Assessment of 17 Pediatric Cases With Colchicine Poisoning in a 2-Year Period

Demet Alaygut, MD, Suar Caki Kilic, MD,† Ali Kaya, MD,‡ Mehmet Burhan Oflaz, MD,§ Fatih Bolat, MD,‡ Ömer Cevit, MD,‡ and Fusun Dilara Icagasioglu, MD‡*

Aim: The aim of the study is to discuss clinical effects, treatments, and outcomes of pediatric colchicine poisoning.

Method: This study was designed as an observational case series study. The medical records of children aged between 0 and 18 years, who were hospitalized for colchicine poisoning at the Department of Pediatric Intensive Care Unit, Cumhuriyet University Faculty of Medicine, between January 2010 and January 2012, were retrospectively evaluated.

Results: We presented 17 children with colchicine poisoning. The mean (SD, range) age of patients was 71.5 (69.19, 18–204) months. The period to apply to the hospital after taking the medications was 7.3 hours (7.97, 30 minutes-26 hours) on average. The use of colchicine was due to diagnosis of Familial Mediterranean fever (FMF) in the families of 8 patients, diagnosis of Behçet disease in 1 patient's father, diagnosis of Behçet disease in 1 patient herself, and diagnosis of FMF in 6 patients themselves. Thirteen patients had taken colchicine at the dose of less than 0.5 mg/kg known as subtoxic and 1 patient had taken colchicine at the dose of greater than 0.8 mg/kg, and doses taken by 3 patients were not known. Fourteen patients (82.4%) had involuntary drug intake. Fifty percent of them were symptomatic at the moment of application and all had gastrointestinal complaints. All patients were observed in intensive care unit upon first admission and received supportive care. One of patients showed total alopecia, one showed leucocytosis, and another one showed acute abdomen picture. None of the patients showed mortality.

Conclusions: Mortality of colchicine toxicity is high and quick assessment is absolutely required. In regions where FMF is common and the use of colchicine is high, clinicians should pay attention to symptoms and findings related to colchicine intoxication and keep them in mind in differential diagnosis.

Key Words: colchicine, poisoning, management

(*Pediatr Emer Care* 2016;32: 168–172)

Colchicine is an alkaloid that is commonly used for treatment of multiple diseases including gout, primary biliary cirrhosis, Behçet disease, sarcoidosis, psoriasis, scleroderma, Familial Mediterranean fever (FMF), and amyloidosis.[1] Despite its merits, its narrow therapeutic index has been the source of several incidences of successful suicides by overdose.[2] Deaths caused by colchicine overdoses are uncommon but well documented and associated with a high mortality rate. They usually result from multiorgan failure, due to ensuing sepsis or directly colchicine toxicity.[3] Overdose with colchicine constitutes a toxicological emergency and rapid intervention is required. In regions where FMF is endemic and colchicine use is common, physicians should maintain a high index of suspicion, because of the fact that symptoms of colchicine may be misdiagnosed for other systemic diseases (eg, enterocolitis). The city in which our hospital is located is in a region, where FMF disease is common, in northeastern Turkey. Because the number of patients receiving colchicine treatment is high, suicidal or unintentional colchicine toxicity cases are very common. This article has been reported to emphasize the importance of colchicine toxicity and to assess the pediatric patient data acquired in a short period of 2 years.

METHODS

Current study was designed as a case series study. The medical records of children aged between 0 and 18 years who were hospitalized for colchicine poisoning at the Pediatric Intensive Care Unit of Cumhuriyet University Faculty of Medicine, in Sivas, Turkey, between January 2010 and January 2012, were retrospectively evaluated. Patients' ages, sexes, drug doses they take, their reasons to be exposed to toxic dose, family histories, use of additional medication along with colchicine, their complaints when applied to hospital, the period elapsed between medication intake and the application to hospital, their hospitalization periods, their laboratory values when applied to hospital (complete blood count, kidney and liver function tests, electrolytes, blood gas, and bleeding diathesis parameters), treatments administered, and their results were recorded from patients' archive. The computerized automation system of the hospital was used for the records. Dose ingested was revealed from the parents' declaration in the anamnesis forms. Dose, to which the patients were exposed, was specified as milligram per kilogram and as subtoxic (<0.5 mg/kg), toxic (0.5–0.8 mg/kg), and lethal (>0.8 mg/kg) doses reported in the literature.[2] Statistical analysis was performed by using SPSS 18.0.

