Medicines that cause and alleviate gout

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Abstract
Gout, a condition caused by increased levels of serum uric acid, is an extremely painful condition and often only treated when an acute attack is experienced. The factors contributing to raised serum uric acid levels, for example lifestyle choices and the use of various medications, will be evaluated in this article, as well as the role of medicines used in the prevention and management of gout.

Introduction
Although gout has been recognised as one of the oldest metabolic diseases, patients often do not understand the factors that can contribute to their disease and how these factors can be controlled. Patient compliance is often poor, as patients do not always understand the need for prophylactic and chronic treatment of a condition that might just flare up occasionally.

Pharmacists are in the unique position of being able to educate patients about the pathophysiology of the disease, and the importance of compliance and associated complications if not treated adequately.

Pathophysiology
Gout is characterised by elevated serum uric acid (SUA), and the deposition of monosodium urate (MSU) crystals and associated inflammation in joints, bones or soft tissue. Uric acid is the metabolic end-product of purine degradation. Purine is a crystalline organic base-containing nitrogen. The purine bases include adenine and guanine, which are parent compounds of various biologically important substances, including deoxyribonucleic acid or DNA. Uric acid is the end-product of purine metabolism. Purines are found in high concentration in meat and meat products, especially internal organs such as liver and kidney.

Two factors contribute to elevated serum uric acid levels (hyperuricaemia): either overproduction or under excretion of uric acid, and/or overconsumption of purine-rich foods. In most mammals, uric acid is converted to allantoin by uricase, but this enzyme is absent in humans, predisposing to high SUA levels following the ingestion of purine-rich food.

Pharmacists should be aware of the various factors that can affect SUA levels. SUA levels are determined by the difference between the secretion and absorption of uric acid. Uric acid is typically secreted through the digestive (33%) and renal (66%) systems. The renal urate transporter 1 (usually referred to as URAT1) in the proximal tubule appears to be primarily responsible for the reabsorption of uric acid through the exchange of urate with organic anions.

The pathogenesis of gout, therefore, starts with the crystallisation of urate within the joint, bursa or tendon sheath, which leads to inflammation. Macrophages recognise the urate crystals as foreign and phagocytose them, releasing interleukin-1 and other inflammatory cytokines. The cytokine release rapidly ignites a broader inflammatory response, causing the redness, pain and swelling that is characteristic of an acute flare-up of gout. The pain gradually gets worse within the first 24 hours, and will then slowly start to subside after two or three days. In 85-90% of the cases, acute gouty arthritis typically presents as monoarthritis, i.e. affects a single joint.

Risk factors
Gout is the most common inflammatory joint disease in men over 40 years of age. It is also clear that certain lifestyle choices can have an effect on the occurrence of gout attacks. Various nonmodifiable and some modifiable factors contribute to the development of gout. Awareness of these factors is critical to the pharmacist, in order to be able to counsel patients effectively.

Nonmodifiable risk factors include:

- Male gender
- Postmenopausal women
- Age
- Genetic influences
- End-stage renal disease
- Organ transplantation.
The following are examples of modifiable risk factors:

- Diet (red meats, seafood and foods containing high-fructose corn syrup)
- Medication, e.g. thiazide diuretics
- High alcohol intake
- Weight (body mass index of 25 kg/m² or more)
- Untreated high cholesterol or blood pressure, or diabetes.

Patients can take various measures to reduce these modifiable risks:

- Drink less beer and alcohol: Beer is high in purines and, like other grain-based alcohol, can increase the amount of uric acid in the body.
- Keep track of uric acid levels: Uric acid levels should ideally be checked at least twice a year. The ideal value for serum uric acid levels is 6.0 mg/dl.
- Regular exercise: Moderate activity is recommended, for at least 30 minutes a day for three to five days of the week. This means activities such as brisk walking, swimming, cycling, even dancing and mowing the lawn.
- Maintain a healthy diet: Obesity increases the risk of developing gout fourfold when compared to a person with an ideal body weight. High-protein diets may be a problem for people with gout, because of the high purine content of foods such as red meat and shellfish.
- Drink plenty of water: Water aids the body in the transportation of nutrients and toxins, and can also assist in preventing kidney stones and constipation.
- Have cholesterol, blood pressure and sugar levels checked at regular intervals.

The four disease stages of gout

**Stage 1: Asymptomatic hyperuricaemia**

At serum urate concentrations greater than 6.8 mg/dl, urate crystals may start to deposit, although no clinical presentation may be apparent. It is possible that some patients with asymptomatic hyperuricaemia will never experience a gout attack, but in other individuals, a cascade of events is triggered and the patient will suffer an acute gout attack and move into the second stage.

