Severe Theophylline Intoxication, Rhabdomyolysis, Disseminated Intravascular Coagulopathy And Death: Case Report

Şiddetli Teofilin Zehirlenmesi, Rabdomiyoliz, Dissemine İntravasküler Koagülopati ve Ölüm: Olgu Sunumu

Yunsur Çevik[1], Cemil Kavalcı[2], Murat Daş[1], Seval İzdeş[3]

[1]Sağlık Bakanlığı, Atatürk Eğitim Ve Araştırma Hastanesi, Acil Tıp Kliniği, Ankara, Türkiye
[2]Trakya Üniversitesi, Tıp Fakültesi, Acil Tıp Ana Bilim Dalı, Edirne, Türkiye
[3]Sağlık Bakanlığı, Atatürk Eğitim Ve Araştırma Hastanesi, Anestezi Kliniği, Ankara, Türkiye

ABSTRACT

Background: Severe intoxication which is induced by theophylline which is used in the treatments of broncospastic pulmonary diseases is quite rare. In literature, there is limited number of rhabdomyolysis cases induced by theophylline toxicity. The statement of disseminated intravascular coagulopathy which develops after theophylline intoxication has not been detected in the literature.

Case report: We present the case which has resulted with rhabdomyolysis, disseminated intravascular coagulopathy and death after overdose theophylline intake of a female patient at the age of seventeen.

Conclusion: The overdose theophylline intake can cause quite mortal toxicity as a result of negative effects it causes on cardiovascular, neurological and metabolic systems. It should not be forgotten that in severe intoxications, rhabdomyolysis and disseminated intravascular coagulopathy can be developed, although the patient's condition is good, she/he should be monitored with close monitorization under intensive care conditions.

Key words: Emergency department, Disseminated intravascular coagulopathy, Theophylline

ÖZET

Giriş: Bronkospastik akciğer hastalıklarının tedavisinde kullanılan teofiline bağlı şiddetli zehirlenme oldukça nadirdir. Literatürde teofilin toksisitesine bağlı sınırlı sayıda rabdomiyoliz olgusu mevcuttur. Teofilin zehirlenmesi sonrası gelişen dissemine intravasküler koagülopati tablosu literatürde saptanmamıştır.

Olgu: On yedi yaşında bayan hastada yüksek doz teofilin alımı sonrası, rabdomiyoliz, dissemine intravasküler koagülopati ve ölümle sonuçlanan olguyu sunuyoruz.

Sonuç: Yüksek doz teofilin alımı, kardiyovasküler, nörolojik ve metabolik sistemler üzerinde meydana getirdiği olumsuz etkiler sonucu oldukça ölümcül seyreden toksisiteye neden olabilmektedir. Şiddetli zehirlenmelerde rabdomiyoliz ve dissemine intravasküler koagülopati gelişebileceği unutulmamalı, hastanın durumu iyi olsa bile yoğun bakım şartlarında yakın monitorizasyonla takip edilmelidir

Anahtar Kelimeler: Acil servis, Dissemine intravasküler koagülopati, Teofilin

İletişim Adresi ve Sorumlu Yazar:
Yunsur ÇEVİK
Ankara Atatürk Eğitim ve Araştırma Hastanesi Acil Servis Bilkent 06800 Ankara – Türkiye
E-mail: yunsurcevik@yahoo.com
Telefon: 0 532 301 72 24

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INTRODUCTION

Theophylline (1,3-dimethylxanthine) is widely used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. The therapeutic range of theophylline is very narrow; most patients begin to experience adverse effects at concentrations >20 µg/ml [1]. Acute theophylline poisoning occurs in conscious or accidental overdose intakes. Severe toxicity from theophylline overdose is a relatively rare event. It has a potential to form undesired effects on especially cardiovascular system, central nervous system, gastrointestinal system and metabolic system. The death frequently happens due to the hemodynamic and neurological effects [2]. In this case presentation, we have aimed to present the statement of rhabdomyolysis and disseminated intravascular coagulopathy (DIC) developed after overdose theophylline intake with suicidal aim.

