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CASE SERIES

Colchicine intoxication: a report of two suicide cases

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Abstract: Colchicine, an old and well-known drug, is an alkaloid extracted from *Colchicum autumnale* and related species. Colchicine inhibits the deposition of uric acid crystals and is an inhibitor of mitosis. Nausea, vomiting, abdominal pain, and diarrhea, with a massive loss of fluid and electrolytes are the first clinical symptoms of colchicine poisoning. Stomach lavage and rapid gastric decontamination with activated charcoal are crucial. An acute dose of about 0.8 mg/kg of colchicine is presumed to be fatal. We report the clinical outcomes of two different cases of colchicine intoxication for attempted suicide. The dose required for morbidity or mortality varies significantly. The dose of 1 mg/kg in the first case was directly related with mortality, while the dose of 0.2 mg/kg in the second was related with survival. The other difference between the patients was the time of arrival to hospital after ingestion. This period was 4 hours for case 1 and only 1, hour for case 2. The initiation of treatment later than 2 hours after ingestion of colchicine may significantly impair treatment because the absorption time for colchicine after oral administration is about 30–120 minutes. The rising lactate level and high anion gap metabolic acidosis in our patient (case 1) were attributed to lactic acidosis, so hemodialysis was performed, and the duration of hemodialysis was prolonged. Lactic acidosis in the first case was one of the reasons for mortality. The most important parameters which define the chance of survival are the dose of ingested drugs and the arrival time to hospital after ingestion. The patients must be monitored closely for lactic acidosis and the decision to start hemodialysis must be made promptly for patients who develop lactic acidosis.

Keywords: colchicine intoxication, metabolic acidosis, mortality

Introduction

Colchicine is an old and well-known drug, which is an alkaloid extracted from *Colchicum autumnale* and related species. It has an anti-inflammatory effect based on the ability to impair the mobility and activity of neutrophil leukocytes. In addition, colchicine inhibits the deposition of uric acid crystals and is an inhibitor of mitosis. It is a liposoluble alkaloid, which prevents the storage of amyloid, and it is used both in the management of acute gouty arthritis and familial Mediterranean fever (FMF).[1] Presumably due to unidentified linkage sites with the microtubules of gastrointestinal cells, the absorption of colchicine is highly variable. Nausea, vomiting, abdominal pain, and diarrhea, with a massive loss of fluid and electrolytes are the first clinical symptoms of colchicine poisoning.[2] As well as a cardiotoxic effect, reduced blood volume may also cause bradycardia.[1] Stomach lavage and rapid gastric decontamination with activated charcoal have proven to be crucial measures of treatment. Ingestion of an acute dose of about 0.8 mg/kg of colchicine is thought to be fatal.[3,4] We report the clinical

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outcomes of two different cases of colchicine intoxication for attempted suicide.