**Stage 2: Acute gouty arthritis**

Urate crystallisation in the joint causes acute inflammation. This is commonly referred to as a “flare” or “flare-up”, and although this stage is self-resolving, it is likely to recur.

**Stage 3: Intercritical periods**

This stage is defined as the interval between acute gout attacks. During this stage, crystals may still be present at a low level, but they do not evoke an inflammatory response.

**Stage 4: Chronic gout**

Patients with chronic gout have extended, persistent, uncontrolled hyperuricaemia, active, untreated gout or repeated episodes of painful attacks. More than one joint can be involved and at this stage, chronic gout is often misdiagnosed as rheumatoid arthritis. However, this advanced stage of gout can be avoided if the patient adheres to prophylactic treatment.

**Medications that increase serum uric acid levels**

Pharmacists need to be aware that various medications can affect serum uric levels, and that patients need to be advised in this regard. It may be necessary to contact the prescribing doctor in order to change the prescription.

**Diuretics**

Loop or thiazide diuretics decrease urate excretion by increasing net urate reabsorption, either by enhanced reabsorption or by reduced secretion. However, not all patients on diuretic treatment will experience gout attacks, even though their uric acid levels may exceed 15 mg/dl. Gouty arthritis occurs primarily in patients with a personal or family history of the disease.

**Low-dose salicylate**

Despite the cardioprotection offered by low-dose aspirin, this drug may be associated with the precipitation of gout, mediated via a decrease in renal urate excretion.

**Ciclosporin**

The use of ciclosporin in organ transplant patients has been reported to cause a type of gout which occurs rapidly, and is swiftly ascending and polyarticular in distribution. The pathomechanism would appear to be ciclosporin-induced increased renal tubular urate reabsorption, in most cases. The hyperuricaemia induced by ciclosporin is not restricted to renal transplant recipients, but is also frequent in heart or heart-lung transplant patients.

**Ethambutol**

Studies have shown that in a small percentage of patients, ethambutol (an antituberculotic drug) may cause hyperuricaemia and acute gouty arthritis, as the drug decreases renal urate excretion. On withdrawal of treatment, the symptoms abate.

**Tacrolimus**

Like ciclosporin, tacrolimus can also elevate SUA levels, because of increased renal tubular excretion in renal transplant patients.

**Medications acting on the renal urate transporter 1**

According to Sawin, "URAT1 in the proximal tubule appears to be primarily responsible for the reabsorption of uric acid through the exchange of urate with organic anions. The pharmacological importance of this finding is that many drugs seem to act on this transporter." Examples include pyrazinamide, lactate, nicotinate and acetoacetate.
ReView

Drugs for the acute treatment of gout

Without any form of treatment, acute gouty arthritis can resolve spontaneously within a few days to several weeks. However, symptoms will improve more quickly when anti-inflammatory drugs are administered. Other than anti-inflammatory medication, colchicine and corticosteroids are also often used to help resolve an acute gout attack (Table I).1,3,10

Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors

The first line of treatment in an acute gout attack is usually nonsteroidal anti-inflammatory drugs (NSAIDs), unless contraindicated (e.g. peptic ulcers, renal insufficiency and heart failure). Typical choices would include naproxen, diclofenac and ibuprofen. The elderly are more prone to the adverse effects of NSAIDs and low doses of the shorter-acting NSAIDs should be prescribed for older patients.12 Aspirin is usually avoided because of the paradoxical increase in serum urate caused by salicylates.10

Corticosteroids

Corticosteroids are an effective alternative for patients in whom other treatment options are contraindicated. They can be administered orally, intramuscularly, intravenously or intra-articularly (if no more than two joints are affected). According to Becker et al, “clinical experience suggests that prednisone or prednisolone in doses of 30 to 50 mg/day (or other equivalent glucocorticoid) for one or two days, then tapered over seven to ten days, effectively reduces acute symptoms to a similar extent as do NSAIDs. However, rebound attacks are relatively common once glucocorticoids are withdrawn, especially in patients who have previously suffered a number of prior attacks and whose intercritical periods have progressively shortened.”10

Colchicine

Treatment with colchicine is usually initiated within 12-36 hours of the start of an acute attack. The use of oral colchicine is recommended under the following circumstances:10

• Intolerance to NSAIDs
• If glucocorticoid therapy is not appropriate
• Successful colchicine use in the past
• The absence of contraindications.