CASE REPORT

The female patient at the age of seventeen was applied gastric lavage in a district state hospital at the 2nd hour of approximately 52.5 grams of slow release theophylline (talotren ®) intake with suicidal aim and was given 50 grams of activated charcoal and was sent to the emergency department of our hospital. At the first inspection we realized in the emergency department, the patient's general condition was bad, she was inclined to sleep, she had headache and nausea-vomiting. Her blood pressure was 100/68 mmHg, her heart rate: 124 beats/minute, her number of respiration was: 25/minute. Her blood theophylline level was measured as 56.2 µg/ml (~311 umol/L), glucose was as 342 mg/dl, potassium (K) was as 2.1 mmol/L. In the emergency department, 0.9 %NaCl liquid infusion, 50 grams of repeating dose of activated charcoal once in every two hours (4 doses), 10 mg metaclopramide (metpamid®) and 50 mEq sodium bicarbonate was given via intravenous (iv). To the patient in whose electrocardiography (ECG) supraventricular tachycardia was determined totally 15 mg metoprolol (Beloc®) was given via iv. When she had generalized tonic-clonic seizure activity at the approximately 24th hour of her arrival, 5 mg diazepam (diazem®) was given via iv, seizure's stopped and was taken into intensive care unit. When the cardiopulmonary arrest was developed in the 15th minute of her taking, she was intubated and cardiopulmonary resuscitation was realized, the patient who did respond to resuscitation was taken to hemodialysis which could not be realized due to technical reasons till this period. To the patient who had frequent epileptic attack midazolam (Dormicum®) and vecuronium (norcuron®) infusion were realized. The patient whose kidney function tests were impaired and who was anuric went into dialysis for totally 7 times. On the 9th day of her acceptance to the hospital following that her hemoglobin value decreased to 6.9 g/dL, there were extensions in the values of prothrombin time (PT), activated partial thromboplastin time (aPTT) and ecchymoses were formed in her body, 2 IU AB RH(+) full blood was given, in dialysis the heparin irrigation was not realized. On the 10th day of her hospitalization the cardiac arrest was developed and when the realized CPR was not responded exitus was accepted. The metabolic parameters of the patient can be observed at *Table-1*.

***Table.1**: Metabolic Parameters of Patient*

	Normal range	Day							
		1	2	3	4	5	8	9	10
Glucose (mg/dL)	74-106	**342**	**37**	130	142	69	152	132	69
Teophylline (µg/mL)	10-20	**56.2**	ND	ND	ND	ND	ND	ND	ND
AST (U/L)	5-37	10	**2364**	**2213**	**2475**	**2022**	586	605	628
ALT (U/L)	20-65	28	**447**	**547**	**589**	**595**	364	259	169
CPK (U/L)	21-215	991	ND	ND	ND	ND	**5851**	ND	1657
Fibrinogen (mg/dL)	150-400	ND	ND	766	879	ND	**1455**	ND	ND
D-Dimer (ng/mL)	0-500	ND	ND	ND	633.13	**965.84**	ND	ND	ND
PT (sn)	10-15	13	ND	12.6	16,3	12,2	13.2	15,1	**17.2**
INR	0.85-1.15	1.1	ND	1.1	1.4	1.4	1.2	1.3	**1.5**
aPTT (sn)	22-31	25,3	ND	44	115.7	**>160**	**>160**	**>160**	**>160**
Thrombocyte (K/uL)	170-450	416	293	202	153	**104**	**63.6**	**43**	**36.4**
WBC (K/uL)	4.5-11	23.2	33.8	32.7	12.2	**1.91**	1.2	15.5	**44.2**
Hemoglobin (g/dL)	12-16	14.3	12.4	11.7	11,7	13,6	11,1	**6.9**	**6.43**
Hematocrit (%)	36-45	42.9	37.3	35.8	35,1	39,5	32,7	21.2	**18.7**
Amylase (U/L)	25-115	75	ND	ND	ND	ND	ND	ND	**822**
Lipase (U/L)	114-286	169	ND	ND	ND	163	1220	ND	**1952**
BUN (mg/dL)	10-50	35	68	**83**	65	58	77	61	**149**
Creatinin (mg/dL)	0.5-1.1	1.4	2,6	**3,7**	**3,2**	**3,1**	**4,1**	2,6	**3,4**
Na (mmol/L)	135-145	141	145,9	139,2	133	139	135	133	138,1

K (mmol/L)	3.5-5.1	**2.1**	3,9	3,4	3,6	3,4	3,5	4,1	5,6
Ca (mg/dL)	8.5-10.5	9.6	6,3	**4,8**	6,4	6,7	8.4	9,2	8
Mg (mg/dL)	1.8-2.4	ND	**3.1**	3	2.1	1.6	ND	**1.3**	1.9
P (mg/dL)	2.5-4.9	ND	**7.8**	**10**	4.5	ND	ND	ND	4.8
PH		7.417	7.509	7.331	7.681	7.554	7.405	**7.234**	**7.251**
PCO2 (mmHg)		22.1	10.3	27.4	13.9	17.3	35.1	46.3	46.5
PO2 (mmHg)		118.2	110	135	139	92	127	68.3	54.2
HCO3c (mmol/L)		**14**	**8.2**	**14.1**	**16.8**	**15.3**	21.5	18.9	19.7

ALT= alanine aminotransferase, AST= aspartate aminotransferase, CPK= creatine phosphokinase PT= prothrombin time, aPTT= activated partial thromboplastin time, WBC= white blood cell, BUN= blood urea nitrogen, Na= sodium, K= potassium, Ca= calcium, Mg= magnesium P= phosphate ND: not done

DISCUSSION

The theophylline intoxication can be seen in the acute, subacute or chronic form. As a standard, the subacute or chronic intoxication occur due to the overdose intake of a patient taking the drug or the drug clearance which decreases as a result of cardiac failure, liver disease or drug interaction. The acute intoxication frequently originates from suicidal aimed or accidental overdose intakes. The theophylline is a drug the therapeutic index of which was narrow (10-20µmg/ml). In its intoxication, it is has a potential to develop mortal, severe metabolic abnormalities [(3)]. It has negative effects on particularly cardiovascular system, central nervous system, gastrointestinal system and metabolic system. [(4)].

