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Colchicine Poisoning Revisited, Case Report

INTRODUCTION

Colchicine is an alkaloid of *Colchicum autumnale* (autumn crocus, meadow saffron), which is the drug of choice for treatment and prophylaxis agent for various diseases. It is recommended in preventing attacks of familial Mediterranean fever (FMF) [1], acute gouty arthritis, in the treatment of primary biliary cirrhosis [2], amyloidosis [3] and condyloma acuminata[4]. Colchicine overdose is uncommon but potentially life threatening. The consequences appear to be dose related. Overdose must be recognized early and treated appropriately to prevent multiple organ failure [5, 6]. The consequences appear to be dose related.[6] We present here a suicidal colchicine intoxication who had pancytopenia, liver enzyme elevation and cardiac enzyme elevation and discharged uneventfully.

CASE REPORT

A 26 years old suicidal female patient, having 4 years of FMF history, was brought to emergency room (ER) unconscious after taking 40 tablets of 0.5 mg colchicine. She probably vomited before she was found unconcinous at home. Activated charcoal was given after nasogastric lavage of the gastric content. O2 saturation was 89% on admission, which was controlled with face mask only. On the fourth day of her stay in ER pancytopenia, liver enzyme, troponin-T and creatinine kinase MB (CK-MB) elevations were developed, which necessitated the transfer to the intensive care unit (ICU) because of the diagnosis of colchicine induced myocardial injury.

She was cooperated and orientated, with O2 saturation of 85%. She had tachycardia with a blood pressure of 135/95 mmHg. Breathing was laboured and shallow with a respiratory rate of 38 breaths/minute. During her stay in ICU bilateral fine crackles and diffuse abdominal sensitivity were developed. Plain abdominal X-ray and USG were normal. Her blood sodium level was 130 meq/lt, so she was accepted as syndrome of inappropriate ADH and water restriction applied. EKG showed a sinus tachicardia, and echocardiography examination revealed that ejection fraction was %50 with normal chamber sizes. Whereas chest radiograph showed bilateral infiltration in the lungs.

Cardiac enzyme elevation was thought to be a transient myocardial injury due to colchicine overdose (Table 1). Body temperature was 38.9 C and parenteral antibiotic therapy, sefoperazone + sulbactam, was initiated for nosocomial pneumonia. Because of ongoing tachypnea and hypoxemia she was entubated and mechanically ventilated with sedation. Enteral feeding was started via nasojejunal feeding tube.

Trombosit counts fell down to 18.000/ul. She had vaginal bleeding and oral contraceptives as well as platelet suspension were given according to platelet counts. Then rebound thrombocytosis of 1.043.000/ul and leukocytosis of 35.000/ul were seen. She had tachycardia that necessitated addition of metoprolol to her current treatment. A rare microorganism, Acinetobacteria *baumania*,was isolated in bronchoalveolar aspirate culture and colistin was started. On the 8th day of intubation she was successfully weaned from mechanical ventilation followed with venturia mask and then just nasal oxygen. She had an episode of agitation and in delirium state, although her oxygen saturation was normal, so i.v. haloperidol was given to control the patient. Subsequent psychiatry consultation was made and olanzapine was started.

Cardiac markers turned to normal and BNP fell to 696. She had partial hair loss due to late effects of colchicine. Antibiotics were used for 10 days and then body temperature turned to normal. Her mood was better so she was discharged at day 20 with olanzapine and oral contraceptive medication. She had elevated liver function tests at the time of discharge, at the control visit after one month LFTs were all normal and patient was doing well.

Table 1: Laboratory values of the patient at the admission and during her stay in the ICU. All of the abnormal laboratory values returned to normal after 2 months of admission. (Abnormal values are written in bold characters. BNP: Brain Natriuretic Peptide, N/A: These tests were not studied at the follow up)

Days/ Laboratory Values (Reference Range)	1st	3rd	7th	12th	20th	50th
Hb(11.7-15.5gr/dL)	**10.1**	**10.8**	**9.7**	**11.3**	**10.3**	11.5
WBC (4.1-11.2 x 10^3/μL)	**3.3**	**3.2**	**19.7**	**37.2**	**21**	5.2
Plt (159-388x10^3/μL)	180	**18**	**246**	**1127**	**478**	165
ALT (0-33 U/L)	**48**	**48**	**302**	**465**	**78**	22
AST (0-31 U/L)	**110**	**63**	**310**	**189**	27	18
GGT (0-33 U/L)	**69**	**64**	**409**	**377**	**106**	32
ALP (0-104 U/L)	84	56	**195**	**194**	97	91
CKMB (0-2.88 ng/mL)	**4.25**	**7.27**	**5.35**			N/A
Myoglobin (25-51 ng/mL)	**164**	**869**	**62.7**			N/A
Troponin T (0-0.1 ng/mL)	**0.189**	**0.172**	<0.01			N/A
BNP (0-100 pg/mL)	**2122**		696			N/A

DICCUSSION

Colchicine is a naturally occurring alkaloid with weak anti-inflammatory activity. Colchicine has potent antimitotic activity, which is caused by its binding, both reversibly and selectively to microtubules causing metaphase arrest and preventing cell functions, such as degranulation, chemotaxis, and mitosis [5]. The most effected organs are those that have a high rate of cell turnover such as gastrointestinal tract and bone marrow [7]. Mitosis blockade accounts for diarrhea, bone marrow depression, and alopecia.

