COMMON PROBLEMS

Preventing acute gout when starting allopurinol therapy

Colchicine or NSAIDs?

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Acute gout is a well known complication of the commencement of allopurinol therapy. Prophylaxis is needed for some months, even after serum urate levels have returned to normal. Colchicine is usually preferable to NSAIDs for this purpose, being cheaper, and better tolerated, especially in patients with peptic ulcer, gastrointestinal bleeding or dyspepsia or who are taking anticoagulants. ***(Med J Aust 1993; 159: 182-184)***

Acute gout is a well known complication of the commencement of allopurinol therapy.[1] Also, individuals who are erratic in their consumption of allopurinol are at great risk of suffering attacks of acute gout. Such attacks in the course of allopurinol therapy are particularly undesirable because they increase the chance of patient non-compliance. To prevent this, it is important to educate the patient in the goals of therapy, the mechanism of action of the drug, and the need to take it consistently. In particular, patients must know that there is an increased risk of acute gout during the early months of allopurinol therapy, even when the drug is taken consistently. However, patients can be assured that prophylactic use of either colchicine or a non-steroidal anti-inflammatory drug (NSAID) is effective in preventing acute attacks of gout in this period.[2,3] The purpose of this paper is to argue that colchicine is a good choice for prophylaxis against acute gout caused by the introduction of allopurinol therapy, and that preventing such attacks optimises the chance of successful long-term therapy.

There has been a marked decline in the use of colchicine for acute gout, because of its adverse effects — in particular diarrhoea, which is dose related. NSAIDs are effective for this indication and do not cause severe diarrhoea. The question is: which to use when starting allopurinol therapy?

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Initial and maintenance dosage of allopurinol

The risk of inducing acute gout during the early stage of allopurinol treatment can be reduced by starting with a low dose, particularly in patients who are elderly or have renal impairment.[2] For adults with normal renal function, the starting dose of allopurinol should be 100 mg/day. The dose can then be increased weekly by 100 mg, up to a final dose of either 200 mg or 300 mg/day, or until the desired serum urate level is achieved. The latter goal is optimal, as many patients will be accommodated by doses of less than 300 mg/day.

Duration of prophylactic drug treatment after the commencement of allopurinol therapy?

There is conflicting opinion about selection of drug and the period of time for prophylactic therapy, but no formal clinical trials have addressed the issue. Some authors recommend therapy with colchicine or NSAID for one to two months after commencement of allopurinol therapy.[2] Others recommend that colchicine prophylaxis should be prescribed, along

with the urate-lowering drug, for at least the first six to 12 months of therapy.[4] Lo suggests that colchicine, 0.5 mg twice a day, be continued until the serum urate concentration has been normal for six to 12 months.[5] Champion states that "non-steroidal anti-inflammatory drugs are useful to minimise recurrence during the introduction of therapy with drugs which reduce the total body urate content".[3] Thus, both colchicine and NSAIDs are recommended for this task and there is no clear guidance from the literature about the duration of co-prescription of either of these drugs with allopurinol.

The goal of prophylactic therapy with colchicine or NSAIDs is to prevent acute gout and this therapy needs to be continued until the risk of acute gout is low. This is best gauged by a knowledge of the severity and duration of gout prior to allopurinol therapy, the plasma urate level prior to allopurinol therapy, the rapidity of the fall of the plasma urate level induced by allopurinol, the level of understanding the patient has achieved and his/her ability to collaborate in the exercise of deciding when to withdraw colchicine or NSAIDs. Thus, patients with long-standing tophaceous gout commencing allopurinol therapy will require co-prescription of colchicine or NSAIDs for much longer than a patient who has no tophi and has suffered only a limited number of attacks of acute gout over a short period.

The dose of colchicine for prophylactic therapy

For prophylaxis against acute gout attacks, the dose of colchicine is usually 1 mg/day, taken as 0.5 mg twice daily. However, some patients achieve good control with 0.5 mg/day and others may need 1.5 mg/day.[3] The most common adverse reactions to colchicine are gastrointestinal effects which include diarrhoea, nausea, vomiting, abdominal discomfort, loss of taste and a metallic taste in the mouth, but these effects are dose related and are infrequent at the low doses used for prophylaxis.[6-9] For example, in a descriptive survey of 540 patients with gout, who were taking colchicine as prophylaxis without any urate-lowering drug therapy, only six failed to tolerate colchicine owing to persistent and unexpected diarrhoea.[6] Colchicine should be used with caution in elderly and debilitated patients, and the prophylactic dose should begin at the lower end of the usual range — e.g., 0.5 mg/day. Colchicine is contraindicated in patients with serious gastrointestinal, renal or cardiac disorders,[7] but mild to moderate organ impairment is not a contraindication provided care is taken with dosing. The danger of colchicine in deliberate and accidental overdose should be emphasised, as fatalities due to bone marrow and gastrointestinal damage are well known.