The study was approved by "Medical Research Local Ethics Committee" of Cumhuriyet University.

RESULTS

Data of 17 pediatric cases in total were acquired within the period of 2 years. Ten (58.8%) of patients were female. The mean (SD, range) application age was 71.5(69.19, 18–204) months. Three patients (17.6%) were exposed to toxicity because of suicidal purposes, the others were exposed to toxicity through involuntary means. When the patients' ways of reaching the medication were questioned, it was observed that families of 8 patients (mother, father, or siblings) had members diagnosed with FMF. One patient and father of 1 patient were using the colchicine because of Behçet disease. Six patients were FMF patients themselves. There were no data regarding 1 patient. Thirteen patients (76.5%) took the colchicine in subtoxic dose (<0.5 mg/kg), whereas 1 patient took it in lethal dose (>0.8 mg/kg). Doses taken by 3 patients were not known. Although 82.4% of patients (n = 14) applied to the hospital within the first 24 hours after the medication intake, 3 patients applied to the hospital within 24 to 72 hours. The mean (SD, range) application period was 7.3 hours (7.97, 30 minutes-26 hours). There were no additional medications that could interact with colchicine and all patients took orally medications. The

From the Departments of *Pediatric Nephrology, †Pediatric Hematology, ‡Pediatrics, and §Pediatric Cardiology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey.

Disclosure: The authors declare no conflict of interest.

Reprints: Demet Alaygut, MD, Cumhuriyet University Faculty of Medicine, Department of Pediatric Nephrology, Kayseri cad. 58110, Sivas, Turkey (e-mail: alaygutdemet@gmail.com).

ISSN: 0749-5161

TABLE 1. General Characteristics of Patients

Patient Number	Sex	Age, mo	Dosage, mg/kg	Family History	Admitting Time, h	Reason	Presenting Signs	Therapy	Complication/Outcome
1	F	18	Unknown	FMF: mother	4	Unintentional	Absent	GL, AC	No/CR
2	M	37	0.38	FMF: patient	0.5	Unintentional	Absent	GL, AC	No/CR
3	F	18	0.25	Unknown	26	Unintentional	Vomiting, abdominal pain	GL, AC	No/CR
4	F	180	0.09	FMF: patient	0.5	Suicide	Vomiting	GL, AC	No/CR
5	M	48	Unknown	FMF: brother	0.5	Unintentional	Absent	GL, AC	No/CR
6	M	66	Unknown	FMF: patient	5	Unintentional	Absent	GL, AC	No/CR
7	F	19	0.13	FMF: mother	0.5	Unintentional	Absent	GL, AC	No/CR
8	F	180	0.50	FMF: patient	6	Unintentional	Diarrhea, vomiting, abdominal pain	GL, AC	Acute abdomen/CR
9	F	24	0.05	Behçet disease: father	4	Unintentional	Absent	GL, AC	No/CR
10	F	192	0.88	Behçet disease: patient	5	Suicide	Diarrhea, vomiting, abdominal pain	GL, AC, FFP, TS	Alopecia (total)/CR
11	F	204	0.40	FMF: mother	21	Suicide	Diarrhea, vomiting	GL, AC	No/CR
12	M	72	0.11	FMF: patient	6	Unintentional	Vomiting, abdominal pain	GL, AC	No/CR
13	F	26	0.17	FMF: father	12	Unintentional	Absent	GL, AC	No/CR
14	M	30	0.19	FMF: mother	16	Unintentional	Vomiting	GL, AC, FFP, TS, G-CSF	Leucocytosis, sepsis, HSP/CR
15	F	36	0.17	FMF: mother	16	Unintentional	Absent	GL, AC	No/CR
16	M	48	0.29	FMF: patient	0.5	Unintentional	Absent	GL, AC	No/CR
17	M	18	0.16	FMF: father	1	Unintentional	Absent	GL, AC	No/CR

AC indicates activated charcoal; CR, complete recovery; F, female; FFP, fresh frozen plasma; GL, gastric lavage; HSP, hepatosplenomegaly; M, male; TS, thrombocyte suspension.

