Colchicine, a case of unexpected fatal toxicity

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Colchicine is an effective treatment for acute gout but is potentially toxic and can be fatal, as described in this case. The recommendations for colchicine dosing for acute gout have changed in the past year.

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A disadvantage of working in a hospital emergency department as a GP is that you see the complications of illnesses and therapy. In other words, there is a select casemix of patients, often referred by fellow GPs, biased towards pathology and needing resuscitation, diagnosis and, frequently, hospital care.

As one of the more experienced doctors, you also attend patients with a triage category of 2. These are patients who are attended to immediately in a resuscitation cubicle because they have a potential life-threatening condition, such as cardiac chest pain, or abnormal vital signs, including decreased level of consciousness.

THE CASE

You and the registrar notice at the same time an obviously ill patient on a trolley being pushed into resuscitation by ambulance officers. You both reflexly rise to see the patient.

Ambulance handover informs the quiet, listening nurses and doctors of a 65-year-old man to whom they had been called because of his decreased level of consciousness (dizzy, confused) and inability to stand up. Their examination revealed an impalpable pulse, systolic blood pressure of 80 mmHg, respiratory rate of 24 breaths/min, Glasgow Coma Score of 14/15, a sinus tachycardia of 124 beats/min on cardiac rhythm trace and a pulse oximetry of 95 to 100% with supplemental oxygen. A finger prick blood sugar level estimation was 6.8 mmol/L. His temperature orally was 38.9°C.

The initial clinical impression was of septic shock. In line with recent

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TABLE. THE PATIENT'S BLOOD TEST RESULTS

Clinical pathology	Result	Typical normal range
Blood chemistry		
Sodium	141	137 to 146 mmol/L
Potassium	4.3	3.5 to 5.0 mmol/L
Chloride	102	95 to 110 mmol/L
Bicarbonate	19*	24 to 31 mmol/L
Urea	14.1*	3.0 to 8.5 mmol/L
Creatinine	206*	40 to 90 µmol/L
Estimated glomerular filtration rate (eGFR)	21*	Over 60 mL/min/1.73m^2
Inorganic phosphate	1.43*	0.70 to 1.40 mmol/L
Magnesium	1.70*	0.70 to 1.05 mmol/L
Calcium	1.90*	2.10 to 2.60 mmol/L
Albumin	21*	36 to 52 g/L
Total protein	44*	60 to 82 g/L
Total bilirubin	5	0 to 18 µmol/L
Alanine aminotransferase (ALT)	58*	0 to 30 U/L
Aspartate aminotransferase (AST)	104*	0 to 30 U/L
Alkaline phosphatase (ALP)	127*	30 to 100 U/L
Gamma glutamyl transferase (GGT)	29	0 to 35 U/L
Creatine kinase (CK)	545*	0 to 110 U/L
Troponin T, high sensitivity (hs)	163*	0 to 14 ng/L
Troponin T commercial	Delta troponin = 163% over nine hours	Changes greater than +/- 30% in the right clinical setting are supportive of a diagnosis of myocardial infarction
Free thyroxine (fT4)	15.5	11.0 to 22.0 pmol/L
Thyroid stimulating hormone (TSH)	0.11*	0.40 to 4.20 mIU/L
Full blood count		
Red blood cell count (RBC)	2.8*	3.8 to 5.8 x 10^{12}/L
Haemoglobin	92*	115 to 165 g/L
Haematocrit (Hct)	0.27*	0.37 to 0.50
Mean corpuscular volume (MCV)	94	76 to 96 fL
Mean corpuscular haemoglobin (MCH)	32.7*	27.0 to 32.0 pg
Mean corpuscular haemoglobin concentration (MCHC)	348	320 to 360 g/L
Red cell distribution width (RDW)	13.9	11.5 to 14.5%
Platelets	105*	150 to 400 x 10^9/L
White blood cell count (WBC)	0.9*	4.0 to 11.0 x 10^9/L
White cell differential count		
Neutrophils	0.8*	2.0 to 7.5 x 10^9/L
Lymphocytes	0.1*	1.5 to 4.0 x 10^9/L
Monocytes	<0.1*	0.2 to 1.0 x 10^9/L
Eosinophils	0.0	0.0 to 0.4 x 10^9/L
Basophils	0.0	0.0 to 0.1 x 10^9/L
Nucleated RBC	2% WBC	0
Toxic changes	+	
Morphology		
Anisocytosis	+	
Polychromasia	+	
Burr cells	+	
Elliptocytes	+	
Acute phase reactants		
C-reactive protein (CRP)	38.4*	<10.0 mg/L

* Abnormal result.

evidence-based 'early goal-directed therapy', an aggressive and protocolised attention-to-detail approach to treating septic shock is instigated.[1]

The history

While further observations are being made, intravenous lines inserted, fluids given and blood tests, chest x-rays and ECG performed, a clear history is obtained from the patient.