The prophylactic dose of NSAIDs

Although some authorities believe NSAIDs are indicated for prophylaxis against acute gout during the introduction of therapy with allopurinol, probenecid or other uric acid-lowering drugs, there have been no comparative studies with colchicine.[2,3] Also, there have been no studies to indicate the doses required with particular NSAIDs. In general, low doses of most NSAIDs would seem to be appropriate. Aspirin has been superseded by newer NSAIDs because aspirin in low dosage may increase the chance of attacks of acute gout.[7] NSAIDs have a profile of adverse reactions which includes gastrointestinal effects, salt and water retention and oedema, and the potential for nephrotoxicity. Phenylbutazone is no longer used owing to its potential for causing severe blood dyscrasias.[10] As well, NSAIDs interact with many classes of drugs, in particular antihypertensive agents and diuretics. The most common problem with NSAIDs is dyspepsia or gastric discomfort. However, dyspepsia does not correlate with the presence of peptic ulcer or with the risk of serious upper gastrointestinal problems such as haemorrhage or perforation of peptic ulcer. The relative risk for these events is of the order of 2–5 compared with subjects not taking NSAIDs.[11-13] There are special groups at risk, in particular those with previous or recent peptic ulcers and the elderly. The drugs are clearly contraindicated in people who have recurrent or active peptic ulceration. These adverse effects of NSAIDs occur at doses used in prophylaxis against allopurinol-induced acute gout and in our view, are considerably more prevalent and problematic than adverse effects with low doses of colchicine.

What is usual practice for prophylaxis against gout induced by hyperuricaemic therapy?

As has been noted, there has been no research to elucidate whether colchicine or an NSAID is more appropriate as prophylactic therapy against acute gout associated with allopurinol, or other urate-lowering agent. However, there have been a number of surveys of current practice in this respect.

Researchers have surveyed prescribing practice in Ontario, and found that 17% of general practitioners and 70% of rheumatologists "always covered the introduction of uricosuric therapy with either colchicine or NSAID".[14] Rheumatologists favoured colchicine whereas general practitioners favoured NSAIDs.

In a 1987 Australian study, Faragher and Caelli reviewed the computerised records of 11 515 patients in a general practice in Victoria, of whom 111 had gout and hyperuricaemia. Sixty-nine per cent of

these were taking or had taken allopurinol. However, in 67% there was no record of measures to prevent acute attacks of gout during the introduction of allopurinol therapy.[15] Bellamy and others surveyed every rheumatologist and a random sample of general practitioners in active practice in New South Wales and Queensland in 1989 about selection and prescription of drugs in patients with acute gout, chronic tophaceous gout and asymptomatic hyperuricaemia.[16] Responses were received from 72 rheumatologists (85% return) and 254 general practitioners (59% return). During the introduction of urate-lowering therapy, the majority of rheumatologists "always" (85%) or "usually" (13%) attempted to reduce the risk of a "flare" of gouty arthritis by coadministering either colchicine or NSAID. In comparison, a smaller proportion of general practitioners "always" (35%) or "usually" (24%) prescribed either drug. This difference between rheumatologists and general practitioners was statistically significant ($P<0.001$). Of the rheumatologists, 45% favoured colchicine alone, 20% favoured NSAID alone and 25% used both drugs, while of the general practitioners 22% used colchicine alone, 67% used NSAID alone and 8% used both drugs for this indication.

It is apparent that prophylaxis against the attacks of acute gout induced by the commencement of allopurinol or other hypouricaemic therapy is not widely practised in general practice and that there is discordance between general practitioners and rheumatologists.

Comment

The prevention of acute attacks of gout during the introduction of therapy with allopurinol or other urate-lowering drugs is an important goal of therapy, since this will improve patient compliance and hence outcome. The risk of acute attacks can be reduced by proper patient education, the prescribing of a slowly escalating dosage of allopurinol and prophylactic therapy with either colchicine or NSAIDs. Prophylactic therapy will be required for at least some months, and possibly much longer, even after plasma urate levels have returned to the normal range. Severity of tophaceous gout, duration of gout prior to therapy, the plasma urate level and the ability of the patient to collaborate in the therapeutic program are some of the factors which will determine an appropriate duration of co-prescription with colchicine or NSAIDs.

In our opinion prophylaxis with low-dose colchicine is a better option than with NSAIDs. In the doses used for prophylaxis, colchicine is usually better tolerated than NSAIDs, particularly with regard to dyspepsia. Also there is no risk of upper gastrointestinal haemorrhage.[17] If patients have a history of peptic ulceration, gastrointestinal bleeding or dyspepsia, or are currently taking anticoagulant drugs or have an intolerance to NSAIDs, then colchicine is clearly favoured.

Colchicine is substantially cheaper than NSAIDs. An average prophylactic dose of colchicine, 0.5 mg twice daily, would cost $25.20 for six months under the Pharmaceutical Benefits Scheme. This compares favourably with low doses of any NSAIDs. Thus if ibuprofen (400 mg three times a day) was taken for six months this would cost $68.58, prescribed as an "SP" item. These prices exclude the dispensing fee. Overall, the greater cost and the incidence of dyspepsia and other adverse effects and, in particular, the higher risk for upper gastrointestinal bleeding with NSAIDs suggest low dose colchicine as the drug of choice during induction of allopurinol therapy.

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