Gout — pharmacological management

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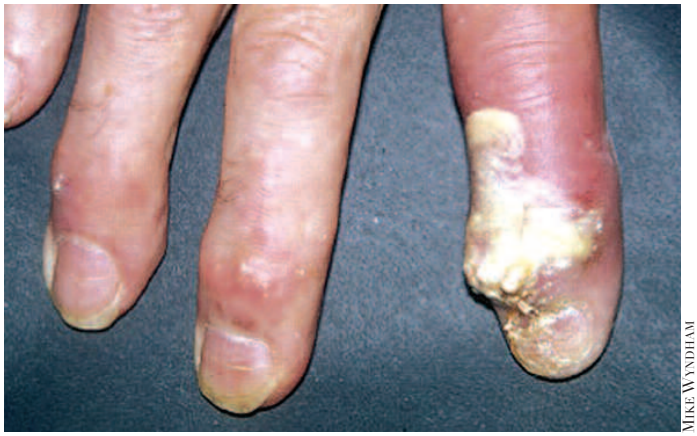
The pharmacological treatment of gout is generally split into the treatment of acute attacks and the management of hyperuricaemia. This article explains the drugs used and their action in acute and chronic gout



MIKE WYNDHAM

Fingers showing tophaceous gout

Gout is a term used to represent a heterogeneous group of diseases usually associated with hyperuricaemia. The hyperuricaemia may be due to an increased rate of synthesis of the purine precursors of uric acid or to a decreased elimination of uric acid by the kidney, or both.[1]

Gout is a clinical diagnosis whereas hyperuricaemia is a biochemical condition. Gout is characterised by recurrent episodes of acute arthritis, due to deposits of monosodium urate in joints and cartilage, and formation of uric acid calculi in the kidneys (nephrolithiasis) may occur. Prolonged hyperuricaemia is necessary but not sufficient for the development of gout.

This article reviews the pharmacological management of acute and chronic gout. It also addresses drug-induced gout and advice that should be given to patients with gout.

Drug management

The management of gout is often split into managing the acute attack and then managing hyperuricaemia in patients with chronic gouty arthritis. There are essentially three stages in the treatment of the disease:

- Treating the acute attack
- Reducing uric acid levels to prevent deposition of urate crystals into tissues, especially joints
- Prophylactic treatment with hypouricaemic therapy

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The aims of treatment are set out in Panel 1, p396. Patient education and an understanding of the basis for therapy are critical for the successful management of gout. Avoidance of factors that may trigger an attack is also a fundamental part of the management strategy. Factors known to trigger a gouty attack are set out in Panel 2, p396.

Acute attacks

Rest and rapid treatment with full doses of non-steroidal anti-inflammatory drugs (NSAIDs), eg, indometacin 200mg per day or diclofenac 150mg per day, are first-line management in acute attacks of gout, providing there are no contraindications to NSAID therapy. Aspirin should be avoided in the management of gout as it competes with uric acid for excretion and can exacerbate an acute attack. An alternative, but second-line, agent in the management of acute gout is colchicine.

The decision on whether to choose an NSAID or colchicine depends on patient features — eg, co-morbidity, concomitant interacting drug therapy and renal function. This is because there are no controlled studies comparing colchicine with NSAIDs in the management of gout. However, patients with cardiovascular disease, including hypertension, those receiving diuretics in cardiac failure and those with gastrointestinal toxicity, bleeding diathesis or renal impairment should be treated with colchicine.

Agents that decrease serum uric acid levels (allopurinol or uricosuric agents such as probenecid and sulfinpyrazone) should not be used in an acute attack. Patients generally have been hyperuricaemic for several years so there is no need to treat the hyperuricaemia immediately. In addition, such agents may cause mobilisation of uric acid stores as the serum level falls. This movement of uric acid may prolong the acute attack or precipitate another attack of gouty arthritis. However, if the patient is already stabilised on allopurinol at the onset of an acute attack, the drug should be continued.

The management of acute gout is summarised in Panel 3 (p399)[2]. The use of NSAIDS, cyclo-oxygenase-2 (COX-2) inhibitors, colchicine and steroids for acute attacks are discussed below.

