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Management of Gout — A Rational Approach

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INTRODUCTION

Acute gouty arthritis is considered one of the most painful experiences of human being. The first goal in managing a patient with gout and hyperuricaemia is to terminate the acute attack. Next attention should be given to preventing the recurrence of acute attacks. Finally, there is a need to reverse the complications of this disease. This includes eliminating sodium urate crystals deposited in the joints and kidneys, as well as other sites, and preventing or reversing the commonly associated conditions of hypertriglyceridaemia, obesity, hypertension, and alcoholism.

ACUTE GOUTY ARTHRITIS

The acute gouty attack may be successfully treated with several drugs (Fig. 1). These include colchicine, cortico-trophin (ACTH), a corticosteroid preparation, or a non-steroidal anti-inflammatory drug (NSAID). Whereas all these drugs relieve symptoms and help to terminate the initial attack, their mechanisms do not correct the underlying mechanism of hyperuricaemia, nor do they alter the progression of urate crystal deposition in body tissues. The crucial issue is not so much which of these agents is selected. Rather it is how quickly its use is initiated. The sooner after symptoms are experienced that treatment is started, the more satisfying the response will be[1]. Because of this, the patient should be advised to keep an oral agent close at all times and instructed to take a dose at the very earliest sign of an attack. This strategy may abort the attack and allow resolution with the use of a minimum of medication.

NSAIDs are preferred than others. Unfortunately, many patients have contraindications to NSAIDs, especially those with heart failure, renal insufficiency, or gastrointestinal disease. If the patient cannot take the medications by mouth or has acid peptic disease, the choice is among parenteral or intra-articular corticosteroids, intramuscular ACTH, or intravenous colchicine. Because these agents each work by a different mechanism, they may be used in combination in severe or refractory attacks. Under those conditions, analgesics, including narcotics, may be used to help treat the pain.

Drugs that will affect the serum urate levels, including urate-lowering drugs, should not be changed, either initiated or discontinued, during the acute attack. Just as sudden changes in levels of serum urate levels may precipitate an acute attack of gout, an inflammatory reaction already in progress may be made substantially more severe by major fluctuations in the serum urate level.

NSAIDs

For the majority of patient with acute gout, especially those in whom the diagnosis is confirmed by joint aspiration with urate crystal identification, NSAIDs are preferred over colchicine because of their more favourable side-effect profile, and increased duration of action[2,3]. Currently there are numerous NSAIDs from which to select. These include traditional agents, such as indomethacin, ibuprofen, naproxen sodium, and diclofenac, that inhibit the isoforms of cyclo-oxygenase 1 and 2 (COX-1 and COX-2), and the newer ones, such as celecoxib and etoricoxib, that are selective inhibitors of COX-2. With respect to the relief of pain and inflammation, there is no convincing evidence that one of these agents is better than another, as evidenced by a recent study that found similar relief in patients treated with indomethacin or a selective COX-2 inhibitor. Therefore, the choice of which NSAID to prescribe is

made in consideration of the patient's associated diseases, risk of side-effects, and cost issues. Traditionally, indomethacin has been used at 100 mg initially followed by 50 mg every 6 hours. Diclofenac sodium 50 mg is prescribed every 8 hours. Naproxen sodium 500 mg is to be taken every 8 or 12 hours. These medications should be administered until the symptoms resolve completely and then tapered gradually over the next 7 to 10 days.

Risk of coronary artery disease should also be weighed in making the decision to use a particular NSAID[3,4]. Those patients taking concurrent aspirin therapy are at the greatest risk for these treatment problems, even at low doses. There are good data that these patients should be treated with proton pump inhibitors to reduce the risk of gastric symptoms and/or injury[5]. The use of parenteral non-steroidal therapy, such as ketorolac, carries the same risk as oral NSAIDs[2,3].

COLCHICINE

Orally a dose of 0.6 mg is taken every 1 to 2 hours until one of three things occurs: (1) joint symptoms resolve, (2) the patient has taken 10 doses without relief, or (3) gastrointestinal side-effects develop. Alternative regimens include loading the patient with 1.0 mg orally followed by 0.5 mg every 2 to 6 hours or 1.0 mg three times a day[6,7].