The most recent international treatment guidelines promote a low-dose regimen of colchicine: an initial dose of 1.2 mg is followed by one additional dose of 0.6 mg in one hour, for a total dose of 1.8 mg. Adherence to the low-dose regimen reduces gastrointestinal side-effects (diarrhoea, abdominal cramps, nausea and vomiting) that often accompany a high-dose regimen.1,10

Treatment of chronic gout

The goal to strive towards when dealing with the long term treatment of gout, is to lower uric acid levels to at least 6 mg/dl.11 This can be achieved by making use of urate-lowering therapy, mainly uricosuric drugs and xanthine oxidase inhibitors.

Table I: Drugs used in the treatment of acute gout1,11,12

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult dose</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs and COX-2 inhibitors</strong></td>
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<tr>
<td>Diclofenac</td>
<td>100-150 mg/day in two or three divided doses for a maximum of five days (over the counter)</td>
<td>All NSAIDs have been associated with adverse gastrointestinal, renal, dermatological, hepatic, haematological, immunological and neurological side-effects</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>900-1 200 mg/day in divided doses for a maximum of five days (over the counter)</td>
<td></td>
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<tr>
<td></td>
<td>2 400 mg/day in divided doses (schedule 3)</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>50 mg three or four times daily (schedule 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum 200 mg daily (schedule 3)</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>750 mg stat, followed by 250 mg three times daily for a maximum of five days (over the counter)</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>40 mg stat, followed by 40 mg daily for four to six days (schedule 3)</td>
<td></td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>120 mg once daily during the acute symptomatic period, and limited to eight days (schedule 3)</td>
<td>Cardiovascular, cerebrovascular and gastrointestinal events, cutaneous reactions</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>30-50 mg/day, or equivalent</td>
<td>Gastrointestinal side-effects, increase in blood sugar, increase in blood pressure</td>
</tr>
<tr>
<td><strong>Colchicine</strong></td>
<td></td>
<td>Dose-related gastrointestinal side-effects, myopathy, neuropathy, bone marrow suppression</td>
</tr>
<tr>
<td></td>
<td>1.2 mg initial dose, followed by one more dose of 0.6 mg in one hour, to a maximum of 1.8 mg</td>
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</tbody>
</table>
Both allopurinol and uricosurics may precipitate an acute attack of gout, particularly if uric acid levels are reduced suddenly. This can be prevented by using small doses of these agents initially, with concurrent administration of moderate but regular doses of an NSAID or colchicine. This prophylaxis should be carried out for about the first three months of treatment, especially in patients who have had previous attacks of acute gout (Table II).

Uricosuric drugs

Uricosuric agents should only be used if the following criteria are met:
- Patient is under 60 years of age
- Underexcretion of uric acid
- No history of reduced renal function (creatinine clearance over 60 ml per minute) or kidney stones
- Patient does not require aspirin or diuretic therapy

The importance of high fluid intake and alkalinisation of the urine, especially during the first weeks of therapy, should be emphasised.

Xanthine oxidase inhibitors

Xanthine oxidase inhibitors block xanthine oxidase, thereby reducing the generation of uric acid. Allopurinol is one of the best-known xanthine oxidase inhibitors and is a structural isomer of hypoxanthine. It inhibits uric acid formation and purine synthesis. Allopurinol is effective in both underexcreters and overproducers of uric acid.

Inappropriate treatment and noncompliance with treatment can increase the number of flares and complications of gout; therefore adequate treatment and compliance are essential.

Various medications may be used to treat acute and chronic gout and referral to a doctor is essential to ensure that adequate treatment is provided. Pharmacists are reminded that some NSAIDs are schedule 2 when used for the emergency treatment of gout and may be administered for a maximum duration of five days.

References


Table II: Summary of serum urate-lowering drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uricosuric drugs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Probenecid</td>
<td>The starting dose is 250 mg twice daily; increments in dose are titrated according to the urate concentration. The dose is typically raised every several weeks to a usual maintenance dose of 500 to 1 000 mg two or three times daily; the maximal effective dose is 3 g/day.</td>
<td>Kidney stones, renal dysfunction</td>
</tr>
<tr>
<td><strong>Xanthine oxidase inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>The average daily dose is 200 to 300 mg for mild gout, 400 to 600 mg for moderate gout and 700 to 800 mg for severe gout. Experts recommend starting with 100 mg per day, then increasing by 100 mg per day once every one to four weeks until target serum uric acid is achieved. For patients with renal insufficiency, the starting dose is 50 to 100 mg per day.</td>
<td>Rash, fever, very rarely allopurinol hypersensitivity syndrome (treatment should be stopped if a skin rash or fever develops)</td>
</tr>
</tbody>
</table>