Case 1

A 23-year-old, 50 kg female patient was admitted to a local hospital with the complaints of nausea and vomiting 4 hours after taking 50 mg or 1 mg/kg (100 tablets of 0.5 mg) colchicine for suicide. She had a history of FMF. Stomach lavage and activated charcoal gastric decontamination was performed, and she was transferred to the Kayseri Training and Research Hospital 10 hours after ingestion. She was conscious, orientated, and cooperative, and complained of diarrhea and abdominal pain. She had pale and cold skin, and her vital signs in the emergency facility revealed a blood pressure of 94/58 mmHg, body temperature of 36.8°C, respiratory rate of 16 breaths/minute, and heart rate of 77 beats/minute. She had tenderness on the epigastrium, and other system examinations were unremarkable. The patient was admitted to the intensive care unit. The results of initial laboratory studies were: white blood cells (WBC), 19.330 (10^3 μL); hemoglobin, 15.4 g/dL; hematocrit, 45%; platelets (PLTs), 250,000/mm^3; aspartate aminotransferase (AST), 87 U/L; alanine aminotransferase (ALT), 19 U/L; sodium, 143 mmol/L; potassium (K), 3.8 mmol/L; calcium (CA), 8.3 mmol/L; total creatine kinase (Total-CK), 116 U/L; serum creatine kinase myocardial band isoenzyme (CK-MB), 45 U/L; lactate dehydrogenase (LDH), 1,568 U/L; troponin I, 0.39 ng/mL; D-dimer, 6,795 ng/L; international normalized ratio (INR), 2.27; activated partial thromboplastin time (aPTT), 27.7 seconds; blood urea nitrogen (BUN), 15 mg/dL; serum creatinine (Cr), 1.0 mg/dL. Serologic tests for hepatitis B and hepatitis C were negative. Blood gas values were: pH, 7.372; partial pressure of carbon dioxide (pCO$_2$), 41.6 mmHg; (bicarbonate) HCO$_3$, 23 mmol/L; base excess (BE), −1.2 mmol/L. Following the recommendation of the contacted poison control center, gastric lavage was performed again and activated charcoal was given every hour for 6 hours (0.25 g/kg per hour) to reduce the intestinal colchicine absorption. Sodium bicarbonate at a dose of 80 mEq was replaced in 12 hours. Electrolytes and blood gases were monitored every 6 hours. Table 1 shows the results of blood gas monitoring. On the 12th hour of her admission, lactate was 10.4 mmol/L and HCO$_3$ <15 mmol/L. The patient developed high anion gap (AG) metabolic acidosis due to lactic acidosis. Hemodialysis was performed because of the patient's insufficient urine output. Intravenous fluids and positive inotropic agents were used for persistent low central venous pressure. On followup of the patient, AST, ALT, Total-CK, CK-MB, troponin I, LDH, and INR rose progressively and PLTs declined (Table 2).

Table 1 Blood gas monitoring for case 1

	pH	pCO$_2$	pO$_2$	HCO$_3$	BE	AG
On admission	7.372	41.6	49.2	23	−1.2	12
12 hours	7.391	23.0	65.3	13.7	−9.1	21
24 hours	7.464	23.6	53.4	16.7	−6.4	16
36 hours	7.341	42.0	36.4	20.5	−3.1	15
42 hours	7.225	42.2	30.6	15.0	−10.4	20
48 hours	7.415	31.0	46.9	20.8	−3.7	21
55 hours	6.665	76.0	43.1	5.2	−26.0	30

Abbreviations: AG, anion gap; BE, base excess; HCO$_3$, bicarbonate; pCO$_2$, partial pressure of carbon dioxide; pO$_2$, partial pressure of oxygen.

Sinus tachycardia was determined by electrocardiography, and echocardiography revealed normal systolic function of the left ventricle, with an ejection fraction of 50%–55%. Peripheral blood smear revealed schistocytes. Blood tests showed raised D-dimer, aPTT, prothrombin time and INR, and decreased fibrinogen. Eventually disseminated intravascular coagulopathy (DIC) developed. Fresh frozen plasma and platelet infusion at a dose of 1 unit per 10 kg was given. K and Ca were also replaced for the treatment of hypokalemia and hypocalcemia. At 42 hours following hospital admission, the patient's general condition worsened. She had a heart rate of 132 bpm, respiratory rate of 33 breaths/minute, peripheral oxygen saturation of 94%, a Glasgow coma scale of 12, and invasive arterial blood pressure was 82/51 mmHg. Blood gas analyses were pH, 7.225; pCO$_2$, 42.2 mmHg; arterial oxyhemoglobin saturation (SaO$_2$), 96%; HCO$_3$, 15 mmol/L; BE, −10.4 mmol/L. The patient had diffuse abdominal pain, tenderness on palpation, and hyperactive bowel sounds. Blood samples taken from the central venous catheter revealed WBC, 18.220 (10^3 μL); hematocrit, 44.1%; PLTs, 73,000/mm^3; ALT, 93 U/L; AST, 561 U/L; BUN, 11 mg/dL; Cr, 1.3 mg/dL; Total-CK, 1,415 U/L; CK-MB, 135 U/L; LDH, 6,105 U/L; troponin I, 34.04 ng/mL; INR, 6.18; aPTT, 157.3 seconds. The patient was thought to have developed lactic acidosis, DIC, and multiorgan failure with rhabdomyolysis due to colchicine intoxication, and supportive treatments (fresh frozen plasma, platelet infusion, nasal oxygen, etc) were continued. Hemodialysis was performed again for decreased urine output (400 cc/day). At 54 hours following hospital admission, cardiopulmonary arrest developed. She responded to resuscitation after 50 minutes, and mechanical ventilation was performed. Blood gas analyses were: pH, 6.665; pCO$_2$ 76 mmHg; HCO$_3$, 5.2 mmol/L; BE, −26 mmol/L. Because of continuing lactic acidosis, hemodialysis was performed again, and the duration of hemodialysis was prolonged. At 58 hours following her admission, the patient went into cardiac arrest again, remained completely unresponsive to resuscitation, and died.