NSAIDs

NSAIDs are effective first-line therapy for otherwise healthy patients presenting with acute gout. The most important factor determining therapeutic success is not the NSAID chosen but how soon NSAID therapy is initiated.

NSAIDs should be administered in full doses for the first 24–48 hours or until the pain has settled. Lower doses should be continued until all symptoms and signs have

Panel 1: Treatment goals in the management of gout

- Relieve pain and inflammation of an acute attack
- Terminate an acute attack as quickly as possible
- Prevent exacerbation of further attacks and so prevent long-term:
  - Joint damage
  - Associated organ damage eg, renal disease
- Reduce serum urate levels in symptomatic patients
- Reduce the risk of uric acid stones
- Reduce the formation of tophi

resolved. NSAIDs usually take between 24 and 48 hours to work, although complete relief of gouty signs and symptoms is usually seen after five days of treatment. Patients known to have gout should carry a supply of NSAIDs with them to treat an acute attack following the first symptom.

Indometacin is commonly prescribed for an acute attack of gouty arthritis, initially at a dose of 75–100mg twice a day. This dose should be reduced after five days as the acute attack settles. Adverse effects of indometacin include headaches and gastrointestinal upset, although these will resolve with the decreasing dose.

Azapropazone is another potential agent for treating acute gout. This NSAID lowers serum urate levels — the exact mechanism of action is unknown. The Committee on Safety of Medicines (CSM) has restricted azapropazone to acute gout only when other NSAIDs have been tried and failed. Its use is contraindicated in patients with a history of peptic ulceration, in moderate to severe renal impairment and in the elderly with mild renal impairment.

Other NSAIDs commonly used to treat acute episodes of gout include:

- Naproxen — 750mg initially, followed by 250mg three times a day
- Piroxicam 40mg initially, followed by 10–20mg per day
- Diclofenac 100mg initially, then 50mg three times a day for 48 hours, followed by 50mg twice daily for eight days

COX-2 inhibitors

Etoricoxib is the only licensed COX-2 inhibitor for the management of acute gout.[3] It is an effective but comparatively expensive agent which may have a role in some patients, particularly those with gastrointestinal intolerance of non-selective NSAIDs.

COX-2 inhibitors have been shown to have a lower risk of serious upper gastrointestinal side effects than non-selective NSAIDs and much has been written about this class of drugs, particularly about cardiovascular safety since the withdrawal of rofecoxib. The European review into the safety of selective COX-2 inhibitors and subsequent CSM advice have confirmed the suggestion that these agents may cause an increased risk of thrombotic events (eg, myocardial infarction and stroke) compared to that for non-selective NSAIDs and placebo. The CSM advises that patients with established ischaemic heart disease, cerebrovascular disease or moderate to severe heart failure should not be prescribed COX-2 inhibitors. In addition, it says that for all patients, the balance of gastrointestinal and cardiovascular risk should be considered before prescribing a COX-2 inhibitor.

The CSM also advises that there is evidence that etoricoxib may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and non-selective NSAIDs, particularly at high doses. As such, etoricoxib should not be initiated in patients whose hypertension is not under control and careful blood pressure monitoring is advised for all patients taking etoricoxib.[4]

Colchicine

Colchicine is an effective and specific treatment for the management of acute gout. However, it is less favoured than NSAIDs because of its slow onset of action and high incidence of adverse effects.

Oral Oral colchicine has historically been the first-line treatment for acute gout, although only one double-blind placebo controlled trial of oral colchicine has been reported.[4] This trial showed that two-thirds of patients treated with colchicine improved within 48 hours of beginning therapy compared with only one-third of those receiving placebo.

For oral colchicine to be effective it must be administered as quickly as possible after the onset of symptoms because it becomes less effective as symptoms progress. Traditionally, an initial dose of 1mg has been used followed by 0.5mg every two to three hours during an acute attack until there is relief of joint pain, the patient develops gastrointestinal symptoms or a maximum dose of 6mg has been given. Titration of the dose between therapeutic response and gastrointestinal toxicity is difficult to achieve because the therapeutic dose is close to the toxic dose. Deaths have occurred in patients who have received as little as 5mg of colchicine. Recent authors have suggested a lower dose of 0.5mg every eight hours should be used in order to reduce the risk of toxicity, especially in the elderly and patients with renal impairment.[6]

A course of colchicine should not be repeated within three days of the previous course in order to prevent toxic reactions from occurring.