TABLE 2. Laboratory Findings of Case 10

	Case Number 10																		
Day	**WBC, /mm^3**	**ANC, /mm^3**	**Hb, g/dL**	**Plt, /mm^3**	**PT, s**	**aPTT, s**	**BUN, mg/dL**	**Cr, mg/dL**	**AST, IU/L**	**ALT, IU/L**	**LDH, IU/L**	**CK, mg/dL**	**Na, mmol/L**	**K**	**Ca**	**P**	**UA**
1	17.500	14.000	15	253,000	15	24	10	0.6	54	12	486	92	145	3.7	9.2	2.9	4.7
3	13.600	10.880	13.2	166.000	21.9	57.6	18	1.0	346	35	1730	1089	133	3.3	7.4	1.5	5.5
5	1.570	942	11.9	35.000	9.8	24.1	16	0.4	443	119	3003	3700	136	4.1	10.4	1.3	3.8
8	5630	1690	8.7	55.000	15.9	17.2	16	0.5	54	67	468	506	132	4.5	9.6	0.4	2.5
12	45,450	38,630	10.5	394.000	—	—	7	0.6	33	38	350	35	138	3.5	8.4	3.6	3.0
35	10.200	6630	11.8	453.000	—	—	5	0.5	18	19	147	—	136	3.7	9.7	4.2	3.5

ALT indicates alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated thromboplastine time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; Hb, hemoglobin; K, potassium; Na, sodium; P, phosphorus; Plt, platelet; PT, prothrombin time; UA, uric acid; WBC, white blood cell.

service where all patients were first accepted was pediatric intensive care unit. Then, they were hospitalized for a mean (SD) of 4.5 (2.5) days[2–10] including clinical follow-ups. Seven patients had symptoms when applied to the hospital. They were all gastrointestinal (GI) symptoms; and 3 patients had only vomiting, 1 patient had abdominal pain and vomiting, and 3 patients had diarrhea, vomiting, and abdominal pain complaints. Table 1 illustrates general characteristics of patients.

Extensive laboratory analysis was performed for all patients upon first admission. They included complete blood count, kidney, and liver function tests, lactate dehydrogenase (LDH), creatine kinase (CK), electrolytes, blood gas, and bleeding diathesis. Laboratory values upon first admission except for patient numbers 8, 10, and 14 and follow-up laboratory values except for these 3 patients were within normal ranges. Tables 2 and 3 illustrate laboratory values of patient numbers 10 and 14. Gastric lavage and activated charcoal were given to all patients. Because laboratory values disrupted during the follow-up, fresh frozen plasma and platelet suspension were given to 2 patients (cases 10, 14) in repetitive doses. Because of pancytopenia and sepsis development in case 14, the patient received treatment of broad spectrum antibiotics and granulocyte-stimulating factor (G-CSF). Intubation was not necessary for any of the cases. Multiple organ failure did not develop. Complications were not observed except for bone marrow suppression, total alopecia, and acute abdomen. All patients showed complete recovery. No mortality was seen.

