

# Safer prescribing of high-risk medicines

## Colchicine – extremely toxic in overdose

Colchicine is a plant-based alkaloid, extracted from *Colchicum autumnale* (autumn crocus, meadow saffron) and *Gloriosa superba* (glory lily) used to treat gout and some other inflammatory conditions.<sup>1</sup> It is considered a high-risk medicine because it is associated with significant toxicity when not used correctly.

Colchicine has long been used to treat acute flares of gout, due to its anti-inflammatory properties. Although not an approved indication, colchicine is also used for prophylaxis of gout flares, particularly during the first few months of urate-lowering treatment (usually allopurinol). Colchicine inhibits neutrophil migration, chemotaxis, adhesion and phagocytosis in the area of inflammation. It reduces the inflammatory reaction to urate crystals, but has no effect on uric acid production or excretion.<sup>2</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs), e.g. naproxen, and low-dose corticosteroids are also used for acute management of gout flares and prophylaxis of flares during the initiation of urate-lowering treatment. For many patients, NSAIDs are associated with less adverse effects and risk of toxicity than colchicine,<sup>3</sup> and may be the preferred treatment. However, colchicine is still an important treatment option as it is particularly useful for patients with co-morbidities, such as diabetes, renal impairment and peptic ulcer disease, in whom NSAIDs and prednisone may cause significant adverse effects.<sup>4</sup>

### Colchicine can cause significant toxicity and death

Colchicine has a narrow therapeutic index, which means that the range between therapeutic and toxic doses is small, and in some cases they overlap.<sup>1</sup> Acute overdose exceeding 0.5 mg/kg is usually fatal.<sup>1</sup> Fatalities have been associated with doses as low as 7 mg. In contrast, patients have survived doses up to 60 mg.<sup>5</sup> In a case series of nine patients presenting with colchicine overdose in the Auckland region over a 15 year period, eight died.<sup>5</sup> Four of the patients had taken an accidental overdose of colchicine (ranging from 18 – 24 mg) due to lack of knowledge about the medicine.<sup>6</sup> Colchicine is particularly toxic to children and even one or two tablets can cause serious toxicity.<sup>5</sup>

### Gastrointestinal disturbance is usually the first sign of toxicity

Abdominal pain, diarrhoea, nausea and vomiting are usually the first symptoms of colchicine toxicity. A burning sensation in the throat, abdomen or on the skin has also been reported. These symptoms, particularly diarrhoea, can also occur with doses within the therapeutic range. Later features of toxicity (24 hours to seven days after ingestion) include tachypnoea, electrolyte disorders (e.g. hypocalcaemia, hypophosphataemia), hypovolaemia, haematological effects (e.g. leukopaenia, thrombocytopaenia), cardiac dysrhythmias, renal failure and liver damage.<sup>1,5,6</sup> The cause of death is usually progressive multiple organ failure and sepsis.<sup>1</sup>

## Adverse effects can occur even at “safe” doses

Prior to 2005, colchicine dose instructions included the advice to continue dosing until the pain settled or gastrointestinal adverse effects occurred. The standard dose instructions have now been changed to improve safety. Patients are advised to stop taking colchicine immediately if they experience abdominal pain, diarrhoea, nausea or vomiting, or a burning feeling in their throat, stomach or on their skin.<sup>5</sup>

Table 1 shows the current New Zealand dosing recommendations for colchicine used in patients with gout.<sup>7,8</sup> Internationally, specifically in Australia and the United States, even lower doses are recommended. A study comparing low-dose colchicine (1.2 mg followed by 0.6 mg in 1 hour; 1.8 mg total) with high-dose colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours; 4.8 mg total) found that efficacy of the low-dose regimen was comparable to the high-dose regimen, however, there was a significant reduction in the rate of adverse effects with the low dose regimen.<sup>9</sup> The lower dosing regimen is now recommended in colchicine guidelines in Australia and the United States.

## Interactions increase the risk of colchicine toxicity

The risk of colchicine toxicity is increased when inhibitors of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) are taken concurrently, e.g. some azole antifungals (e.g. fluconazole), calcium channel blockers (e.g. diltiazem, verapamil) and macrolide antibiotics (e.g. erythromycin) (see New Zealand Formulary for full list).<sup>8</sup>

If these medicines are required at the same time as colchicine, the dose of colchicine should be reduced and the patient

monitored for symptoms and signs of colchicine toxicity. These combinations are contraindicated in patients with renal or hepatic impairment, as this increases the risk of toxicity.<sup>10</sup>

## Managing colchicine toxicity

All patients with known or suspected overdose of colchicine, or displaying symptoms of colchicine toxicity, should be immediately referred to hospital. There is no specific antidote for colchicine when taken in overdose and treatment options are limited. Haemodialysis and haemoperfusion are not effective because colchicine has a large volume of distribution, binds significantly to plasma proteins and has rapid distribution.<sup>6</sup> If a patient presents soon after ingestion, repeated doses of activated charcoal can be given to remove colchicine from the gastrointestinal tract. Although colchicine is rapidly absorbed from the gastrointestinal tract, removal of even a small amount can improve the patient's prognosis.<sup>6</sup> Patients who do not present soon after ingestion, and those with pre-existing renal or hepatic impairment, have a less favourable prognosis.<sup>6</sup> Patients with colchicine toxicity are managed with supportive care.