Intravenous Intravenous colchicine is no longer licensed for use because it has been associated with severe toxicity. However, a review of the published experience with intravenous colchicine suggested that the toxicity was due to inappropriate use of the drug and usually involved dosage errors.[7]

Adverse events Adverse effects of oral colchicine include severe nausea and vomiting, diarrhoea and abdominal pain. These affect 80 per cent of patients who take a therapeutic oral dose. Dehydration may be a major complication of therapy. Other side effects include seizures, respiratory depression, hepatic and muscle necrosis, renal damage, fever, granulocytopenia, aplastic anaemia, disseminated intravascular coagulation and alopecia. Many of the serious side effects occur in patients with hepatic or renal dysfunction.

Steroids

An alternative strategy to NSAIDs or colchicine is to use intra-articular steroids. These can provide quick relief when only one or two joints are involved. However, a differential diagnosis between septic arthritis and acute gout must be certain because intra-articular steroids will exacerbate infection. Patients with a suboptimal response to NSAIDs may benefit from the administration of an intra-articular steroid.

Systemic steroids can also be used to treat acute gout. In certain patients, such as those with severe or polyarticular attacks or those with renal disease or heart failure which may preclude the use of NSAIDs or colchicine, prednisolone 20–40mg per day initially may be useful. These agents usually take 12 hours to work and the recommended duration of therapy is from one to three weeks.

Panel 2: Factors known to trigger an acute attack of gout

- Trauma
- Unusual physical exercise
- Surgery
- Severe systemic illness
- Severe dieting
- Initiation of B_{12} in pernicious anaemia
- Cytotoxic drug therapy
- Dietary excess
- Alcohol
- Drugs
- Diuretics
- Initiation of uricosuric or allopurinol therapy
- Drug allergy

Alternatively, intravenous methylprednisolone 50–150mg daily or intramuscular triamcinolone 40–100mg daily may be administered and tapered over five days.

Management of chronic gout

Long-term control of hyperuricaemia is important in order to prevent acute attacks of gout, chronic tophaceous gout, renal involvement and production of uric acid stones. The evidence on when to start urate lowering drugs is conflicting and controversial.

Initial attacks of gout are usually infrequent and self-limiting, and long-term therapy is often not indicated. Some advocate only starting treatment in patients who experience more than four episodes per year, while others suggest commencing treatment in patients who have only one recurrent attack per year. Expert consensus opinion appears to support long-term hypouricaemic agents for patients who suffer two or more gouty attacks per year. Expert opinion also suggests that urate lowering drugs should not be started during an acute attack as described earlier. Long-term agents should not be used for asymptomatic hyperuricaemia, or for protecting renal function or cardiovascular risk in asymptomatic patients.

A summary of treatment options for chronic gout is provided in Panel 4. The use of allopurinol, uricosuric agents and febuxostat (under development) in the treatment of chronic gout are discussed below.

Allopurinol

The hypouricaemic agent of choice in the management of chronic gout is allopurinol. As well as controlling symptoms, it may also protect renal function.

Allopurinol reduces uric acid production by inhibiting the enzyme xanthine oxidase. Allopurinol is not active but 60–70 per cent of the drug undergoes hepatic conversion to its active metabolite oxipurinol. The half-life of allopurinol is approximately two hours and for oxipurinol is 12 to 30 hours in patients with normal renal function. Oxipurinol is excreted renally together with allopurinol and allopurinol riboside, the second main metabolite.

