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The etiology and autopsy findings in Colchicine intoxication-related deaths

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Abstract
Colchicine is a drug which has a very narrow therapeutic range. This drug has been commonly used for Familial Mediterranean Fever (FMF), Behçet's disease, gout arthritis and acute pseudo gout attacks. In this study, the investigation reports and autopsy reports written by the Council of Forensic Medicine of Ankara between the years 2010-2014 were retrospectively analyzed to find out presence in the cases related to colchicine. Six cases were identified as colchicine intoxication, while three of them used colchicine for medical purpose. In four cases, colchicine was found to have been used for suicidal purpose. Among these four cases, two used colchicine for treatment. In all of our cases, colchicine was detected in bile specimen. Alveolar pulmonary edema and petechial hemorrhage were observed in the lung in all cases. Colchicine was detected in blood in four of the cases. In two cases, the concentration was found to be in therapeutic ranges (0,012 mg/L and 0,018 mg/L), while the other two, in lethal levels (0.099 mg/L and 0,264 mg/L). The most frequent histopathological finding is alveolar pulmonary edema in colchicine intoxication autopsies. Colchicine is widely used alkaloid drugs with narrow therapeutic ranges. More than 0.8 mg / kg in the acute high dose has usually fatal effects. The deaths resulted from colchicine intoxication are mainly suicide-oriented. Similar to other suicides with medicines, they are common among women. In our cases, colchicine was used for intention of suicide in four incidents (66, 66%).

Keywords: Autopsy, death, suicide, drug, colchicine, intoxication, forensic medicine, accident

Introduction

Colchicine, a drug derived from a plant named Colchicum autumnale, is a well-known alkaloid for long years. A subtype of this plant, Colchicum speciosum Steven, is particularly prevalent in the Eastern Black Sea costs. This drug is commonly used for Familial Mediterranean Fever (FMF), the Behçet's disease, the Gout Arthritis and acute pseudogout attacks. The underlying mechanism of anti-inflammatory effect is the inhibition of the polymerization of α-β-tubulin heterodimers' microtubules, resulting as a barrier to neutrophil and monocyte chemotaxis. [1-6].

Colchicine is absorbed rapidly after oral intake, then undergoes deacetylation via liver. 10% -20% is excreted through the kidneys, while the remaining is excreted by feces. It is stable in tissues for a long time, mostly more than 10 days. It accumulates in bone marrow, testes, lung, liver, kidney, spleen, GIS wall and leukocytes [7,8].

Colchicine is a drug which has a very narrow therapeutic range. There is no definite boundary between non-toxic, toxic and lethal doses. High acute doses more than 0.8 mg/kg usually culminate in death. The reported lowest lethal doses range from 7 to26 mg. Cytochrome P450 3A4 (CYP3A4) inhibitors such as clarithromycin, erythromycin, ketoconazole, and P-glycoprotein inhibitors increase the concentration of colchicine [9-12] The first toxic symptoms of colchicine intake at high doses are usually abdominal pain, diarrhea, nausea and vomiting. Tachypnea, electrolyte disorders, hypovolemia, hematologic effects, cardiac symptoms, kidney and liver failure can occur following these symptoms. The cause of death is usually multiple organ failure and sepsis [13,14].

In this study, based on the autopsy results, the main target is to describe the characteristics and statistical findings of colchicine intoxication. Emphasizing the most frequent symptoms in severe cases is considered to be important for the clinical diagnosis of colchicine intoxication cases beyond toxicological analyses in emergency services.

Materials and Methods

In this study, the autopsy reports between 2010- 2014 of the Council of Forensic Medicine of Ankara were analyzed retrospectively. Additionally corpse examination reports and prosecution investigation files were examined. Age, gender, physical properties, medical history, colchicine levels and histopathological findings were all evaluated as descriptive characteristics.

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Results

Data on colchicine intoxication cases were analyzed retrospectively. General data on the cases are presented in Table-1. All cases had a treatment in hospital at least 2 days. The age range of the cases consisting one man and five women is 9-28 and the average age is 17±8.5.

Three of the cases used colchicine for medical purpose while the others have no colchicine-related diseases. At first sight, it is thought that all of the six cases must have had the intake for suicidal purpose. But, it was later understood through the examination of the investigation reports that four of the cases were suicide and the other two were accidentally intake.

It was also understood that one of these two cases had used her mothers' FMF drug for stomach ache and the other who had renal failure had accidentally used high dose of it.

Alveolar pulmonary edema and petechial hemorrhage was observed in the lungs in all cases. Petechial hemorrhage under the scalp in three cases, petechial hemorrhage under the skin in two cases, emphysematous changings in the lungs in two cases, intraalveolar hemorrhage in the lungs in three cases, petechial hemorrhage in the heart in one case, ischemia in the heart in one case and coronary artery intimal thickness in two cases were observed (Table 2).

Discussion

Colchicine is an alkaloid drug which is widely used and which has a narrow therapeutic range. A 0.8 mg/kg and a higher dose of it have fatal effects. The deaths from colchicine intoxication are mainly suicide-oriented. Similar to other suicides with medicines, they are common among women [15]. In our cases, colchicine was used for intention of suicide in 4 (66.66%) incidents.