Table 2 Complete blood count, coagulation tests, and biochemistry measurements for case 1

	PT (sec)	INR	aPTT (sec)	AST (U/L)	ALT (U/L)	LDH (U/L)	Total-CK (U/L)	CK-MB (U/L)	PLTs (/mm³)	Trop I (ng/mL)
On admission	27.7	2.27	27.7	87	19	1,568	116	45	250,000	0.39
12 hours	36.3	3.09	45.2	174	24	2,905	602	117	209,000	5.47
24 hours	34.4	2.91	43.2	233	30	3,650	704	125	138,000	7.70
36 hours	40.2	3.47	67.9	297	36	4,940	1,874	195	113,000	16.32
42 hours	66.7	6.18	157.3	561	93	6,105	1,415	135	73,000	34.04

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; INR, international normalized ratio; LDH, lactate dehydrogenase; PLTs, platelets; PT, prothrombin time; Total-CK, total creatine kinase; Trop I, troponin I.

Case 2

A 17-year-old, 47 kg female patient with a diagnosis of FMF was admitted to a local hospital with the complaints of nausea and vomiting after taking 9.5 mg or 0.2 mg/kg (19 tablets of 0.5 mg) colchicine for suicide attempt. She underwent stomach lavage and treatment with activated charcoal at that facility, and was transferred to our hospital an hour after ingestion. She was conscious, responsive, and cooperative, and she had diarrhea. On physical examination she had a blood pressure of 125/55 mmHg, body temperature 36.5°C, respiratory rate 15 breaths/minute, and heart rate 70 beats/minute. The patient was pale and cold, and she had abdominal tenderness on palpation. Other system examinations were unremarkable. She was admitted to the intensive care unit. Her initial laboratory findings in the intensive care unit were WBC, 6.640 (10^3 μL); hemoglobin, 13 gr/dL; hematocrit, 40.3%; PLTs, 428,000/mm³; AST, 32 U/L; ALT, 21 U/L; sodium, 139 mmol/L; K, 4.1 mmol/L; Ca, 9.5 mmol/L; Total-CK, 112 U/L; CK-MB, 25 U/L; LDH, 156 U/L; troponin I, 0.00 ng/ml; D-dimer, 1,833.78 ng/L; INR, 1.14; BUN, 13 mg/dL; Cr, 0.7 mg/dL. Blood gas values were: pH, 7.48; pCO_2, 21.2 mmHg; HCO_3, 20.0 mmol/L; BE, −5.9 mmol/L. Following the recommendation of the contacted poison control center, gastric lavage was performed again and activated charcoal was given every hour for 6 hours (0.25 g/kg per hour) to reduce the intestinal colchicine absorption. Blood gas analyses were performed every 12 hours (Table 3). On follow-up of the patient, AST, ALT, Total-CK, CK-MB,

troponin I, LDH, and INR remained normal (Table 4). Normal sinus rhythm was determined by electrocardiography, and echocardiography revealed the left ventricle had normal systolic function and an ejection fraction of 60%. She did not need hemodialysis and was transferred to the internal medicine service on the fifth day of her admission. The consultant psychiatrist diagnosed a depressive episode as the underlying cause for her suicide attempt. She recovered without sequelae and was discharged on the seventh day of her follow-up.