Panel 3: Treatment of acute gout[2]

- Confirm diagnosis
- Initiate treatment with full dose NSAIDs early in the attack, unless contraindicated
- Consider oral colchicine if NSAIDs not appropriate. Use within 24–48hrs of acute attack
- Use colchicine cautiously because of toxicity and monitor response
- If one or two joints affected consider intra-articular steroids
- If severe disease or NSAIDs/colchicine not tolerated consider systemic steroids
- Do not treat hyperuricaemia in acute attack

Dose In patients with normal renal function the initial allopurinol dose should not exceed 300mg in 24 hours. In practice, most patients are started on 100mg daily and the dose is then titrated appropriately. The usual maintenance dose is 100–600mg daily and a dose of 300mg daily reduces serum urate to normal in approximately 85 per cent of patients. A response to allopurinol which is reflected by a decrease in serum urate concentration is seen about two days after starting therapy and is maximal after seven to 10 days. The serum urate concentration should be checked after two to three weeks of allopurinol to ensure a fall in levels.

Allopurinol may prolong an acute attack of gout or it may precipitate another and should therefore not be started until an attack has subsided. The risk of inducing an acute attack can be reduced by co-administration of an NSAID or colchicine (1.5mg daily) for the first three months of chronic therapy.

Adverse events Allopurinol causes side effects in 3–5 per cent of patients, and these usually manifest as hypersensitivity reactions. A syndrome of allopurinol toxicity, including rash, fever, worsening renal insufficiency, vasculitis and death, has been reported. This syndrome is more common in elderly patients with renal insufficiency and in those taking concomitant thiazide diuretics. Skin eruptions are the most common effect, but others include hepatotoxicity, acute interstitial nephritis and fever. These hypersensitivity reactions subside when treatment is stopped. However, if treatment is continued, severe exfoliative dermatitis, various haematological abnormalities, hepatomegaly, jaundice, hepatic necrosis and renal impairment can occur.

Many patients with severe reactions have had reduced renal function when the dose of allopurinol used was too high. This toxic syndrome most commonly occurs within the first two months of treatment, although reactions occurring later have been reported. Patients who have had minor hypersensitivity rashes can undergo an allopurinol desensitisation regimen whereby the dose of allopurinol is gradually increased over a period of three to four weeks.

Although allopurinol is generally well tolerated, it is important to note that many of the common adverse effects, especially pruritic maculopapular rash, which affects up to 2 per cent of patients, relate to using inappropriate dosages in patients with renal impairment. Renal function should be checked before allopurinol is started and doses adjusted accordingly. Guidelines have been published for allopurinol dosing in patients with renal impairment and recommendations made for appropriate dosages according to creatinine clearance (see Panel 5, p400).

Panel 4: Treatment of chronic gout[2]

- Start urate-lowering drugs in patients who have two or more attacks per year (urate lowering drugs should not be started during an acute attack, allopurinol is the urate lowering drug of choice in the majority of patients)
- Use uricosuric drugs in patients intolerant or allergic to allopurinol and in under-excreters with normal renal function
- Consider concomitant colchicine until serum urate levels have been lowered and no acute attacks have recurred for six to12 months
- Monitor serum urate levels every three to six months and adjust therapy according to levels in symptomatic patients

Concomitant cytotoxics Allopurinol enhances the toxicity of cytotoxic drugs metabolised by xanthine oxidase. The doses of such cytotoxics (eg, azathioprine) should be reduced during concurrent allopurinol therapy. In addition, allopurinol enhances the bone marrow toxicity of cyclophosphamide.

Uricosuric agents

Most patients with symptomatic hyperuricaemia under-excrete uric acid and can be managed with uricosuric agents. Uricosuric agents such as probenecid (500mg to 1g twice daily) and sulfinpyrazone (100mg three or four times a day) may offer an alternative to allopurinol, especially in allopurinol-intolerant patients. However, availability of these drugs needs to be considered bacause probenecid has been discontinued in the UK and is only available as an unlicensed product on a named patient basis.

Uricosuric agents should be avoided in patients with urate nephropathy and those who over-produce uric acid. They are ineffective in patients with poor renal function (creatinine clearance of less than 20–30ml/min). Approximately 5–10 per cent of patients receiving long-term probenecid suffer nausea, heartburn, flatulence or constipation. A mild pruritic rash,

Panel 5: Suggested maintenance doses of allopurinol for patients with impaired renal function[9]

Creatinine clearance (ml/min)	Allopurinol dose
0	100mg thrice weekly
10	100mg alternate days
20	100mg daily
40	150mg daily
60	200mg daily
> 100	300mg daily

drug fever and renal disturbances can occur. Its major limiting factor is a lack of efficacy due to poor compliance, concurrent low dose salicylates or renal insufficiency.