DISCUSSION

Colchicine is a neutral and liposoluble alkaloid with weak anti-inflammatory activity.[2] It has potent antimicotic activity, which is caused by its binding, both reversibly and selectively, to tubulin, the microtubular protein. Toxicity occurs through the interruption of mitosis by preventing polymerization of tubulin into microtubules. Therefore, although colchicine is absorbed in all cells of the body, it most adversely affects cells with increased mitotic activity such as those in the GI tract and in the bone marrow.[4] Colchicine is rapidly absorbed from the GI tract after ingestion. Serum concentration had peak values at 0.5 to 3.0 hours after ingestion.[2] The period for the patients in the series to apply to the hospital after taking medication was 7.3 hours on average. Absorption is not significantly delayed even after an overdose.[5] It undergoes significant first pass hepatic metabolism, which primarily involves deacetylation and accounts for its relatively low systemic bioavailability, 25% to 50%.[6,7] After absorption, colchicine is rapidly distributed to all tissues, where it binds to intracellular elements. Colchicine is eliminated primarily by hepatic metabolism by the CYP 3A4 isoform of cytochrome P450, which involves deacetylation and demethylation, followed by biliary excretion.[8,9] Colchicine and its metabolites undergo significant enterohepatic recirculation.[2] Renal clearance also accounts for 10% to 20% of colchicine removal and if normal renal function exists larger fractions can be excreted in this way if a toxic amount is ingested. Increased urinary excretion also occurs in the presence of hepatic disease, because there is a reduction in the capacity for deacetylation.[4] In addition, drugs such as clarithtomycin and cyclosporin, which inhibit P-glycoprotein, can also potentiate colchicine toxicity. Inhibition of P-glycoprotein induces both increased GI absorption and decreased efflux, which leads to increased serum and intracellular colchicine concentrations.[2] None of the cases in series had additional medication use. They all took medication through oral route.

The mean elimination half-life of oral colchicine is 4.4 to 16 hours in therapeutic doses and may reach 11 to 32 hours in poisoned patients.[5] In general, the risk of colchicine poisoning is dose

TABLE 3. Laboratory Findings of Case 14

Case Number 14																
Day	WBC, /mm^3	ANC, /mm^3	Hb, g/dL	Plt, /mm^3	PT, s	aPTT, s	BUN, mg/dL	Cr, mg/dL	AST, IU/L	ALT, IU/L	LDH, IU/L	CK, mg/dL	Na, mmol/L	K	Ca	P	UA
1	30,810	20,210	15.1	301,000	20.6	39	40	0.5	368	54	3471	831	137	5	7.7	—	13
3	2110	1030	11	53,000	11.3	27.9	26	0.5	3357	646	9039	75,643	139	2.7	5.7	1.9	8.7
6	18,210	3130	10.2	27,000	10.2	25	12	0.2	451	381	2690	11,840	134	3.9	8.4	0.4	2.2
7	20,850	6740	9.2	139,000	—	—	7	0.19	152	307	—	14,781	128	3.8	9	0.2	1.2
12	51,110	32,690	8.7	497,000	—	—	5	0.2	30	55	574	116	132	4.2	10	2.4	1.9
45	5450	1700	11.2	225,000	—	—	—	—	—	—	—	—	—	—	—	—	—

ALT indicates alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated thromboplastine time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Hb, hemoglobin; Na, sodium; P, phosphorus; Plt, platelet; PT, prothrombin time; UA, uric acid; WBC, white blood cell.

dependent. However, the drug has a low therapeutic index, and there is an overlap between therapeutic and toxic doses and a high fatality rate when ingestion exceeds 0.5 mg/kg in acute cases.[10] Gastrointestinal and coagulation disorders were reported in doses less than 0.5 mg/kg, bone marrow aplasia, and a 10% mortality rate in patients ingesting 0.5 to 0.8 mg/kg in acute ingestions.[2] However, cardiogenic shock and death also occurred with doses less than 0.5 mg/kg.[11] These different pictures shown by the cases can be explained with varying dissolution rate of colchicine tablets, the pH at the absorption site, and interindividual variations in gastric emptying and enteral motility. In this study, all cases except for one were exposed to toxicity at the dose of less than 0.5 mg/kg. Dose data of 3 patients were not reached.

