RETROSPECTIVE EVALUATION OF CASES OF COLCHICINE TOXICITY IN A PEDIATRIC INTENSIVE CARE UNIT

Halil İbrahim Yakut[1], Ganime Ayar[2], Şanlıay Şahin[2], Mutlu Uysal Yazıcı[2], Ramiz Coşkun Gündüz[2], Gökhan Kalkan[3]

[1]Zekai Tahir Burak Gynecology Training and Research Hospital, Pediatrics
[2]Ankara Child Health, Hematology Oncology Education and Research Hospital, Pediatric Intensive Care Unit, Ankara
[3]Gazi University School of Medicine, Pediatric Intensive Care Unit, Ankara

ABSTRACT

Objective: *Colchicine is a pharmacological agent used in the treatment of many rheumatic diseases such as gout, psoriasis and Familial Mediterranean Fever. Colchicine toxicity is uncommon and it is associated with high morbidity and mortality. Colchicine is known to have a narrow therapeutic index and the exact toxic dose seems to be unknown. In this article, we review factors that should be considered when prescribing colchicine, its presentation form in pharmacy and storage conditions.*

Material and Method: *We investigated children with the diagnosis of colchicine toxicity retrospectively between 2009 and 2012 in a pediatric intensive care unit.*

Results: *In this study, we found that ten children were diagnosed with colchicine toxicity in last three years. The ages varied from one to sixteen years, and the amount of colchicine was 0.11 mg/kg to 1 mg/kg. Nine patients took colchicine accidently, one was a suicide attempt. Two patients died because of toxicity.*

Conclusion: *Colchicine has a narrow therapeutic index and it is not possible to assume its precise non-toxic, toxic and lethal dose. Overdose is associated with high mortality and such drugs should be avoided from the easy reach of children.*

Keywords: *Colchicine, poisoning, pediatric intensive care unit.* ***Nobel Med 2015; 11(2): 24-28***

ÇOCUK YOĞUN BAKIM ÜNİTESİNDE KOLŞİSİN İNTOKSİKASYONU TANISI İLE TAKİP EDİLEN HASTALARIN RETROSPEKTİF DEĞERLENDİRİLMESİ

ÖZET

Amaç: Kolşisin, gut, psöriazis, çeşitli romatizmal hastalıklarda ve Ailevi Akdeniz Ateşi gibi bir çok hastalığın tedavisinde kullanılan farmakolojik bir ajandır. Kolşisin intoksikasyonu ise nadir görülmekle beraber mortalitesi ve morbiditesi yüksektir. Kolşisinin terapötik indeksi dardır ve kesin toksik doz bilinmemektedir. Bu makalede kolşisin reçete ederken dikkat edilmesi gereken durumlar, kolşisinin piyasaya sunum formu ve saklanma koşullarının gözden geçirilmesi amaçlanmıştır.

Materyal ve Metot: Bu çalışmada 2009-2012 yılları arasında çocuk yoğun bakım ünitesinde kolşisin intoksikasyonu tanısı ile izlenen on çocuk hasta retrospektif olarak incelendi.

Bulgular: Hastaların yaşları 1-16 yaş arasında olup alınan kolşisin miktarı 0,11 mg/kg ile 1 mg/kg arasında değişiyordu. Suisid amaçlı kolşisin alan 1 vaka dışında tüm hastalar kolşisini kazara içmişti. İki hasta eksitus olmuştu.

Sonuç: Kolşisinin terapötik indeksi dardır ve toksik, non-toksik veya lethal doz kesin olarak bilinmemektedir. Yüksek mortalite nedeni ile kolşisin drajeleri çocukların ulaşamayacağı yerde saklanmalıdır.

Anahtar kelimeler: Kolşisin, zehirlenme, çocuk yoğun bakım ünitesi **Nobel Med 2015; 11(2): 24-28**

INTRODUCTION

Colchicine is a herbal alkaloid that is obtained from the colchicum autumnal (glory lily and gloriosa superba). It has anti-inflammatory and anti-mitotic effects.[1-3] Colchicine is a pharmacological agent used in the treatment of rheumatic diseases such as gout, psoriasis and Familial Mediterranean Fever (FMF). The most common side effects of colchicine are nausea, vomiting, diarrhea, and abdominal pain. The therapeutic index of colchicine is restricted and differentiation of non-toxic, toxic, and lethal dose cannot be determined precisely.[2]

MATERIAL AND METHOD

In this study, we retrospectively reviewed ten cases, which had been admitted to the Pediatric Intensive Care Unit (PICU) of Ankara Child Health, Hematology Oncology Education and Research Hospital with the diagnosis of colchicine toxicity between August 2009 and August 2012. Age, gender, symptoms at admission, PRISM III scores, need for mechanical ventilation, length of stay in the PICU, laboratory parameters and complications were recorded. P-MODS criteria were evaluated according to organ involvement. Statistical analysis was performed using the Statistical Package for Social Sciences, version 20 (SPSS, Inc., Chicago, IL). Age and length of stay in the PICU were calculated as means and standard deviations. The data was evaluated using the non-parametric Spearman's Correlation test. $p<0.05$ was considered statistically significant. Demographic data are investigated and clinical features and treatment results were reviewed. Local ethics committee approval for the study was taken.