Benzbromarone The uricosuric agent benzbromarone, which is unlicensed in the UK, can be used at a dose of 100mg daily when imported on a named patient basis for patients with moderate renal impairment for whom other uricosuric agents are ineffective or allopurinol is precluded owing to hypersensitivity. It is particularly useful in that its uricosuric activity is maintained in patients with moderate renal impairment. Its use is, however, strictly monitored and controlled by the Medicines and Healthcare products Regulatory Agency as it has been linked to severe hepatotoxicity.

Febuxostat

Febuxostat is currently being evaluated in phase III trials and is not yet available in the UK. It is a novel, oral, non-purine xanthine oxidase inhibitor which is being developed for hyperuricaemia associated with gout. Early studies show the drug to be well tolerated in patients with gout for up to four weeks.[8] A licence application has recently been filed in the US.

Drug-induced gout

As well as medicines being used to treat gout, hyperuricaemia and gout can result from using particular drugs that reduce uric acid excretion or increase uric acid production. Thus, hyperuricaemia and gout can occur with drugs such as diuretics, especially thiazides. Where possible an alternative agent should be used, but when this is not possible, allopurinol should be used to lower urate levels.

Other drugs that reduce renal urate excretion include low-dose aspirin and alcohol. Ciclosporin-induced hyperuricaemia and gout have been reported, especially in men. Acute gout associated with omeprazole has also been reported. Some drugs may interfere with renal excretion of uric acid and these drugs include ethambutol, pyrazinamide, niacin and didanosine.

Radiotherapy and chemotherapy in patients with neoplastic disorders can also cause hyperuricaemia. This can be treated prophylactically with allopurinol, starting three days before therapy.

Non-drug treatment

Non-drug treatment of gout has been covered in the first article in this series (pp391–4). It must be stressed that this is an essential part of the management strategy. Since gout is a metabolic disorder, it is influenced by factors such as diet, alcohol intake, hyperlipidaemia and weight. Thus rest, cold applications, dietary modifications, reduction in alcohol intake and weight loss in overweight patients have all been shown to be effective interventions.[2]

Advice to patients

Patients with gout should be advised about factors that may contribute to hyperuricaemia, such as fasting, obesity and alcohol excess. If these are avoided or corrected, drug treatment may not be needed and asymptomatic hyperuricaemia need not be treated — but renal function can be checked to ensure that it is not deteriorating.

Patients at risk of recurrent gouty attacks should receive a supply of NSAIDs and must be adequately informed to start treatment at the first signs of an attack. They should be advised to avoid aspirin and use paracetamol instead for analgesia.

Patients receiving allopurinol should be informed of the need to continue single daily dose treatment in the absence of any symptomatic response. They must be warned of potential side effects and told to report any adverse skin reactions.

Patients receiving uricosuric agents should be advised to maintain a fluid intake of at least 2L per day to reduce the risk of uric acid stone formation in the kidneys.

Summary

The options available for the management of acute gout are NSAIDs, COX-2 inhibitors, colchicine, and systemic or intra-articular corticosteroids.

In most patients without complications or co-morbidity, NSAIDs are the agents of choice. However, the most important factor for successful management is how soon the NSAID can be started. Colchicine may offer an effective alternative, although its use is limited by toxicity.

Long-term control of hyperuricaemia and the pharmacological management of chronic gout is important to prevent the sequelae associated with high urate levels. This is particularly important for patients who experience two or more exacerbations of acute gouty arthritis per year.

Allopurinol remains the urate-lowering drug of choice, although febuxostat may offer an alternative depending on its progress through its licence application. Uricosuric drugs are alternatives in patients who are intolerant or allergic to allopurinol and for under-excreters with normal renal function. The availability and safety of these agents (especially benzbromarone), however, are factors to consider.

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