He has been unwell for some weeks. It began when he started renovating his home. There had been a lot of dust, and he had suffered asthma attacks again after many years of no attacks. He also coughed a lot, expectorating yellow sputum. His local GP had put him on two courses of amoxycillin plus clavulanate and also nebulised salbutamol and ipratropium. However, there was no improvement.

He stated he had been having fevers at home and recently had been eating less. He also described occasional abdominal discomfort. A month ago he had commenced taking colchicine for gout in his feet. On further questioning, he said he took colchicine 1 mg (two 0.5 mg tablets) four times daily for a few days then 0.5 mg four times daily most other days.

He had loose bowels and watery stools. There was no blood in the stools, and no nausea or vomiting. Today he had been unable to get out of bed, so an ambulance was called.

His past medical history included hiatus hernia repair, obesity, mild renal impairment (resolved), asthma and hypothyroidism. He had no allergies. His current medications are thyroxine 100 µg daily, colchicine and nebulised salbutamol and ipratropium.

Initial investigations and admission

Physical examination revealed no obvious pathology. Initial ECG showed no acute ischaemic changes. Mobile chest x-ray showed possible right basal atelectases but poor inspiration effort. Blood was taken for blood tests and cultures.

The patient was admitted to hospital

with the clinical impression of sepsis (?respiratory, ?gastrointestinal) and colchicine toxicity. The results of his blood tests are given in the Table.

The medical registrar reviewed the patient, and noted on the repeated ECG new ischaemic T-wave inversion on the lateral chest leads.

Diagnosis and outcome

The diagnosis was colchicine causing multiple organ dysfunction/failure. This was made on the basis of the following features:

- hypovolaemic shock
- acute renal failure (anuric)
- myelosuppression, immunosuppression
  – basal pneumonia
- hepatic dysfunction
- diarrhoea – electrolyte disturbance.

Aggressive intensive care (maximal doses of several inotropes, placement of an intra-aortic balloon counterpulsation pump and many consultations with specialists) was commenced. However, despite this and in the presence of his relatives, the patient passed away.

The issue of how the patient came to take such a high-dose regimen of colchicine could not be clarified.

COLCHICINE TOXICITY

Two other cases of colchicine toxicity were seen recently in this emergency department.[2] Fortunately, these patients recovered.

A departmental review of the cases and a tutorial highlighted some complex and potentially confusing historical and formal information on colchicine therapy for acute gout.

COLCHICINE THERAPY

Acute gout

Recent major changes in colchicine dosing recommendations for the treatment of acute gout are the use of lower colchicine doses and an extended dosing interval.[3,4]

Trials have shown no change in efficacy with this revised dosing. A recent trial in the USA demonstrated that low-dose colchicine (1.8 mg over one hour) is as effective as a higher dose (4.8 mg over six hours) when prescribed within 12 hours of onset of an acute gout flare up, and has significantly less adverse effects (diarrhoea and vomiting).[5]

Colchicine is available in Australia as 0.5 mg tablets, rather than the 0.6 mg tablets used in the above trial in the USA. The recommended therapy in Australia for acute gout is:[6]

- take two colchicine tablets initially (1 mg), followed by one colchicine tablet (0.5 mg) one hour later
- do not take more than three colchicine tablets (1.5 mg) during a course of treatment for an acute gout flare
- do not repeat the course of treatment for at least three days.

Other recommendations regarding colchicine dosing are:[3,4]

- use of a smaller colchicine pack size of 30 tablets, rather than the existing 100-tablet pack
- revision of the dosing recommendation and use in patients with renal and hepatic impairment
- provision of clear instructions for patients.

Chronic gout

With chronic gout, the inflammation should usually be resolved if possible before slowly introducing allopurinol with an accompanying NSAID and/or colchicine.[4] Recommended therapy is to:

- begin urate-lowering therapy with allopurinol 50 mg orally, daily for the first week, increasing by 50 mg weekly to a maximum of 300 mg daily (dose adjusted according to urate levels)
- prevent an acute exacerbation of gout, using the following medications with the urate-lowering therapy:
  – colchicine 0.5 mg orally, two to three times daily for three months (higher doses are not justified), and/or
  – indomethacin 25 mg orally, twice daily for six months (or similar NSAID in the appropriate dose).

Corticosteroids are usually reserved for patients in whom NSAIDs and colchicine are contraindicated or ineffective. If necessary, use:

- prednis(ol)one 20 to 25 mg orally, daily, reducing on a weekly basis after symptoms have resolved.

Colchicine and drug interactions

Colchicine interacts with inhibitors of cytochrome P450 3A4 or P-glycoprotein, and this increases its toxicity. Concomitant administration with such drugs, and particularly clarithromycin, must be avoided.

CONCLUSION

Acute gout is a particularly painful condition of joints in which colchicine is effective but potentially toxic, and even fatal. Interactions between colchicine and other drugs increase its toxicity, and should be avoided. Use of lower doses of colchicine (as recommended by the National Prescribing Service and in the *Australian Medicines Handbook*) and good patient education should minimise the risks.[3,6] MT

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