RESULTS

The study included ten cases of colchicine toxicity from August 2009 to August 2012 in the Pediatric Intensive Care Unit of Ankara Child Health, Hematology Oncology Education and Research Hospital. Patients were aged from 1 to 16 years (mean age 6,1 years). Six were girls and four were boys. The average dose was 0.31 mg/kg (median: 0.20 mg/kg, min: 0.11 mg/kg-max: 1mg/kg). The average time between taking colchicine and consulting to the hospital was 16.6 hours. (median: 5.5 hours, min: 0.5 hour-max: 168 hours). Eight patients were administered gastric lavage and activated charcoal during hospital admission, while two patients were not administered any of these because they arrived too late. One patient took colchicine in a suicide attempt, nine patients took it accidently. At admission, five of the patients had symptoms. The most common symptoms were nausea and vomiting (four patients), fever (three patients) and diarrhea (three patients). With the exception of a hypotensive 16 year old patient who was referred from another hospital after seven days (he was hypotensive at admission), the others had normal physical examination findings. It was determined that three patients were using colchicine regularly for FMF but no other drugs. The demographic and clinic features of cases are summarized in Table 1.

PRISM III score was recorded mean: 4.1 (min:0, max:10), duration of hospitalization was mean: 7.1 days (min: 3, max: 27 days, median: 4.5 days). Multiorgan involvement was present in two of our cases, both of whom had cardiovascular, neurologic, hematologic, renal and hepatic involvement, both of which resulted in death. There was no statistically significant relationship between admission time and mortality ($p>0.05$, $r=0.176$) and there was also no relationship between the dosage of colchicine and mortality ($p>0.05$, $r=0.174$).

The laboratory findings of patients who survived were normal at presentation and at follow up (Table 1). One of them had slightly elevated protrombin time level, which improved to normal levels after administration of vitamin K and fresh frozen plasma (Case 1, Table 1).

Echocardiography was performed in 3 of our patients. Two cases were found to have minimal mitral regurgitation, and the other had minimal mitral regurgitation and first degree tricuspid regurgitation and with decreased left ventricular systolic function (EF: %65). Control echocardiography findings were normal.

Three of our patients was on colchicine treatment orally for FMF. Two of these patients died. One was using the drug regularly for two years and the other for 10 years. The third case was using colchicine for 3 months at dose of 0.5mg/kg. Gastric lavage and activated charcoal was administered in 6 hours after taking the medicine. He was discharged with no complaints after 7 days of hospitalization.

A 5-year-old male patient who died (see case 2) was taking colchicine 1 mg/day for two year because of FMF, and he was taken to his local hospital by his mother when she realized 40 tablets (20 mg) had been taken from the box. Gastric lavage was performed and he was given activated charcoal in first 30 minutes. The patient was then referred to our hospital and his treatment continued with repeated doses of active charcoal. At admission to PICU, he had symptoms of fever, nausea and diarrhea. On the second day, the general condition of the patient

Table 1: Patients laboratory results for intensive care unit admission

	Case 1	Case 2	Case 3	Case 5	Case 7	Case 8	Case 9	Case 10
PH	7.48	7.42	7.40	7.40	7.46	7.41	7.42	7.44
PCO_2 (mmHg)	38	42	25	36	39	34	31	33
Lactate (mmol/L)	1.8	1.5	1.2	1.3	1.5	1.2	1.5	1
BUN (mg/dl)	33	27	23	26	21	26	19	28
Creatinine (mg/dl)	0,3	0,4	0,3	0,3	0,2	0,3	0,2	0,3
ALT (IU/L)	15	15	22	37	18	12	17	14
T. Bil (mg/dl)	0.22	0.33	0.26	0.17	0.20	0.47	0.40	0.36
K (mmol/L)	4.3	3.6	3.6	4.3	4.4	3.6	4.2	4.1
LDH (IU/L)	759	487	490	560	731	524	537	571
PT (sec) (N:12-17)	16-26-16	14	17	16	15	17	16	15
PTT (sec) (N:25-38)	38-38-34	39	38	29	31	26	38	41
INR	1.3-1.9-1.3	0.9	1.4	1	1	1.4	1.3	1.2
WBC (K/µL)	10.6	7.2	7.4	5.4	13.6	10	9.2	14.8
Plt (K/µL)	455	216	397	261	274	356	245	470