The clinical presentation of colchicine poisoning may be divided into 3 stages. The first stage (0-24 hour postingestion) is marked by the onset of nausea, vomiting, diarrhea, abdominal discomfort, hypovolemia, and leucocytosis. Stage 2 develops approximately 24 hour postingestion and may include multiorgan failures (bone marrow suppression, hemolytic anemia, pancytopenia, liver damage, renal failure, respiratory distress syndrome, arrhythmias, neuromuscular disturbances such as encephalopathy and brain edema, and disseminated intravascular coagulation, metabolic derangements such as metabolic acidosis, hypokalemia, hyponatremia, hypocalcemia, hypoglycemia or hyperglycemia, hypophosphatemia, myopathy secondary sepsis), often developing between 1 and 7 days after ingestion. Stage 3 is seen in patients who recover from colchicine poisoning and is manifested by transient alopecia and a rebound leucocytosis between 7 and 21 day postingestion.[8,12,13]

In population of this study, the first symptoms were GI and nausea, vomiting, and diarrhea were predominant. The 15-year-old female patient (case 8) took the medication at the dose of 0.5 mg/kg, and after 24 hours, an acute abdomen picture was developed within the follow-up. However, without the need for laparotomy, oral intake was interrupted, nasogastric was applied, and therefore, she recovered spontaneously at the end of follow-up. Hemoglobin and platelet values of the same patient decreased on the fourth day of the follow-up. However, she also recovered spontaneously without the need for additional treatment. There are acute abdomen cases, which are reported to be related to colchicine poisoning in the literature.[14,15] The point that should be emphasized especially in such cases is that colchicine poisonings can imitate acute abdomen and clinicians should have an eye out for this matter.

One of the cases in the study group (case 14) was a male case aged 3 years previously presented by Kilic et al.[16] He received 0.2 mg/kg of colchicine in subtoxic dose and admission was 24 hours after the medication intake. Initial laboratory findings were hyperuricemia, prerenal azotemia, and increase in LDH and CK levels. Pancytopenia developed on the third day of admission and a recombinant G-CSF (filgrastim) was started on the fourth day. We used filgrastim 2 days before the clinical manifestations of extramedullary hematopoiesis characterized by hepatosplenomegaly and markedly elevated leucocytosis. There are a few reports suggesting the development of extramedullary hematopoiesis after G-CSF therapy.[5] Most of cases of extramedullar hematopoiesis have enlargement of the liver and spleen as is our patient. When cases were evaluated in terms of complications, the other case was a 16-year-old patient (case 10) taking 0.88 mg/kg of colchicine for the suicidal purpose. Table 2 illustrates laboratory results of patients. The G-CSF was not given to this patient. Total alopecia and leucocytosis were observed in the third phase of the recovery period. Colchicine-induced acid-base imbalances such as metabolic acidosis, hyponatremia, hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia were reported.[17]

In previous 2 cases, prerenal azotemia and electrolyte imbalance (hypocalcemia, hypophosphatemia, hyponatremia, and hypokalemia) developed. However, no acid-base imbalance was observed. Low serum phosphate level was believed to be caused by severe GI loss rather than renal loss.[18] In addition, low serum calcium level was thought to result from directly suppressing bone resorption osteoclast.[19] Colchicine plasma concentrations may be measured by using liquid chromatography-mass spectrometry, high performance liquid chromatographic method, and radioimmunoassay. This opportunity is technically not present in our hospital and colchicine blood levels of patients were not examined. There have been no enough data related to colchicine blood level and its results in the literature.[20] When the English literature is evaluated, it was observed that most of the cases composed of adult patients. Along with the case statements regarding colchicine poisoning in cases of children, the biggest case series in the literature is from the study by Ozdemir et al[1] who assessed 23 cases of children, 15 of which had involuntary colchicine intoxication and 8 of which had suicidal colchicine poisoning within a period of 26 years. They reported that 16 cases took subtoxic dose, 3 cases took toxic dose, and 4 cases took lethal dose of colchicine. Plasma exchange was applied to 2 of the 4 cases who had lethal dose of intoxication. Three of the cases who took greater than 0.5 mg/kg of colchicine (n = 7) showed mortality.[1] In our study, 17 cases were reported in only a period of 2 years.

