Clinical Case Report

Medicine®

OPEN

Clinical outcomes after colchicine overdose

A case report

Mingjie Fu, MD[a,b,*], Jie Zhao, MD[a,b], Zhitao Li, PhD[a,b], He Zhao, MD[a,b], Anwei Lu, PhD[a,b]

Abstract

Rationale: Colchicine can inhibit cell division and intracellular transport in affected organs by fixing intracellular tubulin and preventing its polymerization into microtubules. A lethal dose of colchicine is considered to be 0.8 mg/kg. The wide distribution of colchicine through 70% of the body following an overdose makes it difficult to eliminate.

Patient concerns: A 56-year-old man with a clear history of colchicine overdose was admitted to our hospital nearly 40 hours after taking 12 mg (0.17 mg/kg) of colchicine. He had a history of gout and chronic kidney disease. As the disease progressed, he showed most of the clinical manifestations and pathological features of colchicine overdose.

Diagnoses and interventions: Colchicine overdose was clear, with symptoms of multiple organ failure including primary gastrointestinal failure, bone marrow hematopoietic inhibition, rhabdomyolysis, cardiac damage, hepatocyte damage. The patient developed secondary septic shock, renal failure, circulatory failure, and respiratory failure. We performed continuous renal replacement therapy and gastric lavage, and administered norepinephrine, frozen plasma, proton-pump inhibitors, adenosylmethionine, antibiotics, granulocyte colony stimulating factor, and total parenteral nutrition.

Outcomes: The patient rapidly developed complete hematopoietic function inhibition, gastrointestinal failure, and cardiac damage 32 hours after admission. Sustained severe infection and circulatory instability caused a progressive deterioration of respiratory function. Tracheal intubation was performed but the patient continued to deteriorate, and death occurred approximately 132 hours after admission.

Lessons: Excessive colchicine levels cause continuous organ damage due to extensive tissue distribution, eventually leading to multiple organ failure. Colchicine metabolism is delayed in patients with liver or kidney dysfunction, and even a low dose of colchicine may result in poisoning in these individuals. Early diagnosis and reduction of colchicine levels is critical to improve prognosis, and colchicine poisoning should be considered in patients with poor liver or kidney function even when the ingested dose is low.

Abbreviations: AC = activated charcoal, ALI = acute lung injury, DIC = disseminated intravascular coagulation.

Keywords: colchicine, continuous renal replacement therapy, multiple organ failure, septic shock

1. Introduction

Cases of colchicine overdose are rarely seen in the clinic. Although the lethal dose of colchicine is considered to be 0.8 mg/kg, patient fatalities have been reported from lower doses, following an acute disease course.[1,2] It has been shown that 7 to 25 mg colchicine can result in patient mortality,[3–5] suggesting that there is an individualized difference in the safe dose of colchicine. Colchicine overdose can cause multi-organ pathological processes, but these have not been comprehensively summarized in the literature to date. In this case, the patient presented typical symptoms and pathological processes after ingesting a low dose of colchicine with alcohol.

2. Case report

The patient was a 56-year-old man with a past medical history significant for gout and chronic kidney disease. After eating and drinking wine late at night, he felt discomfort in his right knee, with local redness and swelling, and ingested 12 colchicine tablets (1 mg per tablet, a total of 12 mg; weight 70 kg, 0.17 mg/kg) for pain relief. Approximately 12 hours later, the patient experienced acute abdominal symptoms, including severe abdominal pain, nausea, frequent diarrhea, and vomiting. He attended the local community hospital where he was diagnosed with acute gastroenteritis and admitted to receive infusion therapy. When he came to the emergency department of our hospital, it had been nearly 40 hours after ingesting colchicine, his symptoms had progressed to scleral yellow stain, chest tightness, shortness of breath, and difficulty breathing. Oliguria, peripheral cyanosis, low body temperature (35.9 °C), low blood pressure

Editor: N/A.

Patient's family has provided informed consent for publication of this case.

The authors have no conflicts of interest to disclose.

[a] Department of Surgical Intensive Care Unit, First Affiliated Hospital, College of Medicine, Zhejiang University, [b] Department of Anesthesiology, Hangzhou Red Cross Hospital, Hangzhou, Zhejiang Province, P.R. China.

[*] Correspondence: Mingjie Fu, Department of Surgical Intensive Care Unit, First Affiliated Hospital, College of Medicine, Zhejiang University, Qingchun Road 79, Hangzhou, Zhejiang Province, 310003, P.R. China (e-mail: 1516074@zju.edu.cn).