Colchicine is rapidly absorbed due to its liposolubility after oral administration, probably from the jejunum and ileum. It undergoes significant first pass hepatic metabolism, and its metabolites undergo enterohepatic circulation [8].

The extended time period during which the gastrointestinal mucosal cells are exposed to colchicine may explain the prominence of the gastrointestinal symptoms of toxicity. Renal clearance also accounts for 10%–20% of colchicine removal. Increased urinary excretion occurs in the presence of colchicine overdose and in hepatic diseases. If renal and hepatic diseases coexist the possibility of toxicity greatly increases [9]. After oral ingestion time to peak concentration is 0.5 to 2.0 hours, volume of distribution is 2.2 L/kg BW [10] Mean half life for eliminaton is 9 to 16 hours in pharmacological conditions and may prolong up to 10 days with toxic doses. The severity and mortality is usually related to the dose ingested [9-11].

The severity and mortality rate of the poisoning is usually related to the dose ingested [11].

First symptoms of acute toxicity occur within the first 24 hours of ingestion and include nausea, vomiting, diarrhea, and abdominal pain. Multiorgan failure develops after 24 to 72 hours after ingestion. Bone marrow depression, hemolytic anemia, liver damage, renal failure, respiratory distress syndrome, arrhythmias, neuromuscular disturbances (myopathy, proximal weakness, dysthesia, diminished deep tendon reflexes, paralysis) and disseminated intravascular coagulation can be detected in the second stage [8]. Hyponatremia, hypocalcemia, and metabolic acidosis can occur.

Overdose with colchicine is uncommon. It exhibits a low therapeutic index although there is great variation in the dose required for significant morbidity. At doses of <0.5 mg/kg minor toxicity develops. Although, in this case colchicine dose was below 0.5 mg/kg, she developed signs of severe toxicity. At 0.5-0.8 mg/kg dose major toxicity develops and %10 mortality is seen. Doses greater than 0.8 mg/kg may cause death due to cardiogenic shock in 72 hours [12, 13]. But there is not any clear cut separation between non-toxic, toxic or lethal doses of colchicine. Overdose with colchicine constitutes a toxicological emergency and rapid intervention is required.

Stapczynski et.al. has divided colchicine toxicity into three characteristic phases [14]. Phase one; first symptoms of acute toxicity occur within the first 24 hours of ingestion and include nausea, vomiting, diarrhea, and abdominal pain. Phase two; Multiorgan failure develops after 24 to 72 hours after ingestion. Bone marrow depression, hemolytic anemia, liver damage, renal failure, respiratory distress syndrome, arrhythmias, neuromuscular disturbances and disseminated intravascular coagulation can be detected [8]. Mortality in this phase is usually due to respiratory depression and cardiovascular collapse. After 10 days, signs of bone marrow recovery are seen such as rebound

leukocytosis and thrombocytosis, which is phase three. After 12 days reversible alopecia can be seen. Cells exposed to colchicine before, as in this case, are more sensitive to its effects, so people taking maintenance treatment with colchicine have more risk for intoxication [14, 15].

Therapy for colchicine toxicity is supportive, as there is no approved antidote available. However, successful treatment with anticolchicine antibodies were reported [16, 17]. Treatment for severe overdose includes gastric lavage and activated charcoal to decrease absorption. Due to colchicine's high volume of distribution and tissue binding, forced diuresis, peritoneal dialysis, hemodialysis, charcoal hemoperfusion, or exchange transfusion is not effective. Supportive care includes correcting dehydration via fluid replacement and instituting other measures to prevent or treat shock. Antibiotics can be used to treat fever, leukopenia and sepsis. Atropine can be used to correct bradycardia. For respiratory distress, endotracheal intubation, administration of oxygen, and assisted respiration may be required. Treatment for bone marrow suppression and coagulation defects includes Vitamin K, fresh frozen plasma, and platelet and red blood cell transfusions. Prolonged observation is recommended because the most severe toxic effects generally do not appear until 24 hour after taking overdose [9].

An effective and life saving treatment with Fab fragments of anticolchicine antibodies was reported in cardiovascular failure [16]. Their mechanism of action is that specific Fab fragments binding to the target drug allow redistribution into the intravascular compartment and thus the removal of substantial amounts from peripheral sites, which is very similar to action on the digoxin toxicity [17]. There is a high affinity between the Fab fragment and colchicine and this acts to prevent the drug returning to these peripheral binding sites [16].

CONCLUSION

Overdose with colchicine is associated with a high mortality rate secondary to rapidly progressive multiorgan failure therefore, it is important that the potential dangers of this drug are recognized by clinicians and that patients are given an understandable explanation of its side effects. There must be a careful watch to avoid unintentional overdoses of tablets prescribed. Colchicine intoxication cases should be hospitalized independent of the clinical status, which may be deteriorated rapidly. These cases should be monitored in intensive care units with appropriate fluid and electrolyte replacement, hemodynamic monitorization of respiratory and circulatory functions.

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ABSTRACT

Colchicine is a unique drug that is effective in treatment of several diseases. It is a safe drug when used according to established therapeutic guidelines. Overdose is uncommon but may causes serious systemic effects. Overdose must therefore be recognized early and treated appropriately. Intentional overdose is rarely encountered. We present here a 26 years old suicidal female who was observed in intensive care unit after ingestion of 40 tablets of 0.5 mg colchicine. We would like to recall the clinical features, management options and outcomes of colchicine intoxication.

Key Words: Colchicine overdose, intoxication, management, clinical features