

*Case Report*

Theophylline Overdose Causing Life Threatening Rhabdomyolysis - A Case Report

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ABSTRACT

Although the use of theophylline is replaced by inhaled beta agonists, theophylline still continues to be a legend drug used in treatment of chronic obstructive airway diseases (COPD) and bronchial asthma. Ingestion of 20-30 tablets of it can cause serious life threatening conditions as well as death. Sub acute or chronic intoxication of theophylline occur as a result of overmedication or accidental use of a drug that interferes with the metabolism of theophylline.

Key words: Theophylline, Rhabdomyolysis.

INTRODUCTION

Theophylline is a xanthine derivative chemically similar to caffeine and theobromine and is one of the common drugs used in treatment of asthma and COPD. The importance of theophylline as a therapeutic agent in the treatment of asthma has waned as the greater effectiveness of inhaled adrenoceptor agents for acute asthma and of inhaled anti-inflammatory agents for chronic asthma has been established, but the low cost of theophylline is an important advantage for economically disadvantaged patients in societies where health care resources are limited.

Because of the narrow therapeutic index of this drug, monitoring of theophylline concentrations in plasma is essential. Majority of the patients

experience unwanted symptoms at higher doses ($>20\mu\text{ml}$), ^[1] theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. The signs and symptoms of theophylline intoxication involve many different organ systems.

In this case report, we present a case of theophylline induced rhabdomyolysis and acute renal injury after a overdosing of theophylline intake with suicidal intent.

CASE REPORT

A 23 year old female patient, with a history of bronchial asthma on medications was brought to the emergency department with eight hours history of fatigue, vomiting, lower limb pain and an episode of passing

orange-brown urine two hours prior to admission. This occurred on a background of ingestion of an unknown amount of sustained release theophylline. Additional symptoms included anorexia, nausea, intermittent insomnia and palpitations. The patient denied history of syncope, seizures, fever, trauma, strenuous exercise or alcohol use.

Past medical history was suggestive of known asthmatic on long term inhaled steroids and inhaled beta agonists with oral theophylline. On examination, her vital signs were, blood pressure of 106/68mmHg, pulse rate of 124 beats per minute, respiratory rate of 30 breaths per minute, temperature of 37.4⁰C and an oxygen saturation of 99% at room air. Abnormalities on physical examination included irritability, pallor, fine resting tremor, twitching, fasciculations, reflex hyperactivity, 2/5 strength in both legs and 4/5 strength in the left arm. No other signs were found on neurological, cardio respiratory or gastrointestinal system examinations. She was immediately taken for gastric lavage and 30 grams of activated charcoal was given which was repeated till the concentrations fall below 20µg/ml.

Investigations are summarized in Table 1 which revealed deranged renal function tests, dyselectrolytemia and hyperglycemia.

Table 1. Laboratory findings at the time of admission.

Variables	Patient's Values
Theophylline (µg/mL)	56.3
Hemoglobin (g/dL)	13.4
Total leucocyte Count (/uL)	14600
Sodium (mmol/L)	125
Potassium (mmol/L)	2.1
Magnesium (mg/dL)	1.2
Calcium (mg/dL)	7.7
Posphorus (mg/dL)	3.9
Glucose (mg/dL)	218
Blood urea (mg/dL)	51
Serum creatinine (mg/dL)	1.8
Creatinine kinase (U/l)	4500
Aspartate aminotransferase (U/L)	278
Alanine aminotransferase (U/L)	208

Her arterial blood gas results revealed metabolic acidosis. Urine analysis showed myoglobinuria, a pH of 5.5, 3+ protein, 2+ blood and 2+ glucose. Electrocardiogram, chest x-ray, and Doppler ultrasound of the deep veins in the legs and ultrasonography of kidney were unremarkable.

She was managed conservatively with intravenous crystalloids and oral hydration. Electrolyte imbalances were corrected and discharged her on 7th day once the creatine kinase and kidney function returned to its normal level.