Medicine (2019) 98:30(e16580)

Received: 17 January 2019 / Received in final form: 22 May 2019 / Accepted: 2 July 2019

http://dx.doi.org/10.1097/MD.0000000000016580

Table 1

Results of laboratory investigations.

Test items (reference range)	Time after admission (h)								
	0	8	32*	46*	56*	80*	99*	110*	127*
WBC (4.0–10.0)	20.1	17.7	9.1	4.4	3.1	0.8	0.3	0.2	0.3
RBC (4.0–5.5)	5.04	4.21	3.37	2.96	2.55	2.59	2.46	2.55	2.33
PLT (100–300)	123	90	26	29	24	22	29	18	12
HB (120–160)	162	137	109	99	86	84	82	84	76
Troponin I (<0.1)	0.292	0.938	12.106	–	43.082	46.18	–	26.146	9.745
BNP (0–40)	–	1402	2368	–	3743	4371	4746	–	>5000

BNP = brain natriuretic peptide (pg/mL), Troponin I (ng/mL), HB = hemoglobin (g/L), PLT = platelet count (×10E9/L), RBC = red blood cells count (×10E12/L); WBC = white blood cells count (×10E9/L).
* After CRRT treatment.

(77/55 mmHg), and rapid heart rate (113 bpm) were indicative of shock. Emergency blood tests showed a 20.1 × 109/L white blood cell count, 92.6% neutrophils, 162 g/L hemoglobin, 123 × 109/L platelet count, 90.9 seconds activated partial thromboplastin time, and 70932 μg/L fibrinogen equivalent units D-dimer levels. Blood gas analysis indicated severe metabolic acidosis (pH 7.12) and respiratory alkalosis. Whole body computerized tomography scan displayed bilateral lung inflammation with a small amount of pleural effusion, kidney stones, right renal cyst, and cholecystitis. He was diagnosed with colchicine overdose, multiple organ failure, metabolic acidosis, and respiratory alkalosis.

We performed a gastric lavage despite the 40-hour interval since colchicine ingestion, but the patient's condition did not improve. He rapidly progressed to abdominal pain, respiratory insufficiency, circulatory failure, acute liver failure, acute renal failure, and coagulopathy. His creatine kinase levels continued to rise. Considering his acute renal failure and unstable circulation, we treated the patient with continuous renal replacement therapy, norepinephrine, frozen plasma, proton-pump inhibitors, adenosylmethionine, antibiotics, granulocyte colony stimulating factor, and total parenteral nutrition. The patient developed complete hematopoietic inhibition and cardiac damage at 32 hours post-admission (Tables 1 and 2). After 60 hours of active treatment, the patient required tracheal intubation for progressive deterioration of respiratory function. Seventy-two hours after admission, the patient's cardiovascular circulatory function deteriorated further, and he was treated with noradrenaline (80 μg/min) and adrenaline (18.67 μg/min) to maintain adequate blood pressure. The patient developed additional comorbidities, including worsening hepatic dysfunction, rhabdomyolysis, and systemic inflammatory response syndrome. His condition continued to deteriorate, and he died approximately 132 hours after admission.

3. Discussion

This case exhibited the typical features of severe colchicine poisoning even though the ingested dosage was relatively small, and this is likely due to patient's poor kidney function. For this case, the outcomes were also strongly associated with later diagnosis and admission.

Colchicine has a potent anti-mitotic activity through reversibly and selectively binding to the microtubular protein tubulin thereby disrupting the mitotic spindles in proliferating cells.[6,7] Though colchicine is taken up equally by all cells, it is thought to have the most effect on those with a high turnover,[8] such as cells of the gastrointestinal mucosa and bone marrow hematopoietic cells. In therapeutic doses, colchicine leads to the downregulation of multiple inflammatory pathways and the modulation of innate immunity.[9] Because it has a broad tissue distribution and a bioavailability of just 25% to 50% when administered orally,[10] extracorporeal removal of colchicine is very limited. In patients with normal renal function, renal clearance accounts for 10% to 20% of colchicine removal; with significant first-pass hepatic metabolism, primarily deacetylation, followed by widespread enterohepatic recirculation of the metabolites before excretion in bile and feces. It is thought that the extended time period of gastrointestinal mucosal cell exposure to colchicine may explain the prominence of the gastrointestinal symptoms of toxicity.

