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Case Report

Theophylline toxicity: An old poisoning for a new generation of physicians

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ABSTRACT

A healthy 4-year-old female presented to the emergency department for vomiting and diarrhea. She was diagnosed with a urinary tract infection, treated with antibiotics and anti-emetics and discharged. Within four hours, her symptoms recurred, followed by decreasing responsiveness and seizures. She had significant hypokalemia, hyperglycemia, and a combined respiratory and metabolic acidosis. A sibling then mentioned that the patient ingested their father's 200 mg sustained-release theophylline tablets the previous morning. A serum theophylline level was immediately ordered and returned $>444 \mu\text{mol/L}$. The patient was intubated and treated with activated charcoal, antiemetics, potassium and intravenous fluids. She underwent continuous renal replacement therapy and her levels declined over the next 24 hours. She was extubated on hospital day 2 and discharged without sequelae. Theophylline ingestions are rare but potentially very serious. Physicians need to know how to diagnose and treat these ingestions. Copyright © 2018 The Emergency Medicine Association of Turkey. Production and hosting by Elsevier B.V. on behalf of the Owner. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Theophylline was once frequently prescribed to acute asthma exacerbations, and ingestions were common. In 1999, the American Association of Poison Control Centers received 1641 calls regarding theophylline exposures, ten of which resulted in death.¹ An additional 65 cases resulted in major toxicity, defined as exhibiting “signs or symptoms as a result of the exposure that were life-threatening”. Such signs could include seizures, respiratory failure, and ventricular tachycardia with hypotension. By 2014, the total number of cases involving theophylline had decreased to 199 encounters, with two deaths and eight major effects.²

Theophylline citations in the medical literature similarly decreased. We conducted a MEDLINE search using the terms “theophylline” and one or more of the words “poisoning”, “overdose”, “toxicity” or “ingestion”. Between 2006 and 2016 there were

eight references (five case reports and three treatment-related articles) while in the years 1996–2005 there were 30.

We managed a case of severe theophylline toxicity in a 4-year-old with an exploratory ingestion. Though her clinical features were not atypical, she was a unique experience for her physicians. We hope that this report reminds clinicians how severe theophylline ingestions can be and how to best treat such patients.

2. Case report

A healthy 4-year-old female presented to her local emergency department (ED) at 2200 for vomiting and diarrhea that had begun several hours earlier. She was diagnosed with a urinary tract infection (UTI), treated with trimethoprim-sulfamethoxazole and ondansetron, and discharged at 0230. Within four hours, her symptoms recurred, followed by progressively decreasing responsiveness with associated new-onset, focal seizures.

She returned to the ED at 0700 and was found to be unresponsive with these vital signs: heart rate 170 beats per minute, blood pressure 82/46 mm Hg and a respiratory rate of 40 breaths per minute. She was afebrile. Laboratory test results revealed hypokalemia, hyperglycemia, elevated creatinine, and a combined

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Abbreviations

ED	emergency department
bmp	beats per minute
CRRT	continuous renal replacement therapy
SDAC	single-dose activated charcoal
SR	sustained-release
MDAC	multi-dose activated charcoal

respiratory and metabolic acidosis. Acetaminophen, salicylate, and multiple anticonvulsants were not detected (Table 1). Urine drug screening via immunoassay tests identified no substances of abuse. An electrocardiogram revealed sinus tachycardia with a rate of 161 bpm, normal axis, QRS duration of 162 milliseconds (normal < 100 milliseconds) and QTc interval of 472 milliseconds (normal < 460 milliseconds). A computed tomography of the head without contrast revealed no acute abnormalities.

During the assessment, a sibling mentioned the patient may have ingested their father's 200 mg sustained-release theophylline tablets the previous morning. A serum theophylline level was immediately ordered and returned >444 $\mu\text{mol/L}$ (therapeutic range 27.8–83 $\mu\text{mol/L}$).

The patient continued to decline clinically, and at 0800 was intubated for airway protection and respiratory failure using 5 mg etomidate and 20 mg rocuronium. Activated charcoal was subsequently administered. The patient was given lorazepam and bolused with 35 mL/kg of normal saline. A 0.5 mEq/kg dose of potassium was provided. The patient was transferred to our tertiary care pediatric hospital. En route the tachycardia persisted, and the patient had additional seizures. She was treated with more lorazepam (0.4 mg/kg total during transport), levetiracetam 30 mg/kg, and another 20 mL/kg of normal saline. The seizures subsequently resolved.

Vital signs upon arrival in the intensive care unit included a heart rate of 176 bpm, blood pressure of 94/40 mm Hg, temperature of 98.9° F, and a respiratory rate of 48 breaths per minute. Physical exam revealed a sedated, well-developed, female weighing 22 kilograms. Lungs were clear to auscultation. The abdomen was soft and non-distended. There was no clonus, hyperreflexia, or focal

Table 1
Initial laboratory test results from referring hospital.

	Patient's value	Reference range
Sodium	140 mmol/L	(135–145 mmol/L)
Potassium	2.4 mmol/L	(3.5–5.0 mmol/L)
Chloride	95 mmol/L	(98–106 mmol/L)
Bicarbonate	14 mmol/L	(18–24 mmol/L)
Blood urea nitrogen	5.36 mmol/L	(2.5–6.4 mmol/L)
Creatinine	0.097 mmol/L	(0.053–0.106 mmol/L)
Glucose	19.48 mmol/L	(3.3–6.1 mmol/L)
Calcium	2.64 mmol/L	(2.10–2.55 mmol/L)
pH (arterial)	<6.84	(7.35–7.45)
PaCO ₂	>13.5 kPa	(6.0–7.33 kPa)
PaO ₂	9.06 kPa	(4.7–6.0 kPa)
Base deficit	27.7 mmol/L	(-2.0–2.0 mmol/L)
Prothrombin time	18.3 s	(10–13 s)
Aspartate aminotransferase	1.01 $\mu\text{kat/L}$	(0–0.75 $\mu\text{kat/L}$)
Alanine aminotransferase	0.2 $\mu\text{kat/L}$	(0–0.84 $\mu\text{kat/L}$)
Acetaminophen	undetected	(66–199 $\mu\text{mol/L}$)
Salicylate	undetected	(1.1–2.2 mmol/L)
Phenytoin	undetected	(40–79 $\mu\text{mol/L}$)
Carbamazepine	undetected	(17–51 $\mu\text{mol/L}$)
Theophylline	>444 $\mu\text{mol/L}$	(27.8–83 $\mu\text{mol/L}$)
Ethyl alcohol	undetected	(<0.01 mmol/L)

