor.^{1,3,6,18} The plasma half-life of allopurinol is 1 to 3 hours, while that of oxipurinol is 14 to 26 hours. Thus, allopurinol can be administered as a single daily dose. Since oxipurinol is excreted solely through the kidneys, reduction of allopurinol dose is indicated in patients with renal impairment.^{1,3,6,18-20} The starting dose of allopurinol is 50 to 300 mg/day (formulations: 100 mg , 200 mg and 300 mg tablets), and the total daily dose ranges between 100 mg and 800 mg , with most patients requiring less than 600 mg/day . However, in a few patients, particularly those with refractory gout and poor GI absorption, doses as high as 800 mg/day are sometimes needed. Reduction of serum urate concentration is noted within 2 days of starting therapy. The level usually falls to normal within 7 to 14 days, although it may take much longer in patients with extensive tophaceous deposits. Gouty attacks often cease within 3 to 6 months of continuous therapy, while dissolution of the tophi may take 6 to 24 months. Discontinuation of allopurinol is followed by a rapid rise of serum urate concentration to pre-treatment levels, although recurrence of acute gouty attacks may not occur for long periods.^{1,6,18} Specific indications for the use of allopurinol are outlined in Table IV.

Uricosuric Drugs

Uricosuric drugs increase the renal excretion of urate and thereby reduce serum concentration. The intense initial uricosuria can result in the deposition of uric acid crystals in renal tubules, and formation of urinary calculi, which in turn can cause renal colic or deterioration of renal function. To minimise this risk, and to prevent the precipitation of acute gouty attacks associated with rapid decline in serum urate concentration, uricosuric drugs are started at low doses, and gradually increased over 2 to 4 weeks.^{1,6,17} The risk of uric acid stones can be

further reduced by maintenance of a high urine volume (>2 L/day), and/or alkalisation of urine with sodium bicarbonate 1 g qid, particularly during the first 4 to 6 weeks of therapy when the uricosuria is greatest.^{1,6,17} Once serum urate normalises, the intense uricosuria subsides, and renal urate excretion approaches pretreatment levels.

Two uricosuric drugs are used to manage chronic gout: probenecid 250 mg bid for 1 to 2 weeks, then 500 mg bid, increasing the dose thereafter to 2500 mg/day (divided doses) if required, and sulphinpyrazone 50 to 100 mg bid for 1 to 2 weeks, then 100 to 200 mg bid, increasing to 400 mg bid if needed.

In the absence of clear-cut indications for treatment with allopurinol (Table IV), uricosuric drugs be used in younger patients with primary gout, normal renal function and 24-hour urinary uric values, and no gross tophi or a history of urinary calculi. Other specific indications for uricosurics include patients who are allergic or intolerant to allopurinol, and those with massive tophaceous deposits who may require treatment with both allopurinol to block uric acid synthesis, and a uricosuric to increase uric acid excretion (Table IV).^{1,3,6,17}

About 75% of patients respond to uricosuric drugs with normalisation of serum urate, control of gouty attacks and resorption of tophaceous deposits. Most failures, in the remaining 25% of patients, are due to intolerable side-effects (particularly GI upset), concomitant intake of salicylates (which nullify the uricosuric action), or the presence of renal impairment.^{1,6,17} Uricosurics are generally ineffective at a creatinine clearance of less than 50 to 60 ml/minute.

Patients with Massive Tophaceous Deposits

Patients with massive tophaceous deposits who do not respond to either allopurinol or a uricosuric drug alone, may benefit from a combination of these drugs. Serum urate concentrations should be kept consistently below 250 to 350 $\mu\text{mol/l}$ (4 to 6 mg/dl), to ensure complete resolution of the tophaceous deposits.^{1,6,17} Surgical excision of bulky tophi may be required, and restriction of both purine-rich foods (such as meats, meat extracts, liver, kidney, heart, sweetbread, poultry, peas and beans) and alcoholic beverages is helpful.