PH: Acidity, **PCO_2:** parsial corbondioxide pressure, **BUN:** blood urea nitrogen, **ALT:** alanine aminotransferase, **T. Bil:** total billirubin, **K:** potassium, **LDH:** lactic dehydrogenase, **PT:** prothrombin time, **PTT:** partial thromboplastin time, **INR:** international normalized ratio, **WBC:** white blood cell, **Plt:** platelet

deteriorated rapidly and he was intubated and mechanically ventilated. Despite supportive care he died at 5th day of hospitalization.

The second death was in a 16 year old who had been using colchicine for 10 years for treatment of FMF (see Case 4, Table 2). She took colchicine every hour (16 tablets in two days, (8 mg/2 days) after complaints of fever and diarrhea. On the third day, she consulted another clinic, was hospitalized and there she continued to take colchicine for 7 days (1 mg/day).

At this point, hypotension was detected and echo is performed. Left ventricular systolic impairment was identified and she was referred to our hospital. Her high fever and hypotension continued and she was admitted to PICU. Sepsis could not be ruled out so antibiotics were administered and supportive treatment was applied. She had respiratory failure and was intubated and mechanically ventilated. Shock and multiorgan deficiency ensued, requiring plasmapheresis and hemodialysis. She died due to multiorgan failure on day 27. The patient took colchicine at dosage of 0.14 mg/kg, but she continued to take the drug at a treatment dose so actual amount of colchicine she took remained unknown. Summary of the patients characteristics is shown in Table 3.

DISCUSSION

Colchicine is an alkaloid which dissolves in oil and is absorbed quickly through the gastrointestinal system. It reaches "peak" plasma concentration 30-120 minutes after oral intake. It diffuses widely to the tissue and binds to intracellular elements. Binding to tubulin into the cell inhibits microtubul polymerization, and therefore mitosis.[2] Colchicine stops mitosis in the metaphase. Breaking the cellular functions, phagocytosis and ameoboid movement, it demonstrates an anti-inflammatory effect.[4,5]

Symptoms of colchicine poisoning includes 3 phases. Phase 1 starts within hours of ingestion, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, stomach ache, anorexia, hypovolemia, electrolyte imbalance and peripheral leucocytosis can be seen. Phase 2 starts after 24-72 hours from ingestion. In this phase, hematological changes such as bone marrow hypoplasia, serious leucopenia, and thrombocytopenia can be seen frequently.

Cardiovascular collapse, cardiac arrythmias, respiratory distress, hypoxia, pulmonary edema, acute respiratory distress syndrome, oliguria, renal deficiency, rhabdomyolisis, electrolyte imbalance, metabolic acidosis, changes in mental status, seizure and peripheral neuropathy can be seen. In the 3rd phase (8th-10th days after medication is taken) healing symptoms of bone marrow (rebound leucocytosis) is observed. Returning alopecia is expected later.[1,3,6,7] Hematological findings can occur in all phases.

Although it is stated that toxicity strength and its mortality is directly proportional, gastrointestinal symptoms and coagulation distress can be seen even under 0.5 mg/kg colchicines after oral intake, so that between 0.5-0.8 mg/kg doses oral colchicine intake can cause serious poisoning and 10-50% of them are mortal, when taken over 0.8 mg/kg dose cardiac collapse and respiratory distress can be seen

and 100% of them are mortal.[8] It is understood that toxic, nontoxic, or lethal doses cannot be precisely determined.[2]

The amount of colchicine intake and severity of clinical findings are not directly proportional. Crucial poisoning was seen even with 0.22 mg/kg oral colchicine.[3] The literature states that 0.5 mg/kg can be toxic or fatal, furthermore, intravenous doses implemented for treatment can cause death.[9-11] Drugs such as clarithromycin, erythromycin, cetoconazole, cyclosporine, as well as natural grapefruit juice may increase colchicine concentration and so low colchicine doses may cause toxicity as well.[2] Furthermore, there are cases in the literature that are not fatal after the consumption of colchicine at a dosage of greater than 0.8 mg/kg.[12]

The time elapsed between colchicine intake and admission to the hospital is reported to be related to mortality.[13] Furthermore, concurrent drugs also effects mortality. The cells that are exposed to the drug are more sensitive to its effects; therefore, the patients who take maintenance treatment doses have a greater risk for toxicity.[14] Our two patients who died were found to have taken colcichine regularly at a dose of 1 mg/day.