It is informed that the theophylline triggers beta adrenergic activity by stimulating catecholamine oscillation and this uncontrolled beta adrenergic activity is also responsible for negative effects in cardiovascular system [(5)]. Cardiovascular effects include hypotension and arrhythmias (eg, sinus tachycardia, premature ventricular complexes, atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation). Beta-blockers such as esmolol or metoprolol reduce the excessive beta stimulation that causes arrhythmias and hypokalemia, usually without inducing bronchospasm. In the case we have presented, on the 1st day, the tachycardia was developed and it was returned to its normal sinus rhythm with metoprolol.

As a result of effects of theophylline on central nervous system, agitation, headache, irritability, insomnia, tremor, myoclonia and seizure activities can be observed. The seizures generally observed over the level of 35µg/mL can frequently be in the form of generalized tonic-clonic and rarely in the form of focal motor activation [(6)]. The presented case had a tonic clonic seizure at the 24th hour after taking into emergency department and the seizure was stopped by diazepam (diazem®). As the theophylline level measured on the same day was 56.2 µg/ml, it is congruent with the literature. As the seizure activities continued on the following days, midazolam (Dormicum®) and vecuronium (norcuron®) infusions were applied. The theophylline toxicity induced seizures are generally resistant to anticonvulsive treatment. Therefore decreasing serum theophylline concentration as soon as possible should be the main aim [(6)].

Various metabolic effects have been reported with therapeutic and supratherapeutic doses of theophylline, including: hyperglycemia, hypokalemia, hypophosphatemia, hypomagnesemia, respiratory alkalosis and less commonly, metabolic acidosis. Some of these metabolic abnormalities may be secondary to increased concentrations of circulating catecholamines [(1)]. In the presented case, differently hiperfosfatemi was also determined. The hypokalaemia observed at the theophylline toxicity is dependent on enzyme inhibition. Also, the insulin and glucose increased with theophylline effect make contributions to development of hypokalemia.

Rhabdomyolysis continued with myoglobinuria and creatine phosphokinase (CPK) increase can rarely be observed in theophylline intoxication. In the literature, limited number of cases is reported [(7, 8)]. In its pathophysiology; there are increases in muscle activities, direct cytotoxic impact and intracytoplasmic calcium sequestration and generalized seizures. In the presented case the CPK value measured on the 8th day was determined as 5851 U/L. The blood urea nitrogen and creatine values increased in the patient, developed renal failure table and increased CPK levels show the rhabdomyolysis. The severe metabolic and electrolyte imbalance, acute renal failure and DIC are important complications of rhabdomyolysis [(9)]. The DIC table can also be developed as depending on various drugs and toxins. The extensions in PT, aPTT values, increases in D-Dimer values and decreases in thrombocytes, formation of bleeding induced ecchymoses generalized on body disturbs the DIC table. The highness in fibrinogen values is seen discordant with the table. But, when it is considered that the fibrinogen is an acute phase reactant, it can be interpreted that the highness is dependant on this. Other than the presented case, no theophylline toxicity incuded DIC table was determined in the literature. As there is limited number of cases as severe theophylline intoxication in the literature, among the presented cases, the highest overdose intake was observed in the case we have presented. [(1, 10, 11)].

Oral activated charcoal is a well-established therapy for treatment of theophylline intoxication. It is suggested to be given once in every 2 hours till the theophylline level decreases below 20-25 µg/mL (10). In our case also 4 doses of activated charcoal were given. Removal of theophylline from the circulation is possible with haemodialysis or charcoal haemoperfusion, because the drug has a small volume of distribution, although 50–60% is protein-bound. As such, haemodialysis is only moderately effective at removing theophylline, clearing approximately 50% of drug delivered to the dialyser. Charcoal haemoperfusion is less widely available, will not correct electrolyte disturbances sometimes seen with theophylline toxicity and is associated with bleeding complications [11]. We also applied hemodialyses to our patient for seven times.

CONCLUSION

The overdose theophylline intake can cause quite mortal toxicity as a result of negative effects it causes on cardiovascular, neurological and metabolic systems. It should not be forgotten that in severe intoxications, rhabdomyolysis and DIC table can be developed, although the patient's condition is good, she/he should be monitored with close monitorization under intensive care conditions.

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