Patients with Gout and Renal Impairment

Uricosuric drugs are generally ineffective at a creatinine clearance of less than 50 to 60 ml/minute.^{1,3,6} Cutaneous reactions to allopurinol occur with increased frequency in patients with renal insufficiency.^{1,6,19,20} This can be avoided by cautious introduction of the drug in reduced doses, starting at 50 mg on alternate days and gradually increasing to a maximal daily dose based upon patient's creatinine clearance, using Hande et al's¹⁹ recommendations: 200 mg daily for clearance of 60 ml/

minute, 100 mg daily for clearance of 20 ml/minute, and 100 mg on alternate days for clearance of 10 ml/minute or less.^{1,6,19,20} Haemodialysis causes reduction of both serum urate and plasma oxipurinol levels, and it is best to administer allopurinol after each dialysis.¹⁸

Gout in the Elderly

Co-morbid medical illnesses, including hypertension, cardiac failure and renal impairment, are frequent in elderly patients with gout.²¹ NSAIDs are potentially hazardous, and are not recommended for the control of acute gouty episodes in these patients.^{7,21} Oral colchicine is also poorly tolerated by the elderly and is best avoided.^{7,21} Oral, IM, IV or IA corticosteroids are increasingly being used for treating acute gouty flares in aged patients with multiple medical conditions, contraindicating NSAID therapy.^{7,11,12,14}

Urate-lowering therapy should be approached with caution in the elderly. Because of concomitant renal impairment, uricosuric drugs are unlikely to be efficacious, and are best avoided. Allopurinol therapy is associated with an increased incidence of both cutaneous and severe hypersensitivity reactions.^{1,6,18-21} To minimise this risk, the doses of allopurinol must be kept low. A starting dose of 50 to 100 mg on alternate days, to a maximum daily dose of 100 to 300 mg, is recommended.^{1,6,19,21}

Cutaneous Reactions to Allopurinol

Although allopurinol is generally well tolerated, about 2% of patients, particularly those with renal insufficiency, develop a pruritic, erythematous rash, preventing further administration.²² More severe reactions, with toxic epidermal necrolysis or exfoliative dermatitis, eosinophilia, leukocytosis, hepatitis, and/or acute interstitial nephritis (allopurinol hypersensitivity syndrome), occur less frequently (about 0.4% of patients).^{19,22} The exact mechanisms responsible for these reactions are not known, but accumulation of oxypurinol, due to renal impairment and/or concomitant administration of thiazide diuretics, has been implicated.^{19,22} Many of those experiencing allopurinol reactions are elderly patients with reduced renal function, in whom the dose of the drug has not been reduced appropriately.

The occurrence of these reactions severely limits the ability to manage hyperuricaemia in patients with gout and renal impairment. As renal function deteriorates, uricosuric agents become ineffective, and there are no suitable alternate urate-lowering drugs. Oxipurinol has been shown to be effective in a few allopurinol-allergic individuals, but cross-hypersensitivity may occur.^{22,23} A new formulation, rapid-release oxipurinol sodium 384 mg/day (equivalent to 300 mg allopurinol), has recently been used for the treatment of hyperuricaemia and gout.²⁴ Its GI absorption is superior to that of standard

oxipurinol, but its therapeutic role in allopurinol-sensitive patients has not been defined.²⁴

Other investigational urate-lowering drugs include IM polyethylene glycol-modified arthrobacter protoformiae uricase²⁵ and urate-oxydase.²⁶

Slow, cautious reintroduction of allopurinol, using a schedule of gradually increasing doses, may be possible in patients with gout and renal insufficiency who have experienced cutaneous reactions to the drug (Table V).²² An initial oral dose of 50 μ g allopurinol daily is progressively increased every third to seventh day, to 100 μ g, 200 μ g, 500 μ g, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, and finally to a target dose of 100 mg allopurinol daily.²² Further dose increments are based upon the patient's serum urate, and creatinine levels, aiming at maintenance serum urate concentrations of 250 to 350 μ mol/l or less. Desensitisation to allopurinol is potentially hazardous, and is not recommended in those who have experienced toxic epidermal necrolysis or other severe reactions to the drug.²²

TABLE V: SUGGESTED SCHEDULE FOR ALLOPURINOL DESENSITISATION

Days (Approximate)	Daily Dose
1 to 3	50 μ g
4 to 6	100 μ g
7 to 9	200 μ g
10 to 12	500 μ g
13 to 15	1 mg
16 to 18	5 mg
19 to 21	10 mg
22 to 24	25 mg
25 to 27	50 mg
> 28	100 mg