Colchicine is most effective if initiated within the first 10 to 12 hours of an attack. If the patient waits longer than 48 hours after the acute attack begins, the efficacy is substantially reduced[2,3]. Unfortunately, colchicine has a low therapeutic index. The steady state plasma concentration after acute treatment ranges between 0.5 and 3.0 ng/mL, but toxic effects occur at approximately 3.0 ng/mL[8]. Therefore, in many patients the side-effects coincide or proceed with improvement in the joint symptoms. The majority of patients will have gastrointestinal side-effects such as increased peristalsis, abdominal discomfort, nausea, vomiting, and diarrhoea. At this point the drug should be stopped promptly[9].

Colchicine can be administered intravenously and, when used properly, can effectively abolish the acute attack with a low incidence of side-effects[6,9,10]. Today, many experts discourage the use of intravenous colchicine, and some even consider it contraindicated because of adverse outcomes, including death in patients receiving inappropriate dosing[2,3,11].

CORTICOSTEROIDS AND ACTH

Corticosteroids are typically reserved for those patients who have refractory gout, who are intolerant of NSAIDs or colchicine, or who have medical conditions that prohibit usage of other drugs[12,13]. The steroid when used are then tapered gradually over the next 2 weeks depending on the response.

Patients in whom corticosteroids are used should be closely monitored for 'a rebound flare-up' during and following the dose tapering, as well as other side effects, including fluid retention, electrolyte shifts, glucose intolerance, diabetes mellitus, slight elevation in blood pressure, and increased susceptibility to infection.

Corticosteroids may also be administered by the intra-articular route[14,15]. This route is useful in those patients who cannot take oral agents, in older patients, those with multiple organ problems (especially renal insufficiency), or patients with organ transplants.

An intramuscular dose of ACTH, or gel (25-80 IU), is effective. Recent studies have shown that corticotrophin may be more effective than corticosteroids because, in addition to inducing endogenous corticosteroid production by the adrenal glands themselves, it interferes with the acute inflammatory response through local activation of melanocortin receptor-3[16].

PREVENTING FURTHER ATTACKS

Once the patient has suffered one attack of acute gout, the likelihood of a recurrent attack is extremely high. In patients not treated with urate-lowering drugs, 62% will experience a recurrence within 1 year of the initial attack, 78% by 2 years, and 89% by 5 years[17]. To eliminate these acute flares and prevent tophi generation and accumulation, it is paramount that the total body pool of urate returns to normal[18,19]. To accomplish this, the serum urate levels must be maintained below 40.8 mmol/L (6.8 mg/dL), and preferably at levels below 30 mmol/L (5.0 mg/dL)[20-22].

Therapy with specific urate-lowering agents should not be initiated for at least 2 to 3 weeks after all symptoms of an acute gouty arthritis flare have resolved.

There have been several suggestions to avoid acute flares of gout when starting urate-lowering agents. Initiating the agent at low dose and increasing the dose every 1 to 2 weeks until the target serum urate level is attained has been recommended by some. An additional strategy, urate-lowering agents involves giving low doses of colchicine or NSAIDs on a daily basis as prophylactic agents. The latter approach is effective in preventing acute attacks of gout in up to 85% of patients[23]. Unfortunately, side-effect profiles may prohibit this practice in some patients.

CONTROL OF HYPERURICEMIA

Once urate-lowering medications are initiated, the treatment is not intermittent; it is continuous and lifelong. In addition, the dose of urate-lowering medicatIon must be sufficient to lower the serum urate level to below 40.8 mmol/L (6.8 mg/dL), and preferably below 30 mmol/L (5.0 mg/dL). Reduction to the target level can be attained by using uricosuric agents or xanthine oxidase inhibitors. Each of these medications will be effective in diminishing acute attacks, reversing tophi, and preventing deterioration of function if used in proper dosage to maintain a serum urate level less than 6.8 mg/dL, although target levels are preferably less than 30 mmol/L (5.0 mg/L)[24,25]. Regardless of the agent selected, the proper dose is the lowest dose of the medication that achieves a serum urate level below that of the target.