Pathological changes caused by colchicine poisoning can be reflected by clinical symptoms, often classified into 3 phases; phase 1 (10–24 hours): early gastrointestinal symptoms, blood volume depletion, hypotension resulting from severe vomiting and diarrhea, and peripheral leukocytosis; phase 2 (generally 2–7 days): change in mental status, oliguric renal failure, rhabdomyolysis, hematopoietic inhibition, electrolyte imbalance, acid-base disturbance, cardiac arrythmias, and cardiovascular collapse; phase 3 (over 7 days): rebound leukocytosis and alopecia.[7] Electrolyte and acid-base imbalances may include metabolic acidosis, hyponatremia, hypocalcemia, hypokalemia, hypophosphatemia, hypomagnesemia, and transient alopecia.

Colchicine-induced mitotic inhibition causes electrolyte imbalances which result in edema in the gastrointestinal mucosa. The electrolyte disturbances in this case were mainly caused by renal failure and acidosis, and manifested as abnormal serum levels of calcium, phosphorus, and magnesium (Table 2). Extensive edema of epithelial mucosal cells in the digestive tract causes abdominal pain, diarrhea, nausea, and vomiting. As lesions worsen, the balance of intestinal bacteria changes, causing systemic infections which may result in sepsis and shock. In this case, the patient presented with septic shock associated with high C-reactive protein (CRP) levels of 543 mg/L, approximately 40 hours after colchicine overdose. Table 2 shows the levels of high-sensitivity-CRP (hsCRP) and procalcitonin after admission.

Colchicine overdose has been associated with blood dyscrasia, including myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia.[9] Myelosuppression results in fewer granulocytes and platelets, leading to severe infection and increased bleeding tendency. Through postmortem examination, Van Heyningen and Watson[5] found that liver sinusoids were congested following colchicine overdose, and there were diffuse macrovesicular fatty changes in hepatocytes indicative of cellular damage, which may explain the release of liver enzymes in this case (Table 2).

Consistent with the literature,[5,11] we found that the serum myocardial zymogram (lactate dehydrogenase, creatine kinase, creatine kinase isoenzyme, brain natriuretic peptide) and troponin I levels indicated that rhabdomyolysis occurred before

Table 2

Trend in the laboratory results over time.

Items	Unit	RR	0 h	4 h	8 h	32 h*	56 h*	80 h*	104 h*	128 h*
AST	U/L	8–40	1002	931	858	972	1031	9840	6004	2097
ALT	U/L	5–40	243	–	–	194	166	1271	855	525
Cr	μmol/L	62–115	599	597	487	232	177	174	151	122
BUN	mmol/L	2.86–7.14	15.81	16.07	15.00	7.93	9.57	12.05	12.61	12.22
UA	μmol/L	150–440	943	940	810	332	235	252	173	147
LDH	U/L	114–240	2346	2181	2212	3226	3507	9796	7409	3636
CK	U/L	38–174	2315	2899	4176	9599	12205	14758	16674	13449
CK-MB	U/L	0–25	229	236	215	191	188	229	156	110
hs-CRP	mg/L	<5.0	543.2	–	400.8	488.2	399.9	377.4	424.9	446.8
PCT	μg/L	<0.5	–	–	>100	>100	42.17	15.84	18.05	12.74
TBIL	μmol/L	2–17	97	–	–	106	93	134	164	188
K^+	mmol/L	3.5–5.0	4.2	4.3	3.9	3.8	4.5	4.0	4.1	4.3
Na^+	mmol/L	135–145	132	129	131	137	143	140	140	139
Cl^-	mmol/L	98–106	89	89	92	99	98	95	99	97
Ca^{2+}	mmol/L	2.25–2.75	1.70	1.56	1.63	1.99	2.17	2.16	2.12	2.19
Mg^{2+}	mmol/L	0.87–1.12	0.85	0.85	0.79	0.93	1.09	1.01	1.01	0.93
P	mmol/L	0.97–1.61	3.99	3.64	2.48	0.72	0.88	0.33	0.10	0.32
INR	–	0.75–1.25	1.54	1.6	1.55	1.51	1.36	1.32	1.27	1.33
Fib	g/L	2.0–4.0	8.3	7.5	4.9	5.7	4.5	4.3	4.9	5.5
APTT	s	25–37	91	93	99	74	–	37	49	50
PT	s	11–14	18	18	17	17	16	15	15	15
D-dimer	μg/L	<500	70932	68641	65355	25659	23109	41795	59203	36242

ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, Cr = creatinine, CK = creatine kinase, CK-MB = creatine kinase isoenzyme, Fib = fibrinogen, hs-CRP = hypersensitive c-reactive protein, INR = international normalized ratio, LDH = lactate dehydrogenase, PCT = procalcitonin, PT = prothrombin time. Time after admission, RR = reference range, TBIL = total bilirubin, UA = uric acid.

