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LETTER TO THE EDITOR

Multiple organ failure caused by near-usual doses of colchicine

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Multiple organ failure (MOF) due to colchicine treatment is rare, even in the presence of concurrent renal and hepatic failure [1]. Here, we present a case of MOF caused by near-usual doses of colchicine in a patient with risk factors for colchicine intoxication.

A 76-year-old male patient with 2 months history of decline in well-being, malaise, and fatigue had been referred to our institution due to elevated alanine aminotransferase (ALT) and aspartate aminotransferase and (AST) levels. His medical history included diabetes mellitus type 2 for 6 months, arterial hypertension for 10 years and gout for 40 years. He had been taking perindopril-hydrochlorothiazide 10/12.5 mg tablet once a day, verapamil sustained-release tablet once a day, and rapeglinid 0.5 mg tablet three times a day. 5 days before the admission, he has been advised to take colchicine tablet 1 mg three times a day by a general practitioner for gout prophylaxis. Physical examination revealed bilateral 3+ pretibial oedema and grade 3 holosystolic murmur on the apex. Lungs were clear to auscultation. Left lobe of liver was palpable.

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On the fifth day of admission, the patient experienced watery diarrhoea four to five times a day lasting for a week. The culture and the microscopic examinations of stool revealed no pathological findings. Oral anti-diabetic drugs were not appropriate for the patient because of hypoglycaemia risk due to chronic liver disease. Angiotensin converting enzyme inhibitors could worsen renal function in a dehydrated diabetic patient. Diarrhoea caused by colchicine overdose resolves by dose reduction, that is why colchicine dose was decreased to 1 mg/day and all the other medications were ceased.

On the day 10, the patient became anuric and febrile. Urea and creatinine levels increased. Bicytopenia was observed on his blood count. Arterial blood gas analysis was consistent with metabolic acidosis. He still had diarrhoea. Thus, colchicine was thought to be responsible for this clinical picture and was stopped. Breathing was shallow and laboured. Chest radiography showed bilateral patchy shadowing throughout both the lung fields. Systemic inflammatory response syndrome (SIRS), sepsis and MOF were considered. Piperacilline-tazobactam 2.25 mg four times a day was started. He was intubated due to respiratory failure but unfortunately died on the same day. Use of the Naranjo adverse drug reaction probability scale in our patient indicated a probable relationship (score of 5) between MOF and colchicine therapy.

Eighty percent of the patients taking therapeutic doses of colchicine and almost all patients who are exposed to overdose experience GI symptoms. These GI symptoms serve as primary warning signs of colchicine toxicity during treatment for any indicated disease and are usually mild, transient, and reversible by discontinuation or lowering of colchicine dose [1]. Common clinical features of colchicine toxicity along with stages are shown in Table 1.

Table 1 Clinical stages and common clinical manifestations of colchicine toxicity

Stages	Time	Clinical features
Latent period	4–12 h	Asymptomatic
The first stage	12–72 h	Peripheral leucocytosis
		GI symptoms: nausea, vomiting, diarrhoea, abdominal pain, anorexia
		Electrolyte imbalance: hyponatremia, hypocalcaemia, etc
		Hypovolemia and shock
		Bone marrow hypoplasia: profound leukopenia and thrombocytopenia
		Fever
The second stage	2–7 days	Cardiovascular arrhythmias, cardiovascular collapse, pulmonary oedema
		Respiratory distress, hypoxia, ARDS
		Oliguric renal failure
		Metabolic acidosis
		Electrolyte derangements
		Rhabdomyolysis
		Mental state changes, seizures, peripheral neuropathy, ascending paralysis
		Hepatic injury
		Coagulopathies
The third stage	7–10 days	Rebound leucocytosis
		Transient alopecia

Colchicine exhibits a narrow therapeutic range. A clear-cut separation between toxic, non-toxic or lethal doses do not seem to exist. Colchicine ingestion up to 0.5 mg/kg is non-fatal, but doses over 0.8 mg/kg are invariably fatal [2]. There are adult patients who survived even after ingesting 350 mg of colchicine [3]. However, 35 mg (0.5 mg/kg) cumulative dose of colchicine resulted in death in our patient.

Up to 30% of the absorbed colchicine may be excreted in the urine. While half-life of colchicine in patients with severe renal failure is prolonged two to threefold, it reaches to as high as tenfold in patients with renal failure and cirrhosis. Therefore, patients with renal or hepatic disease must be closely monitored because reduced clearance of standard dosages of colchicine may result in toxic levels of colchicine, and in some cases, death as in our patient [4].

Death, which commonly occurs within 7–36 h, is caused by respiratory failure, cardiovascular collapse, fatal arrhythmias, or sudden asystole. If death occurs between the 3rd and 7th days of poisoning, the cause is septic shock, which is precipitated by bone marrow suppression. In mild cases, recovery can be seen from 7 to 10 days after ingestion [2].

Common risk factors in case reports of MOF associated with colchicine toxicity include old age, liver dysfunction, concomitant use of CYP3A4 inhibitors (cimetidine, erythromycin, clarithromycin, diltiazem, verapamil and HMG-CoA reductase inhibitors), and, most consistently, kidney dysfunction. In addition to be a CYP3A4 inhibitor, verapamil inhibits P-glycoprotein, which is responsible for colchicine transport from hepatocyte into bile. It can reduce excretion of colchicine [5].

Colchicine is related with high mortality rates secondary to rapidly progressive MOF. Appropriate dose reductions should be made in patients with chronic kidney disease. It is prudent to avoid colchicine in patients with concurrent chronic kidney disease and liver disease. Physicians should consider the possible adverse effects and risk factors associated with colchicine toxicity. Patients should be warned about side effects and that it must be ceased under certain circumstances because near-usual doses may also cause toxicity.

Conflict of interest There is no conflict of interest.

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