DISCUSSION

Theophylline (1,3-dimethylxanthine) is a xanthine derivative structurally related to theobromine and caffeine. It has 2 distinct actions in the airways of patients with reversible obstruction, they are smooth muscle relaxation causing bronchodilation and suppression of the response of the airways to stimuli. Some amount theophylline is also present in beverages such as tea, cocoa and coffee etc. [2]

Theophylline should only be used where there is facility to measure its blood levels are readily available because it has a narrow therapeutic window and toxic effects are related to its plasma concentrations. Improvement in pulmonary function is correlated with plasma concentration in the range of 5–20 mg/L. Anorexia, nausea, vomiting, abdominal discomfort, headache, and anxiety occur at concentrations of 15 mg/L in some patients and become common at concentrations greater than 20 mg/L. Higher levels (> 40 mg/L) may cause seizures or arrhythmias with/without the presence of warning symptoms; hence during intoxication, it is has great potential to develop severe metabolic abnormalities. [3] As mentioned in the literature, it has got negative effects particularly on cardiovascular system, central nervous

system, gastrointestinal system and metabolic system. [4]

Theophylline produces direct bronchodilation and has some anti-inflammatory actions in the airway as well. Several mechanisms have been proposed for these actions but none have been firmly established. At high concentrations, the methylxanthines can be shown in vitro to inhibit several members of the phosphodiesterase (PDE) enzyme family. Since the phosphodiesterases hydrolyze cyclic nucleotides, this inhibition results in higher concentrations of intracellular cGMP. This effect could explain the cardiac stimulation and smooth muscle relaxation produced by these drugs as well as decreased release of inflammatory mediators from mast cells. PDE4 appears to be the isoform most directly involved in the airway actions of methylxanthines. Another proposed mechanism is the inhibition of cell surface receptors for adenosine.

Various metabolic effects have been reported with therapeutic and toxic doses of theophylline which includes hyperglycemia, hypokalemia, hypomagnesemia, metabolic acidosis, respiratory alkalosis and less commonly, rhabdomyolysis. [5]

Theophylline induced rhabdomyolysis is said to occur because of stimulation of intracellular calcium stores in myocytes causing tetanic contractions leading to muscle injury. [6] Another proposed mechanism is due to muscle paralysis occurring as a result of severe hypokalaemia. [7]

In our case report, hypokalaemia may have occurred because of a number of mechanisms that includes stimulation of sodium-potassium ATPase, kaliuresis through increased adrenergic tone acting on the renal tubular system or as a side-effect of theophylline induced vomiting. [8,9]

In the present case study, she was diagnosed with rhabdomyolysis with acute

renal failure due to the elevated creatine kinase, classical triad of myalgia, weakness and myoglobinuria and worsening renal function tests. [10] Other parameters of rhabdomyolysis observed in this case included hypokalaemia, metabolic acidosis, hyperglycaemia, and hypocalcaemia. [11] Some of the other toxic effects of theophylline are highlighted in table 2.

Table 2. Some of the other toxic effects of theophylline.

• Nausea	• Tremors	• Dyselectrolytemia
• Vomiting	• Seizures	• Impaired cognition
• Irritability	• Diuresis	• Ventricular fibrillation
• Insomnia	• Tachycardia	• Dysuria
• Headache	• Tachypnea	• Gastric reflux
• Nervousness	• Arrhythmia	

The modes of treatment for theophylline poisoning are either oral or parenteral. All the cases should be managed in intensive care unit where facilities for serum theophylline measurement are available. Activated charcoal 1gm/kg body weight (upto 30gm) should be administered earliest possible and is repeated every two to four hours until the serum concentrations fall below 20µg/ml. Charcoal haemoperfusion is indicated when serum concentrations are above 60µg/ml. [12] Seizures should be rapidly terminated with intravenous sedatives, adequate oxygenation and respiratory supports are mandatory.

CONCLUSION

Theophylline is one of the common drugs used regularly in respiratory clinic. Because of the narrow therapeutic index, monitoring of theophylline concentrations in plasma is essential. Rhabdomyolysis and the associated complications have a potentially lethal course with a high morbidity and mortality. Hence early suspicion, proper diagnosis and treatment often improve the outcome substantially.

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