* After CRRT treatment.

cardiac toxicity. Rhabdomyolysis was indicated by elevated creatine phosphokinase levels (up to 8500 units/L) and a positive urine test for myoglobin. Various mechanisms have been proposed to explain the effect of colchicine on heart and skeletal muscle, including a direct toxic effect on myocardial cells, resulting in impaired impulse generation and cardiac conduction,[12,13] or indirect effects through the profound acid-base disturbances and electrolyte derangements associated with overdose.[14] Several reports indicate that cardiac toxicity can manifest as arrhythmias, including sinus bradycardia, sinus tachycardia, ventricular fibrillation, and complete atrioventricular block,[7,15] yet these were not present in this patient. Cardiac arrhythmias and shock can cause acute renal failure, which can increase the risk of colchicine myotoxicity.[16]

The severe infection, shock, and liver damage in this case resulted in abnormal coagulation function. D-dimer levels (Table 2) showed microcirculatory disturbance, which can aggravate organ dysfunction. Disseminated intravascular coagulation may be a result of septic shock and multiple organ failure. The trends of lactate acid levels and blood pH (Fig. 1) also

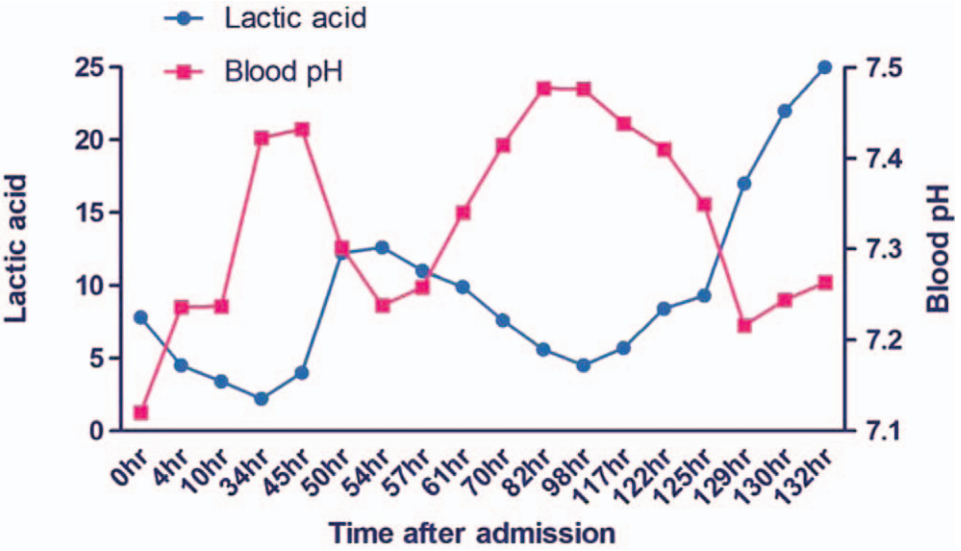

Figure 1. Blood lactate and pH by time after admission.

reflected a lack of microcirculation perfusion, which led to the patient's poor prognosis. Acute lung injury usually occurs in the middle or late stages of colchicine poisoning, and this patient developed respiratory distress and hypoxemia accompanied by bilateral pulmonary infiltrates on the 5th day after ingestion, which we treated with mechanical ventilation and negative fluid balance.

