

## Brief Report

### Colchicine toxicity in patients with chronic renal failure

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#### Introduction

The therapeutic virtues of colchicine have been known since the 6th century AD, and it has been used since the 19th century for the treatment of gouty arthritis (for historical review see [1]). More recently colchicine became the only efficient treatment for familial Mediterranean fever (FMF) [2] and the rare Muckle–Wells syndrome [3]. This drug, a highly lipophilic alkaloid extracted from *Colchicum autumnale* (meadow saffron) (Fig. 1), diffuses into all cells, irreversibly impairing microtubule organization and function and arresting the cell cycle at metaphasis. It blocks intracellular protein trafficking, membrane turnover and exocytosis, thereby hampering leukocyte functions, intestinal water and solute reabsorption, bone marrow cytogenesis, muscle contractility and nerve axonal viability [1]. Colchicine is a powerful poison with a narrow margin between efficacy and toxicity. Doses of

1–3 mg/day are usually followed by diarrhoea within a few days [4], and more than 3 mg/day for several days induces profuse diarrhoea, acidosis, dehydration, bone marrow aplasia and cardiac failure. Rapid death may ensue, due to hypovolaemic, cardiogenic and septic shock [5]. Chronic toxicity is rare in patients with no visceral compromise because diarrhoea usually leads to stopping treatment. Conversely, toxic effects appear early in circumstances that impair colchicine excretion [6], such as hepatocellular insufficiency, chronic renal failure and cyclosporin A treatment [7,8]. Chronic toxicity is marked by a particular form of neuromyopathy [9] and often myocardial failure, which entails a dismal prognosis. Despite its hazards in chronic renal patients, colchicine is still used in gouty arthritis and in pseudogout following metastatic calcification.

We present four cases of colchicine toxicity in patients with severe chronic renal insufficiency. In two, intoxication was characterized by severe neuromyopathy but they survived. The two others died rapidly from cardiac failure and multivisceral compromise. In all, colchicine treatment had been prescribed outside the nephrology unit, and for clinical complaints which could have been easily managed by other means.

#### Case reports

We shall briefly describe the clinical histories. Details are given in Table 1. Typical features of colchicine muscle toxicity (case 3) are described in Fig. 2 and its legend.

##### Case 1

The first patient, a 63-year-old woman with hypertensive nephrosclerosis and hypertrophic cardiomyopathy, was treated for 8 days with 1 mg/day colchicine for acute arthritis of the instep. Day 5 marked the onset of weakness, diarrhoea and dehydration. She was hospitalized on day 8. Intravenous rehydration was shortly followed by pulmonary oedema due to refractory cardiac incompetence. Within 48 h she died of cardiogenic and septic shock.

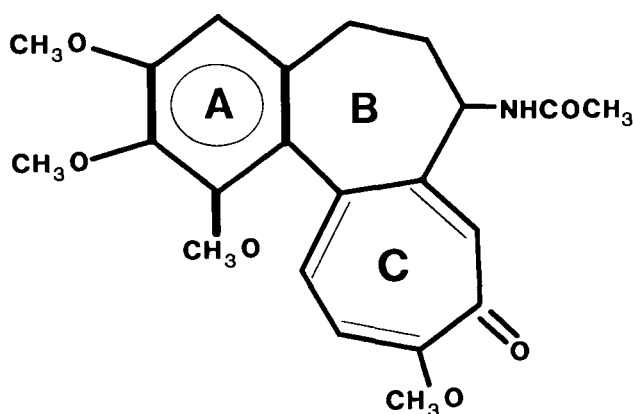


Fig. 1. The colchicine molecule.

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Table 1. Colchicine toxicity in four patients with chronic renal failure