deficits. Skin was warm, dry, and appropriate for the patient's ethnicity. Laboratory tests were repeated, and the patient's theophylline level remained >444 $\mu\text{mol/L}$. An electrocardiogram revealed sinus tachycardia with a rate of 166 bpm, normal axis, QRS duration of 72 milliseconds and QTc interval of 406 milliseconds.

Continuous renal replacement therapy (CRRT) was initiated and the theophylline level steadily decreased over the next 30 hours to 32.2 $\mu\text{mol/L}$, at which time CRRT was discontinued. The patient had no additional seizures or dysrhythmias. Her neurological status improved, and she was extubated on the day after admission. She was discharged with no sequelae.

3. Discussion

Theophylline, a methylxanthine similar to caffeine, was once commonly prescribed for moderate to severe asthma. Its ethylenediamine salt, aminophylline, was used intravenously in the management of bronchospasm, congestive heart failure and neonatal apnea. Theophylline use has decreased significantly since medications with more favorable risk-benefit ratios were introduced. However, it is still obtainable, particularly overseas.

Theophylline has multiple mechanisms of action. It antagonizes adenosine receptors, inhibits phosphodiesterase, directly stimulates beta-adrenergic receptors, and enhances the release of endogenous catecholamines. Most oral formulations of theophylline are sustained-release, so toxicity may not be apparent for 12 or more hours.

Multiple organs may be affected in acute theophylline ingestions. Tachycardia is the most common cardiovascular manifestation and is often associated with hypotension, though hypertension has been reported. Hypotension may result from vasodilation, volume loss secondary to gastrointestinal losses, and/or reduced cardiac output.³ Electrocardiographic manifestations include premature atrial and ventricular beats. In more severe cases, QRS widening, QTc prolongation, and ventricular and supraventricular dysrhythmias may develop.

Neurological manifestations may include tremor, irritability, lethargy and seizures, including status epilepticus and non-convulsive status epilepticus.^{3,4} Gastrointestinal signs and symptoms are common in acute theophylline toxicity.³ Nausea and vomiting are generally present and occasionally are associated with hematemesis. Diarrhea has been observed.

Multiple laboratory abnormalities may be observed in significant theophylline overdoses. Hypokalemia is likely multifactorial, including transcellular shift and gastrointestinal loss. Hyperglycemia results from increased catecholamine activity. Metabolic acidosis is commonly attributed to lactic acid, which may be elevated from tissue hypoperfusion or result from muscular hyperactivity. Respiratory acidosis may be seen in patients with central nervous system depression, while respiratory alkalosis is common in awake patients.

The mainstay of treatment is supportive care. If patients present shortly after ingestion and have no contraindications, single-dose activated charcoal (SDAC) should be administered. Whole-bowel irrigation is also reasonable following ingestion of an SR product, but it probably confers no additional advantage over SDAC.⁵

Immediate resuscitation may be necessary in large ingestions. Endotracheal intubation should be performed if there is any concern for loss of airway reflexes. Hypotension should be treated aggressively with fluid resuscitation. We recommend lactated ringers because normal saline can cause a hyperchloremic acidosis that may exacerbate the wide-gap acidosis observed in theophylline toxicity. Some sources recommend using beta-adrenergic receptor antagonists to improve cardiac output by slowing the heart rate, prolonging diastole and increasing stroke volume.⁶ However,

Table 2Indications for intermittent hemodialysis following acute theophylline overdose.⁸

Theophylline level >100 mg/L
Presence of seizures
Shock
Life-threatening dysrhythmia
Rising theophylline level or clinical deterioration despite optimal care

some patients suddenly decompensate. Additionally, beta blockers may exacerbate pulmonary disease in patients who are prescribed theophylline.

Additional therapies include seizure and symptom control and electrolyte replacement. Benzodiazepines or other GABA agonists are recommended to treat seizures. Hypokalemia should be corrected with potassium and magnesium supplementation. Nausea and vomiting should be treated with non-sedating anti-emetics.

Multi-dose activated charcoal (MDAC) can be used to enhance theophylline elimination. Animal and volunteer human studies show a reduction in mean elimination half-life using MDAC.⁷ However, there is no clear evidence that MDAC improves outcomes and it may be associated with aspiration in patients with CNS depression.

Because of its small volume of distribution (0.5 L/kg) and moderate protein-binding, theophylline is amenable to hemodialysis. The Extracorporeal Treatments in Poisoning workgroup recommends intermittent dialysis following acute theophylline overdose in specific circumstances (Table 2).⁸ If the patient cannot tolerate intermittent dialysis, CRRT or hemoperfusion are acceptable but less effective alternatives.

4. Conclusion

Theophylline poisoning, particularly in the pediatric population, is rarely encountered by the current generation of physicians. However, ingestions have the potential for significant toxicity, and it is imperative that physicians who treat acutely ill children recognize the signs of theophylline poisoning and how to manage it safely and effectively.

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