The relationship between the blood colchicine levels and clinical findings are not clear. Furthermore, even if taken in very large doses, it may not always be detected in the blood [16,17]. Colchicine also enters enterohepatic circulation before entering the bile and feces. Therefore, the bile is the main source in the determination of colchicine. In all of our cases, colchicine was found in the bile.

The therapeutic range of colchicine is 0.0003-0.030 mg/L in the blood. The lethal blood concentration is between 0.021 to 0.25 mg/L [18]. In four of our cases, colchicine levels were detected in the blood.

Considering the fact that all of the cases were hospitalized for at least two days, 2 of them was within the therapeutic range (0,012 mg/L and 0,018 mg/L) two of them at lethal concentration (0.099 mg/L and 0,264 mg/L), respectively.

In our study, it was evaluated that the differences for colchicine except from lethal concentration was due to medical treatment and follow-up process and time. In addition, it should not be forgotten that the individuals using colchicine for treatment may be more sensitive to the drug and they carry a higher risk of acute toxicity [5,19].

Clinical symptoms of colchicine toxicity consist of three stages. Within the first 24 hours following the intake of high doses, gastrointestinal symptoms such as nausea, vomiting, and abdominal pain occur. The second stage takes place between 24 and 72 hours, and multiorgan failure is prominent. During this phase, changes in mental status, respiratory failure, interstitial and alveolar edema, cardiac failure, arrhythmia, hypotension and metabolic acidosis can be observed. Oliguric renal failure and DIC (disseminated intravascular coagulation) may also occur.

83.3 % of our cases were dead in this second period of colchicine intoxication. The third stage occurs in 7-10 days after the intake and patients are expected to recover without sequel at this stage [20,21].

One of our cases who used colchicine for FMF treatment was dead at the 3rd stage of colchicine intoxication. She had consulted to hospital with nausea and vomiting and had been given treatment for six days and plasmopheresis was also carried out. The other five cases were hospitalized for at least two days. ARDS was foreseen as the reason of death for all the cases. It was evaluated that plasmopheresis cannot be efficient for treatment. Because hemodialysis and plasma exchange cannot be effective at colchicine intoxication, since colchicine rapidly disperses into tissues and is engaged into cells with high affinity [19,22,23].

The alveolar pulmonary edema is frequently observed in the histopathological examinations of the deaths due to colchicine intoxication. This situation can arise from direct the toxic effect of colchicine on microtubulles of pneumocyte and inhibition of surfactan production [24-25]. Also, it can occur as a result of decreasing oncotic pressure due to multiorgan failure. Besides, it can be observed after leakage into alveoles from pulmoner capillar owing to cardiac failure. In all of our cases, alveolar pulmonary edema was observed (Table 2).

Table 1. General data of cases

Case	Age	Gender	Disease	Colchicine Level	Days*
1	9	Female	FMF	Blood: 0,012 mg/L, Bile and Urine: +	6
2	14	Female	None	Bile and Urine: +	2
3	20	Female	Behçet's	Blood:0,018 mg/L, Bile and Urine +	2
4	15	Female	None	Blood:0,099 mg/L, Bile and Urine +	2
5	16	Female	FMF	Blood:0,264 mg/L, Bile and Urine:+	2
6	28	Male	None	Bile: +	2

* Duration of follow-up and treatment after intoxication

Table 2. Microscopic and macroscopic findings of cases

Findings	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Petechial hemorrhage under the scalp	Yes	No	No	No	Yes	Yes
Petechial hemorrhage under the skin	Yes	No	No	No	No	Yes
Petechial hemorrhage in lung	Yes	Yes	Yes	Yes	Yes	Yes
Alveolar pulmonary edema in lung	Yes	Yes	Yes	Yes	Yes	Yes
Emphysematous changings in lung	No	No	Yes	No	No	Yes
Intraalveolar hemorrhage in lungs	Yes	No	No	No	Yes	Yes
Petechial hemorrhage in heart	No	No	Yes	No	No	No
Ischemia in the heart	Yes	No	No	No	No	No
Coronary artery intimal thickness	No	Yes	Yes	No	No	No

It was thought that our cases obtained the drug because of the fact that either they or their family members used it. For this reason, all drugs should be kept out of easy reach. Furthermore, at the beginning of the colchicine treatment, the age of the patient, his educational status and the level of the awareness of the parents should all be examined well.

Conclusion

As a result; most of the colchicine poisoning is due to suicides. On the other hand, the possibility of accidentally intake of high doses during treatment should be kept in mind due to the narrow therapeutic range of colchicine [26,27].

The most frequent histopathological finding is alveolar pulmonary edema in colchicine intoxication autopsies. Although the colchicine levels in post mortem blood samples are important, it should be remembered that the values can be within the normal range in the blood analysis due to the rate of elimination. In this case, urine and the bile should be investigated. Information on medical history and psychosocial situation of the person are also of great importance for forensic and medical evaluation of the case correctly.

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