Patient	Sex	Age (years)	Renal disease	Serum creatinine	Colchicine dosage	Time to symptoms	Clinical picture	Haemodynamic status	Blood count	Muscle enzymes	Outcome
1	F	63	Nephrosclerosis	542 µmol/l	1 mg/day (8 days)	5 days	Diarrhoea, muscle weakness	Dehydration masking cardiac failure	WBC 760/mm <sup>3</sup> Hb 8.1 g/dl Pl 150 000/mm <sup>3</sup>	Normal	Death 5 days after first sign of septic and cardiogenic shock Recovery within 1 month
2	M	48	Renal transplant with relapse of primary GN	249 µmol/l	1 mg/day (7 days)	7 days	Diarrhoea, neuromyopathy	Near normal	WBC 1500/mm <sup>3</sup> Hb 12 g/dl Pl 95 000/mm <sup>3</sup>	CPK 31 110 IU LDH 8 330 IU ALAT 290 IU ASAT 495 IU	Recovery within 3 months
3	M	63	Wegener's disease	342 µmol/l	1 mg/day (14 days)	7 days	Biopsy-proven neuromyopathy	Near normal	WBC 4700/mm <sup>3</sup> Hb 9.9/dl Pl 180 000/mm <sup>3</sup>	Normal	Recovery within 3 months
4	M	60	Diabetic nephropathy	520 µmol/l	1 mg/day (13 days)	8 days	Diarrhoea	Dehydration masking cardiac failure	WBC 1630/mm <sup>3</sup> Hb 10.5 g/dl Pl 84 000/mm <sup>3</sup>	Normal	Death 7 days after first sign of cardiogenic shock

GN, glomerulonephritis; WBC, white blood cells; Hb, haemoglobin; Pl, platelets; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase.

### Case 2

A 48-year-old male renal transplant recipient with chronic renal insufficiency was receiving cyclosporin A and prednisone. Seven days before admission he was started on colchicine, 1 mg/day, for leg pain. Diarrhoea set in. He was rapidly paralysed by neuropathy and rhabdomyolysis. After stopping colchicine, nerve and muscle disturbances slowly regressed, and he walked with a cane 1 month later.

### Case 3

The third patient was a 63-year-old man treated for Wegener granulomatosis with renal involvement and severe renal insufficiency. His regimen consisted of high daily doses of prednisone and monthly pulses of cyclophosphamide. He was prescribed 1 mg/day colchicine for ankle arthritis. On day 7 he was unable to walk due to acute myopathy and neuropathy. Colchicine was stopped after 14 days. The appearance of muscle lesions on a biopsy carried out 1 week later is shown in Fig. 2. Recovery of muscle and nerve function took more than 3 months.

### Case 4

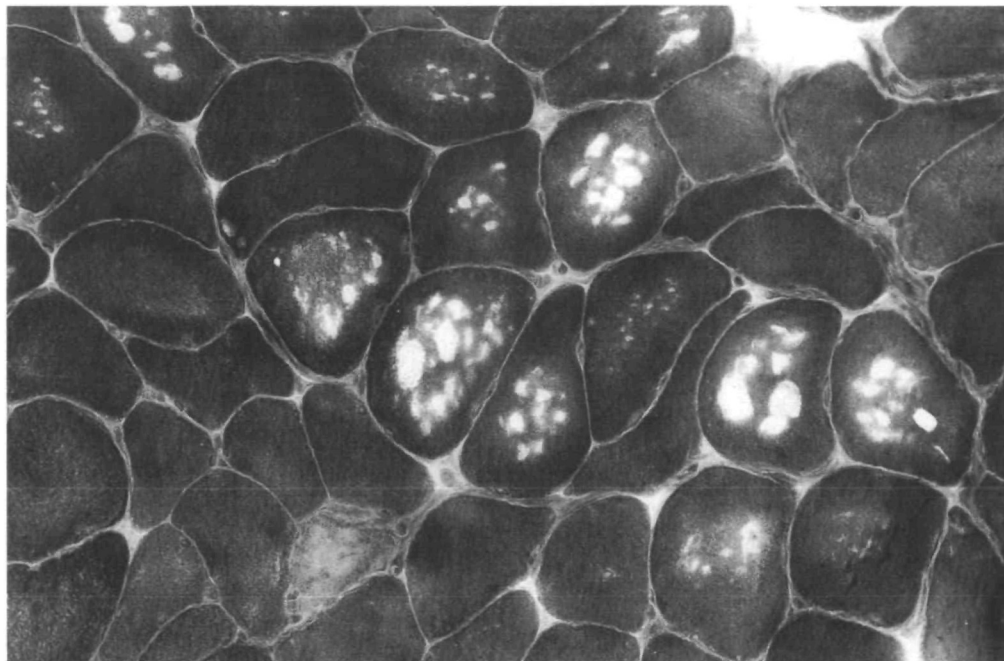
The fourth patient, a 60-year-old male with multivisceral diabetic complications including chronic renal failure, was treated with 1 mg/day colchicine for knee arthritis. On day 8 he was admitted to another unit for diarrhoea, dehydration, acidosis and marrow aplasia. The cause was overlooked and colchicine was continued until day 13. Despite rehydration and supportive measures including mechanical ventilation, he died of multifactorial shock within 2 days.