Gout in the Transplant Patient

Both hyperuricaemia and severe tophaceous gouty arthritis occur with increased frequency in cyclosporine-treated kidney, heart, or lung/heart allograft transplant recipients.^{3,26-28} Cyclosporine induces hyperuricaemia both by inhibiting renal tubular urate secretion, and by enhancing post-secretory tubular urate resorption. Concurrent diuretic therapy and coexistent renal insufficiency are important contributing factors.^{3,27,28}

Both NSAIDs and colchicine are hazardous, and are not recommended for the treatment of acute gouty arthritis in these patients.^{3,27,28} Corticosteroids, administered intra-articularly or systemically, are the preferred drugs. Resistance to adrenocorticotrophic hormone (ACTH) from adrenal suppression by corticosteroids is frequent.

Uricosuric drugs are generally ineffective in cyclosporine-treated transplant patients with creatinine

clearance less than 30 to 50 ml/minute.^{1,6,28} Allopurinol is the preferred urate-lowering drug.^{3,28,29} Its toxicity can be minimised by adjusting the initial dose according to the creatinine clearance, based on Hande et al's¹⁹ recommendations.

Since azathioprine is inactivated by xanthine oxidase, inhibition of this enzyme by allopurinol markedly enhances azathioprine toxicity.^{3,6,28} Reduction of the initial doses of both azathioprine and allopurinol by about two-thirds, is therefore, recommended.

Refractory Gout

Allopurinol is an extremely effective drug in the treatment of gout and other hyperuricaemic states. However, a minority of patients, particularly those with renal impairment and massive tophaceous deposits, may not fully respond to the drug, and continue to experience gouty flares associated with persistent hyperuricaemia.^{1,3,6,29} Possible mechanisms include:

- 1) poor compliance,
- 2) insufficient allopurinol dose; too low to reduce and maintain serum urate levels in the lower half of the normal range (250 to 350 μ mol/L or 4 to 6 mg/dl).^{1,6,17,29-31} Although suboptimal reduction of serum urate may lead to cessation of gouty attacks, it does not prevent silent progression of joint and bone tophi,^{1,6,17,29-31}
- 3) a continued high ethanol intake.³² This is associated with a suboptimal response to allopurinol, as ethanol contributes to hyperuricaemia, both by increasing production of uric acid (increased purine production due to accelerated degradation of adenosine triphosphate to adenosine monophosphate, via the conversion of acetate to acetyl co-A in the metabolism of ethanol), and by interfering with its renal excretion (temporary lactic acidemia during acute alcoholic excesses, leading to reduced renal uric acid excretion and exacerbation of hyperuricaemia),³²
- 4) poor GI absorption of allopurinol leading to subtherapeutic allopurinol and oxipurinol plasma concentrations, and insufficient xanthine oxidase inhibition,³
- 5) impaired ability to eliminate urate due to renal disease despite sufficient xanthine oxidase inhibition.^{29,33}

In allopurinol-treated patients with gout, plasma oxipurinol concentrations in the range of 30 to 100 μ mol/l are considered optimal for effective control of hyperuricaemia.^{1,20,29,33-35} Low oxipurinol levels (less than 30 μ mol/l) may indicate:

- 1) non-compliance,
- 2) poor GI absorption of allopurinol, and/or
- 3) continued high ethanol intake. In those with poor GI absorption and normal renal function, a full therapeutic effect can sometimes be achieved by increasing allopurinol dose as high as 800 mg daily.

Measurements of plasma concentrations of oxipurinol and xanthine may also be useful in patients with gout who are still hyperuricaemic despite seemingly adequate allopurinol dosage.³³ In those with oxipurinol concentrations in the therapeutic range (30 to 100 $\mu\text{mol/l}$), in whom plasma xanthine concentrations have risen to 6 to 9 $\mu\text{mol/l}$ (indicating effective xanthine oxidase inhibition), further increases in allopurinol dose are less likely to control the hyperuricemia, and may in fact lead to toxic reactions. Under these circumstances, additional therapy with a uricosuric drug, and dietary control, should be considered.³³

Acknowledgement

The author would like to thank Ms Kathy Carey for her excellent secretarial assistance.

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