Discussion

Colchicine is a drug which for many years has been routinely used for prevention of both acute attacks of FMF and amyloidosis. Colchicine and its metabolites are excreted mainly in the urine and in the bile. Liver hydrolysis certainly occurs, although other pathways may exist.[5] Due to the high biliary concentration, enterohepatic circulation is presumably the main cause of intestinal distress in acute and chronic poisoning. In patients with hepatic insufficiency, renal excretion is dominant.[6] Besides colchicine's minor therapeutic index, its potential as a toxic agent has raised concerns over its pharmaceutical use.[7,8] Although it is not common, colchicine intoxication may cause mortality. Intoxication by colchicine causes the inhibition of cell division at the affected organs by fixing the intracellular tubulin and arresting their polymerization into microtubules. Thus, mitosis and transport systems within the cells are disrupted. Organs which have a high rate of cell turnover, such as the gastrointestinal tract and bone marrow, are the ones most affected.[9] The symptoms of intoxication can be classified in three phases. Phase 1: early gastrointestinal symptoms, volume depletion, and hypotension resulting from severe vomiting and diarrhea, and peripheral leukocytosis; phase 2: (generally 24 to 72 hours) mental status change, oliguric renal failure, hematopoietic problems, electrolyte imbalance, acid-base disturbance, and shock; and phase 3: rebound leukocytosis and alopecia. Electrolyte and acid-base imbalances such as metabolic

Table 3 Blood gas monitoring for case 2

	pH	pCO₂	pO₂	HCO₃	BE
On admission	7.48	21.2	49.4	20	−5.9
12 hours	7.369	31.7	54.1	19.1	−6.1
24 hours	7.44	26.0	74.8	20.5	−5.6
36 hours	7.448	26.0	74.4	20.6	−4.6
42 hours	7.418	26.2	104	19.3	−6.3
48 hours	7.433	32.1	45.0	22.7	−2.5
72 hours	7.395	35.6	64.8	22.2	−2.1

Abbreviations: BE, base excess; HCO₃, bicarbonate; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen.

Table 4 Complete blood count, coagulation tests, and biochemistry measurements for case 2

	PT (sec)	INR	AST (U/L)	ALT (U/L)	LDH (U/L)	Total-CK (U/L)	CK-MB (U/L)	PLTs (/mm³)	Trop I (ng/mL)
On admission	15.1	1.14	32	21	156	112	25	428,000	0.00
12 hours	18.4	1.42	48	26	147	602	117	417,000	0.01
24 hours	21.9	1.73	52	32	187	147	37	352,000	0.00
36 hours	18.7	1.45	50	35	175	141	37	388,000	0.00
48 hours	16.3	1.24	26	23	214	99	40	325,000	0.01
72 hours	12.7	0.93	24	36	234	63	21	304,000	0.03

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; INR, international normalized ratio; LDH, lactate dehydrogenase; PLTs, platelets; PT, prothrombine time; Total-CK, total creatin kinase; Trop I, troponin I.

acidosis, hyponatremia, hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia have been reported.[2] Metabolic acidosis, which is associated with substantial morbidity and mortality, is a frequently encountered acid-base disturbance in hospitalized patients.[10] Lactic acidosis is the most frequent cause of metabolic acidosis in hospitalized patients, characterized by a high AG (>12 mmol/L) with increased serum lactate concentrations (>5 mEq/L) and often carries a significant risk for mortality. It is commonly associated with clinical situations, such as shock and sepsis as a result of tissue hypoperfusion and hypoxia.[10] The Case 1 patient developed this acid-base abnormality in the presence of normal tissue perfusion and oxygenation. Many drugs have been implicated in the pathogenesis of lactic acidosis.[11] Lactic acidosis progresses despite hemodialysis, when blood lactate is produced faster than it is cleared.[12] As shown in the case report, the hemodialysis must be performed quickly, and the duration of the hemodialysis session must be prolonged when the clinical and biochemical evaluation of the patient shows signs of acidosis.[12] The rising lactate level and high AG metabolic acidosis in our patient (case 1) were attributed to lactic acidosis, so hemodialysis was performed, and the duration of hemodialysis was prolonged. Lactic acidosis in the first case was one of the reasons for mortality.