## Discussion

These cases illustrate the hazards of colchicine treatment in patients with chronic renal insufficiency, even when dosage and duration are not excessive. Toxicity was revealed by diarrhoea, but its most severe expression involved nerves, muscle and heart. This is probably why the patients who died were the two with previous cardiac insufficiency.

That colchicine can be a life-threatening drug was reported by MacLeod and Phillips in 1947 [10], and since then more than 100 cases with acute and/or chronic toxicity have been reported. Massive single-dose suicidal intake of more than 10 mg is fatal within 2–4 days, by cholera-like diarrhoea, hypovolaemia, bone marrow aplasia, sepsis and cardiogenic shock.

The features of colchicine toxicity in chronic renal failure seem to have escaped attention until 1987, when Kuncl *et al.* reported 12 cases of myopathy and neuropathy in patients with mild to moderate renal failure treated with customary doses of colchicine for up to 3 years [9]. The main clinical findings were subacute proximal limb weakness with mild polyneuropathy and muscle pain. Rhabdomyolysis was identified by a rise



**Fig. 2.** Case 3. Biopsy of the peroneus brevis muscle. Light microscopy. Masson's trichrome.  $\times 500$ . Many muscle fibres contain a central cluster of clear vacuoles some of which contain granular material ( $\rightarrow$ ). This is the specific appearance of colchicine toxicity, as described by Kuncel *et al.* [9]. One necrotic muscle fibre ( $\otimes$ ) is also present. There is no sign of inflammation.

in serum creatine phosphokinase (CPK) levels. Light and electron microscopy showed muscle fibres containing large central vacuoles surrounded by smaller ones. Only few fibres were necrotic. Nerve lesions consisted of a mild loss of large myelinated axons and some clusters of regenerating axons. Muscle lesions were sufficiently unusual to be considered distinctive of colchicine toxicity. The evolution was favourable within 3 months.

Since then, few anecdotal cases of chronic colchicine toxicity have been published, mostly as short reports or letters [11–14]. Most followed a benign course. A few observations hinted that colchicine toxicity is greater in renal transplant recipients treated with cyclosporin A [15] and/or azathioprine [7]. Erythromycin might also increase colchicine toxicity [16]. It was hypothesized that these medications interfere with the hepatic metabolism of colchicine. However, these reports do not suggest that customary doses and short treatment can lead to colchicine intoxication and death in a renal patient. Our observations show that colchicine should in fact be considered dangerous and potentially fatal in patients with chronic renal failure, even at the usual dosage of 1 mg/day, and for a treatment duration not exceeding 1–2 weeks.

The present series is small. However, it suggested to us that colchicine toxicity has a twofold expression. In the first and the fourth patients, intoxication was initially marked by diarrhoea and dehydration. Adequate water and electrolyte replenishment were followed by acute pulmonary oedema and cardiogenic shock revealing myocardial incompetence. Both patients had previous left ventricular hypertrophy but

no left ventricular failure. The weight of the evidence favours severe myocardial function impairment by colchicine, as observed in rat experiments [17]. Such a sequence of events, i.e. dehydration induced by diarrhoea and followed by irreversible pulmonary oedema, is close to what is observed in suicidal poisoning in young, healthy persons [1].

In the second and third cases, the clinical picture and subsequent development were closer to the foregoing description of chronic toxicity, with dominant peripheral nerve and muscle involvement. Incidentally, it is worth noting that in the patient whose muscle biopsy showed the typical appearance of colchicine toxicity shown in Fig. 2, CPK serum levels were normal. These patients were not dehydrated and their myocardial function was apparently normal. They followed a slowly favourable course to recovery.

The hazards of colchicine treatment are all the more avoidable since, in a chronic renal patient, the indications for the drug are purely symptomatic and never apply to life-threatening conditions. Colchicine should not be prescribed in cases of borderline cardiac function or in a transplant recipient treated with cyclosporin A. In the rare chronic renal patient where colchicine treatment is considered indispensable, dosage should be limited to 1 mg/day, duration of treatment should not exceed 4 days, and the patient should be advised to avoid self-medication without close medical supervision. These recommendations should apply as well to long-term treatment of FMF complicated with renal and cardiac amyloidosis. Surprisingly, despite the widespread use of colchicine in such patients, reports of toxicity are few. However,

the case of fatal colchicine toxicity in a patient with FMF who had received 3 mg during 4 days [18] shows that this indication does not escape the foregoing caveat.

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