The treatment of colchicine toxicity is generally supportive therapy. The monitoring of the patient must be done perfectly. Early using diuretic (furosemid) and gastric lavage can be life-saving. For binding the medications kept in the gastrointestinal system, activated charcoal can be used. Gastric lavage and emetics are indicated because even if a little colchicine is removed, it can affect the severity of toxicity and prognosis.

The use of activated charcoal dusts repeatedly can be beneficial because of enterohepatic recirculation of colchicine. As colchicine diffuses quickly in tissues and has high affinity for intracellular binding areas, it cannot be removed by hemodialysis and hemoperfusion after absorption.[2,15] Nevertheless, in a study published by Ozdemir et. al, it was stated that the plasma exchange can be beneficial for the patients.[16] Colchicine specific Fab fragments can be life-saving but it is expensive and not widely used.[3,17]

Although colchicine toxicity is reported in patients who commit suicide, it is usually seen to evolve accidently among children.[13,16,18,19] In Turkey, where drugs cannot be kept in lockers that children cannot reach; colchicine is sold as 0.5 mg coloured blister packages as unique form. This image draws the attention of children and probably causes it to be perceived as sugar. This might be the cause of its accidental intake in small children. Therefore, drugs such as colchicine, with high mortality and morbidity, should be presented in packages which cannot be easily opened with a safe cover system boxes and kept in lockers.

Table 2: Other patients (died) laboratory results

	CASE 4			CASE 6		
	1. day	5. day	27. day	1. day	3. day	5. day
PH	7.47	7.4	7.4	7.38	7.29	7.27
PCO_2 (mmHg)	33	40	38	45	80	49
Lactate (mmol/L)	1.6	1.1	12.4	1	3.2	10.2
BUN (mg/dl)	17	17.6	2.8	33	76	51
Creatinine (mg/dl)	0.5	0.4	4.9	0.4	0.4	1
ALT (IU/L)	22	15	183	74	767	1409
T. Bil (mg/dl)	0.38	0.36	6.7	0.18	2.3	2.6
K (mmol/L)	3,4	3.8	2.8	3.9	2.9	3.4
LDH (IU/L)	822	1102	7764	2617	9405	6367
PT (sec) (N:12-17)	16	17	20	28	32	17
PTT (sec) (N:25-38)	32	25	40	36	38	38
INR	1.1	1.1	1.4	2.1	2.4	1.2
WBC (K/µL)	25200	22000	800	15100	1500	200
Plt (K/µL)	217000	350000	46000	277000	46000	31000
CRP (mg/dl) (N:0-8)	3	21	2.2	2.5	12.6	28.7

PH: Acidity, **PCO_2**: parsial corbondioxide pressure, **BUN:** blood urea nitrogen, **ALT:** alanine aminotransferase, **T. Bil:** total billirubin, **K:** potassium, **LDH:** lactic dehydrogenase, **PT:** prothrombin time, **PTT:** partial thromboplastin time, **INR:** international normalized ratio, **WBC:** white blood cell, **Plt**: platelet

Table 3. Patient summary

CASE	Age (year)	Sex	Colchicine dosage (mg/kg)	Admission duration (day)	FMF History	MOD	Exitus
Case 1	4	F	0.55	6	_	_	_
Case 2	2	M	0.2	3	_	_	_
Case 3	6	F	0.11	3	_	_	_
Case 4	16	F	0.14	27	+	+	+
Case 5	7	F	0.38	3	_	_	_
Case 6	5	M	1	5	+	+	+
Case 7	1	M	0.15	9	_	_	_
Case 8	15	F	0.21	4	_	_	_
Case 9	2	F	0.33	7	+	_	_
Case 10	3	M	0.12	4	_	_	_

F: Female **M:** male **MOD**: multiorgan deficiency

CONCLUSION

A relationship with dose, time elapsed to hospital admission, previous use and foods eaten was observed with morbidity and mortality toxicity. Death is generally observed as a result of multiorgan failure. When a patient who uses colchicine presents with any symptom, a careful history must be elicited. Patients with colchicine toxicity must be followed-

up in intensive care units. Optimal liquid/electrolyte treatments, hemodynamic monitoring and optimal nutrition must be administered. The most important issue is the need for not only training but also new measures and strategies to prevent children taking such a potentially toxic drug accidentally.

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C **CORRESPONDING AUTHOR:** Ganime Ayar Ankara Child Health, Hematology Oncology Education and Research Hospital, Pediatric Intensive Care Unit ganimeayar@gmail.com

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