It is difficult to diagnose colchicine intoxication from the chief complaint alone, and misdiagnosis may result in mortality. Komorowski and Rodil[6] reported the case of a patient with unrecognized colchicine overdose, who presented to the emergency department with acute abdominal symptoms which rapidly progressed to multiple organ failure, and who died 16 hours later after unnecessary emergency surgery. Due to the wide distribution of colchicine throughout the body, and the characteristics of its metabolism, early diagnosis does not always reduce mortality in these cases, because an effective antagonistic drug has yet to be developed for clinical practice. Current treatment used to reduce mortality involves a combination of early diagnosis, treatment including antibiotics, and prevention of organ failure. A recent study found that in clinically relevant porcine models of colchicine toxicity, colchicine-specific antigen-binding fragments (Fabs) can be highly effective if administered in high doses at an early stage.[17] It is likely that Fabs bind to colchicine with a high affinity, enabling redistribution of the drug into the intravascular compartment and removal from the peripheral sites.[18] Another study showed significant in vitro binding of colchicine to activated charcoal (AC) in patients presenting to hospital after ingestion of *Gloriosa superba*, a plant which contains colchicine,[19] suggesting that AC may have potential as a treatment for colchicine poisoning.

In conclusion, it is crucial that the potential dangers of colchicine overdose are highlighted by clinicians when it is prescribed, and that patients are educated regarding its effects, including the point at which to stop taking it. Careful monitoring of prescriptions is important to avoid unintentional overdose with this potentially lethal drug, including consideration of pre-existing kidney damage in patients.

Author contributions

Formal analysis: Mingjie Fu.
Writing – original draft: Mingjie Fu, Jie Zhao, Anwei Lu.
Writing – review & editing: Mingjie Fu, Zhitao Li, He Zhao, Anwei Lu.

References

[1] Hirayama I, Hiruma T, Ueda Y, et al. A critically ill patient after a colchicine overdose below the lethal dose: a case report. J Med Case Rep 2018;12:191.
[2] Stapczynski JS, Rothstein RJ, Gaye WA, et al. Colchicine overdose: report of two cases and review of the literature. Ann Emerg Med 1981;10:364–9.
[3] Macleod JG, Phillips L. Hypersensitivity to colchicine. Ann Rheum Dis 1947;6:224–9.
[4] Dickinson M, Juneja S. Haematological toxicity of colchicine. Br J Haematol 2009;146:465.
[5] Van Heyningen C, Watson ID. Troponin for prediction of cardiovascular collapse in acute colchicine overdose. Emerg Med J 2005;22:599–600.
[6] Komorowski AL, Rodil JH. Emergency abdominal surgery and colchicine overdose. J Emerg Trauma Shock 2012;5:342–3.
[7] Maxwell MJ, Muthu P, Pritty PE. Accidental colchicine overdose. A case report and literature review. Emerg Med J 2002;19:265–7.
[8] Milne ST, Meek PD. Fatal colchicine overdose: report of a case and review of the literature. Am J Emerg Med 1998;16:603–8.
[9] Leung YY, Yao Hui LL, Kraus VB. Colchicine — update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 2015;45:341–50.
[10] Terkeltaub RA. Colchicine update: 2008[C]. Semin Arthritis Rheum 2009;38:411–9.
[11] Chattopadhyay I, Shetty HG, Routledge PA, et al. Colchicine induced rhabdomyolysis. Postgrad Med J 2001;77:191–2.
[12] Markand ON, D'agostino AN. Ultrastructural changes in skeletal muscle induced by colchicine. Arch Neurol 1971;24:72–82.
[13] Stahl N, Weinberger A, Benjamin D, et al. Fatal colchicine poisoning in a boy with familial Mediterranean fever. Am J Med Sci 1979;278:77–81.
[14] Borron SW, Scherrmann JM, Baud FJ. Markedly altered colchicine kinetics in a fatal intoxication: examination of contributing factors. Hum Exp Toxicol 1996;15:885–90.
[15] Schaumann W, Kaufmann B, Neubert P, et al. Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. Eur J Clin Pharmacol 1986;30:527–33.
[16] Lee BI, Shin SJ, Yoon SN, et al. Acute myopathy induced by colchicine in a cyclosporine-treated renal transplant recipient–a case report and review of the literature. J Korean Med Sci 1997;12:160–1.
[17] Eddleston M, Fabresse N, Thompson A, et al. Anti-colchicine Fab fragments prevent lethal colchicine toxicity in a porcine model: a pharmacokinetic and clinical study. Clin Toxicol 2018;56:773–81.
[18] Baud FJ, Sabouraud A, Vicaut E, et al. Treatment of severe colchicine overdose with colchicine-specific Fab fragments. N Engl J Med 1995;332:642–5.
[19] Zawahir S, Gawarammana I, Dargan PI, et al. Activated charcoal significantly reduces the amount of colchicine released from Gloriosa superba in simulated gastric and intestinal media. Clin Toxicol 2017;55:1.