Treatment is symptomatic and supportive. An antidotal effect of glutamate or aspartate has been reported in animal studies.[21] An effective and lifesaving treatment with Fab fragments of anticolchicine antibodies was reported in the form of case reports and animal studies.[22] Although there is lack of evidence relying on controlled trials, gastric lavage and activated charcoal may help prevent enterohepatic recirculation of the drug.[1] Gastric lavage and activated charcoal were applied to all patients in this series. Extracorporeal elimination (eg, hemodialysis and hemoperfusion) is ineffective mainly because of the large volume of distribution of colchicine.[2]

Consequently, colchicine intoxication has a potentially high mortality rate although it is relatively scarce. Especially GI, findings may be confused with lots of other systemic diseases. An aggressive treatment including G-CSF and intensive care follow-up are absolutely necessary. Especially in regions where FMF is endemic and colchicine usage is common, colchicine poisoning must be kept in mind by clinicians.

REFERENCES

1. Ozdemir R, Bayrakci B, Teksam O. Fatal poisoning in children: acute colchicine intoxication and new treatment approaches. *Clin Toxicol (Phila)*. 2011;49:739–743.
2. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol (Phila)*. 2010;48:407–414.
3. Iosfina I, Lan J, Chin C, et al. Massive colchicine overdose with recovery. *Case Rep Nephrol Urol*. 2012;2:20–24.
4. Maxwell MJ, Muthu P, Pritty PE. Accidental colchicine overdose. A case report and literature review. *Emerg Med J*. 2002;19:265–267.
5. Rochdi M, Sabouraud A, Baud FJ, et al. Toxicokinetics of colchicine in humans: analysis of tissue, plasma and urine data in ten cases. *Hum Exp Toxicol*. 1992;11:510–516.
6. Rochdi M, Sabouraud A, Girre C, et al. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol*. 1994;46:351–354.
7. Ferron GM, Rochdi M, Jusko WJ, et al. Oral absorbtion characteristics and pharmocokinetics of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol*. 1996;36:874–883.
8. Güven AG, Bahat E, Akman S, et al. Late diagnosis of severe colchicine intoxication. *Pediatrics*. 2002;109:971–973.
9. Tateishi T, Soucek P, Caraco Y, et al. Colchicine biotransformation by human liver microsomes. Identification of CYP3A4 as the major isoform responsible for colchicine demethylation. *Biochem Pharmacol*. 1997;53:111–116.
10. Putterman C, Ben-Cherit E, Caraco Y, et al. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. *Semin Arthritis Rheum*. 1991;21:143–155.
11. Mullins ME, Carrico EA, Horowitz Z. *J Toxicol Clin Toxicol*. 2000;38:51–54.
12. Levsky ME, Miller MA, Masneri DA, et al. Colchicine exposures: the Texas experience. *South Med J*. 2008;101:480–483.
13. Folpini A, Furfori P. Colchicine toxicity-clinical features and treatment. Massive overdose case report. *Clin Toxicol*. 1995;33:71–77.
14. Komorowski AL, Rodil JM. Emergency abdominal surgery and colchicine overdose. *J Emerg Trauma Shock*. 2012;5:342–343.
15. Blackham RE, Little M, Baker S, et al. Unsuspected colchicine overdose in a female patient presenting as an acute abdomen. *Anaesth Intensive Care*. 2007;35:437–439.
16. Kilic SC, Alaygut D, Unal E, et al. Acute colchicine intoxication complicated with extramedullary hematopoiesis due to filgrastim in a child. *J Pediatr Hematol Oncol*. 2013;36:e460–e462.
17. Huang WH, Hsu CW, Yu CC. Colchicine overdose-induced acute renal failure and electrolyte imbalance. *Ren Fail*. 2007;29:367–370.
18. Hood RL. Colchicine poisoning. *J Emerg Med*. 1994;12:171–177.
19. Heath DA, Palmer JS, Aurbach GD. The hypocalcemic action of colchicine. *Endocrinology*. 1972;90:1589–1593.
20. Wasserscheid K, Backendorf A, Michna D, et al. Long-term outcome after suicidal colchicine intoxication in a 14-year-old girl: case report and review of literature. *Pediatr Emerg Care*. 2013;29:89–92.
21. Ben-Cherit E, Levy M. Colchicine: 1998 update. *Semin Arthritis Rheum*. 1998;28:48–59.
22. Baud FJ, Sabouraud A, Vicaut E, et al. Treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Eng J Med*. 1995;332:642–645.