Ingestion of high doses of colchicine results in death, but toxicity might be seen within the therapeutic doses. The dose required for morbidity or mortality varies significantly. Bismuth et al reported the correlation between the clinical process and the ingested dose as follows: minor toxicity with 100% survival after ingestion of less than 0.5 mg/kg of colchicine, major toxicity (myelosuppression) with 10% mortality after ingestion of 0.5–0.8 mg/kg of colchicine, and 100% mortality (cardiogenic shock and death) after ingestion of 0.8 mg/kg or more.[3,4] Conversely, published reports have stated that doses less than 0.5 mg/kg caused cardiogenic shock and death.[13] Cardiogenic collapse and myelosuppression are reported as the main causes of mortality, and most of

the deaths are seen 7–10 days after ingestion.[14] We realized the importance of doses the two cases reported here. The dose of 1 mg/kg in the first case was directly related with the mortality, while the dose of 0.2 mg/kg in the second case was related with survival.

The other difference between the patients was the time of hospital arrival after ingestion. This period was 4 hours for case 1, and only 1 hour for case 2. As well as the total amount of ingested colchicine, the time between intake and therapeutic intervention also affects survival.[15] The initiation of treatment later than 2 hours after ingestion of colchicine may significantly impair the treatment course because the absorption time for colchicine after oral administration is about 30–120 minutes.[15] However, there are also published fatal cases of colchicine intoxication despite immediate presentation and prompt onset of treatment.[16] Varying dissolution rates of colchicine tablets, the pH at the absorption site, and interindividual variations in gastric emptying and enteral motility may be the causes of this difference.[17] Mullins et al described arrhythmia and cardiac insufficiency,[13] and Sauder et al[18] described myocarditis associated with colchicine intoxication. Sauder et al reported that the outcome of colchicine poisoning depends on the occurrence of acute circulatory insufficiency and also reported that an early decrease of cardiac output predicts lethality. However, the mechanisms of shock in acute colchicine poisoning are uncertain; several factors may be important. These are: 1) hypovolemia, mostly due to the intestinal loss of water by diarrhea,[18] 2) the presence of metabolic acidosis, and 3) depressed myocardial function due to the secretion of Myocardial Depressant Factor.[18] In case 1, despite aggressive fluid resuscitation and vasopressor infusion, the patient died after a sudden cardiovascular collapse. Stapczynski et al reported two fatal cases following acute ingestions of 12 mg of colchicine.[19] Like our patient, both of these patients had early leukocytosis (25.3 × 10³ [WBC/mm³]) and 42.6 × 10³ [WBC/mm³], respectively) and died of sudden asystole within 24 hours of presentation. Mullins et al also showed early

leukocytosis in their two fatal cases.[13] We propose that early leukocytosis may be a predictor for mortality. The intoxication causes excessive fibrinolytic activity.[20] Excessive fibrinolytic activity and multiorgan failure were the factors which may have contributed to the formation of DIC in our patient.

A specific experimental treatment (Fab fragment antibodies) for colchicine poisoning has been used, although it is not commercially available as yet.[21] Gastric lavage and activated charcoal are used to prevent absorption in colchicine intoxication, but the main treatment is supportive therapy; it is very important to compensate for initial fluid loss. The use of central venous pressure monitoring of hemodynamic status as an indicator for directing supportive therapy has been proposed.[13] In our patient, the treatment of circulation and multiorgan failure, consisting of fluid resuscitation and inotropic support, were arranged according to central venous pressure monitoring and urinary output.

Conclusion

Colchicine intoxication is a severe, life-threatening situation and patients should be monitored closely in intensive care units. The ingested dose and arrival time to hospital play a critical role in the treatment. Invasive hemodynamic monitoring must be done if there is shock, necessitating intensive fluid and inotropic therapy, and also if there is multiorgan failure.

Disclosure

The authors report no conflicts of interest in this work.

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