## Avoiding adverse effects


### Manage gout more effectively

Patients who frequently use colchicine for acute gout flares should be encouraged to take long-term urate-lowering treatment, e.g. allopurinol. Preventative treatment will reduce the frequency of flares, and therefore reduce the need for acute treatment with colchicine, and the risk of toxicity.<sup>11</sup> Urate-lowering treatment is indicated for patients with gout who: experience recurrent flares, e.g. two or more in one year, have tophi, concomitant renal impairment or changes characteristic

**Table 1:** Recommended colchicine dosing regimen<sup>7,8</sup>

Indication	Dose
Treatment of acute gout	1 mg, followed by 500 micrograms every six hours until relief of pain, up to 2.5 mg (five tablets of 500 micrograms) on the first day; maximum 1.5 mg (three tablets) on subsequent days; total maximum 6 mg (12 tablets) over four days; course not to be repeated within three days  NB: In elderly patients, patients with renal or hepatic impairment, or patients weighing < 50 kg, if it is necessary to use colchicine the initial dose should not exceed 1 mg (two tablets of 500 micrograms) in the first 24 hours; total maximum 3 mg (six tablets) over four days; course not to be repeated within three days
Prophylaxis during initiation of urate-lowering treatment	500 micrograms, once or twice daily, during the first three to six months treatment with a urate-lowering medicine, such as allopurinol

of gout on x-ray. Ideally, urate-lowering treatment should be initiated early before there has been any erosive damage to joints and before tophi have appeared.


 For further information, see: "An update on the management of gout", BPJ 51 (Mar, 2013).

### Provide patients with clear instructions

Patients are at risk of overdose if they have a poor understanding of how to take colchicine and its potential adverse effects. Appropriate patient education includes:

- Providing clear advice about how to take colchicine, especially the maximum dose
- Advising patients to stop taking colchicine and see their doctor if they develop nausea, vomiting or diarrhoea; unusual bleeding or bruising; muscle pain or weakness; or numbness or tingling in their fingers or toes
- Ensuring patients are aware that colchicine is not an analgesic for general use and should not be used to manage pain not due to gout
- Advise patients to tell a doctor or pharmacist about all the medicines they take and to check before taking new medicines

Advice should be tailored to the patient's level of health literacy. This is particularly important for patients for whom English is not their first language. Of the four accidental overdose cases reported in Auckland, three of those patients were of Pacific Island descent. It is possible that language barriers, cultural differences and health literacy may have been contributing factors to these accidental overdoses.<sup>6</sup>

 A patient information handout on colchicine is available from: [www.saferx.co.nz/colchicine-patient-guide.pdf](http://www.saferx.co.nz/colchicine-patient-guide.pdf)

### What can General Practitioners do?

- Provide patients with clear instructions on how to take colchicine, both verbal and written, and check for understanding. Advise patients about the dangers of overdose, overuse and the importance of safe storage.
- Limit prescriptions to 12 tablets for acute attacks of gout (6 tablets for older people)
- Prescribe monthly for prophylactic use and ensure colchicine is stopped after three to six months
- Be aware of significant medicine interactions with colchicine

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### References:

1. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol* 2010;48:407–14.
2. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2011.
3. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. *Curr Rheumatol Rep* 2008;10:218–27.
4. Dalbeth N, Gow P, New Zealand Rheumatology Association. Colchicine prescribing in patients with gout. *N Z Med J* 2011;124:107–8.
5. Waitemata District Health Board. Colchicine - safe prescribing - toe the line!! Saferx. 2011. Available from: [www.saferx.co.nz/full/colchicine.pdf](http://www.saferx.co.nz/full/colchicine.pdf) (Accessed Aug, 2014).
6. Jayaprakash V, Ansell G, Galler D. Colchicine overdose: the devil is in the detail. *N Z Med J* 2007;120:U2402.
7. New Zealand Rheumatology Association (NZRA). NZRA consensus statement on the use of colchicine in the treatment of gout. NZRA, 2005. Available from: [www.rheumatology.org.nz/position\\_statement.cfm](http://www.rheumatology.org.nz/position_statement.cfm) (Accessed Aug, 2014).
8. New Zealand Formulary (NZF). NZF v25. 2014. Available from: [www.nzf.org.nz](http://www.nzf.org.nz) (Accessed Aug, 2014).
9. Terkeltaub R, Furst D, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010;62:1060–8.
10. Medsafe. Colchicine: Beware of toxicity and interactions. *Prescr Update* 2011;32:2.
11. Dalbeth N, Gow P. Prevention of colchicine toxicity in patients with gout. *N Z Med J* 2007;120:U2503.