Uricosuric Agents

Probenecid, sulfinpyrazone, and benzbromarone are uricosuric agents that reduce serum urate concentration by enhancing the renal excretion of uric acid. In general, the candidate for a uricosuric agent is the gouty patient who is younger than 60 years of age, has a creatinine clearance greater than 80 mL/min, a 24-hour urinary uric acid excretion of less than 800 mg on a general diet, and no history of renal calculi. Alkalinization of the urine has been recommended when using a uricosuric agent to decrease the risk of forming uric acid calculi. Some believe adequate hydration may be sufficient to avoid this complication.

Fenofibrate is a fibric acid derivative whose main therapeutic use is for dyslipidaemia. Case reports suggest that it can have a sustained serum urate lowering effect[26]. It has also been reported to enhance serum urate reduction when used as an adjunct to other antihyperuricaemic agents, such as allopurinol[27,28] and benzbromarone[28]. Losartan is an angiotensin II-receptor antagonist. It has an antihypertensive effect and has been shown to increase renal uric acid excretion[29].

Xanthine Oxidase Inhibitors

Xanthine oxidase, the enzyme that catalyses the oxidation of hypoxanthine to xanthine and xanthine to urate, is inhibited by allopurinol, oxypurinol, and febuxostat. These medications do not have anti-inflammatory properties.

As xanthine oxidase inhibitors can be used with minimal restrictions compared to the uricosuric agents, they are the agents of choice for lowering serum urate levels in most gout patients. Currently, the only clinically available xanthine oxidase inhibitor is allopurinol. Allopurinol can be used at doses from 50 mg to 800 mg per day in a single dose, although the most frequently prescribed dose of allopurinol is 300 mg/day. The goal is to find the lowest dosage that will achieve the target range of 30-36 mmol/L (5.0-6.0 mg/dL). Allopurinol is effective in patients with renal failure but dosage must be evaluated carefully. Only 5% of patients taking allopurinol discontinue the medication although about 30% report side effects. These include gastrointestinal intolerance, skin rashes, and minor complaints.

Febuxostat is a xanthine oxidase inhibitor under development. It differs from allopurinol in chemical structure, as it is not a purine analogue, and it is a selective inhibitor of xanthine oxidase. These two characteristics allow prediction that this agent can be used safely in patients who experienced a reaction to allopurinol[30]. In addition, it appears that febuxostat can be used in patients with mild to moderate renal dysfunction without dosage modification. This agent has been shown in phase II clinical trials of doses of 40, 80, and 120 mg to successfully lower serum urate levels below 6.0 mg/dL in 56, 76, and 94% of subjects, respectively[31]. In a phase III trial, target serum urate levels were reached in 53% and 62% of subjects taking febuxostat 80 and 120 mg, respectively, compared to 21% of patients taking 300 mg of allopurinol. The side-effect profiles were similar and no cases of hypersensitivity were reported with the use of febuxostat[32].

Uricase is the enzyme lacking in humans that breaks down uric acid to allantoin. This results in serum urate levels in humans that are approximately 10 times those of most other mammals, and results in the consequences of gout. Phase II clinical trials are currently examining the use of intravenous or subcutaneous injections of uricase attached to polyethylene glycol (pegylated uricase). This formulation is used to increase the half-life and decrease the antigenicity of the enzyme protein. Uricase preparations are potentially beneficial as an alternative for patients with severe tophaceous gout or those with gout and organ transplants, renal failure, patients intolerant to xanthine oxidase inhibitors, and nonresponders to conventional treatments[34].

ASYMPTOMATIC HYPERURICEMIA

The presence of high serum urate levels in the absence of symptoms is not an indication for specific urate-lowering drug therapy; but is not something that should be ignored. But hyperuricaemia is associated with a greater than 2.5-fold higher risk of death from

cardiovascular disease. Another important assiciation is that between hyperuricaemia and insulin resistance. Until the answers to these associations are known, the use of specific urate-lowering agents is not recommended for the patient with asymptomatic hyperuricaemia.

ANCILLARY FACTORS

Alcohol and Diet

In addition to colchicine prophylaxis, urate-lowering therapy, and anti-inflammatory agents, other factors may be important in determining whether a patient has recurrent acute attacks, chronic gouty arthritis, or renal calculi. The association between alcohol consumption and gout has been known for centuries but has recently been better defined. A recent study found that alcohol intake was strongly associated with an increased risk of gout but that the risk varied, substantially according to the alcohol ingested[33]. Beer was found to have the largest risk, substantially greater than spirits. Moderate wine drinking did not. Increase the risk. The quantity of consumption of alcohol is also strongly associated with gout.

Diet is also a factor to be considered in patients with gout and hyperuricaemia. Recent epidemiological studies have demonstrated that serum urate levels increase with increasing total meat or seafood intake and decrease with increasing levels of dairy intake. However, consumption of oatmeal and purine rich vegetables (e.g. peas, lentils, mushrooms, spinach, and cauliflower) was not associated with an increased risk for gout.

Lifestyle Changes

No controlled trials of the effect of lifestyle change on the incidence of recurrent gout have been carried out. Adherence to traditional low purine diets is poor and they are not usually recommended. Data from the health professionals study, however, suggest that the following relatively simple changes may have an impact on incidence of recurrent gout[30,35,36,37]:

- Lose weight
- Eat one less portion of meat or fish a day
- Drink wine instead of beer
- Drink a glass of skimmed milk a day.

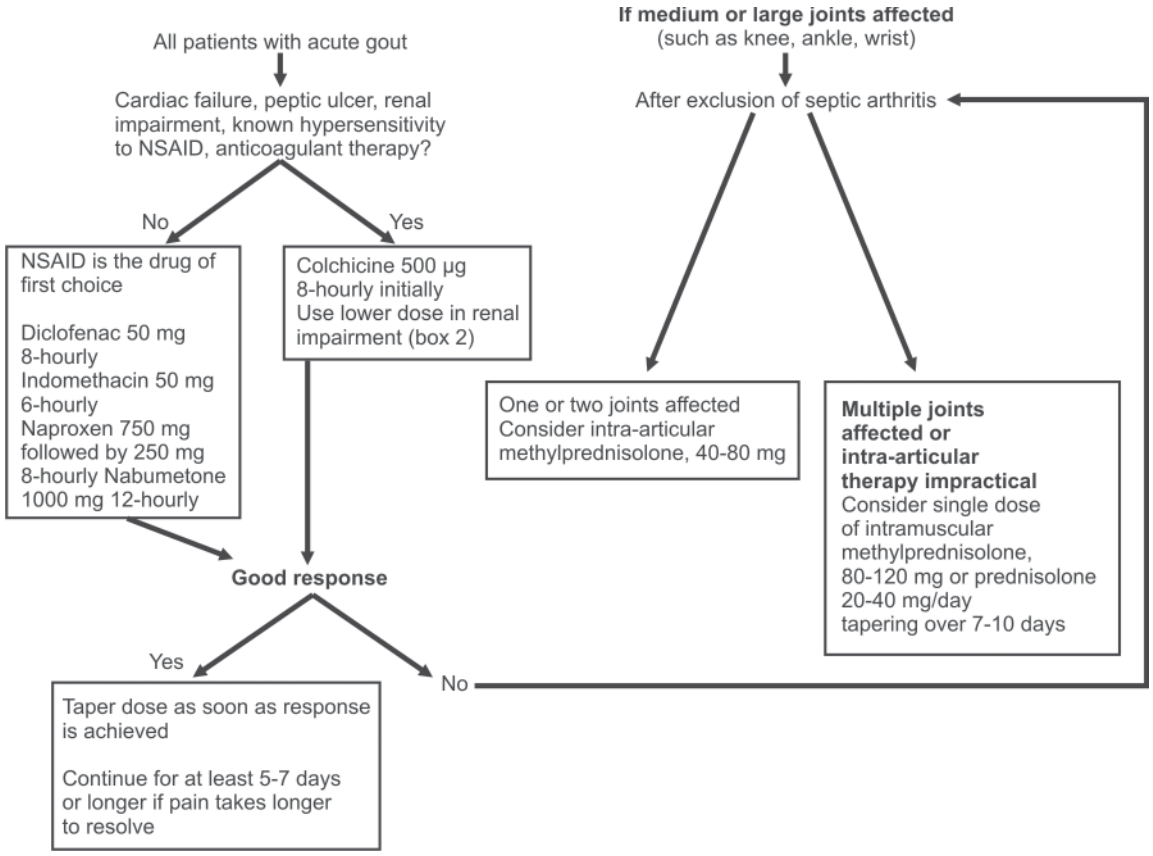

Fig. 1: Diagnosis and management of gout

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