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An Overview on Theophylline Toxicity

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Abstract:

Around the world, theophylline (1,3-dimethylxanthine) is primarily used as a bronchodilator for patients with asthma and chronic obstructive pulmonary disease (COPD). However, in the United States, asthma and COPD are mainly treated with other agents, and theophylline is largely used to treat bradycardia and apnea in premature newborns. Theophylline causes the endogenous release of catecholamines through indirect stimulation of beta-1 and beta-2 receptors, which at therapeutic levels cause desired bronchodilation. Unfortunately, theophylline has a narrow therapeutic window, and even levels slightly above this therapeutic window can have many adverse effects in the setting of acute and chronic toxicity. The excess circulating catecholamines cause serious clinical effects that are associated with theophylline toxicity. Depending on the dose and route of administration, theophylline can have a wide range of cardiovascular, neurologic, metabolic, musculoskeletal, and gastrointestinal manifestations. Emergency department providers should become familiar with managing patients with theophylline toxicity since arrhythmias, seizures, hyperglycemia, and rhabdomyolysis are several of the complications that can arise.

Keywords: Theophylline poisoning, arrhythmias, metabolic derangements, multidose activated charcoal.

Introduction:

Theophylline has a very narrow therapeutic window, meaning toxicity can occur when serum theophylline levels exceed the therapeutic range. This can result from intentional overdose or unintentional factors such as altered metabolism or clearance due to certain physiological stressors **(1)**. Theophylline intoxication may be acute, acute on therapeutic or chronic (**2**).

Toxic exposures to theophylline have decreased significantly since its management for asthma and COPD has declined **(1)**.

At high doses and overdose theophylline undergoes zero-order elimination, and only a fixed amount of the drug can be eliminated in a given time because of saturation of metabolic enzymes **(3).**

Acute toxicity

Clinical picture of acute theophylline toxicity:

Cardiac manifestation:

Tachycardia is the most frequent cardiovascular effect of theophylline toxicity and is often accompanied by hypotension, although hypertension has also been observed. Hypotension can be caused by vasodilation, volume loss due to gastrointestinal losses, and/or decreased cardiac output **(4).** Acute theophylline toxicity can also lead to myocardial ischemia and myocardial infarction. **(3).**

Electrocardiographic manifestations include premature atrial and ventricular beats. In more severe cases, QRS widening, QT prolongation, and ventricular and supraventricular dysrhythmias may develop **(4)**.

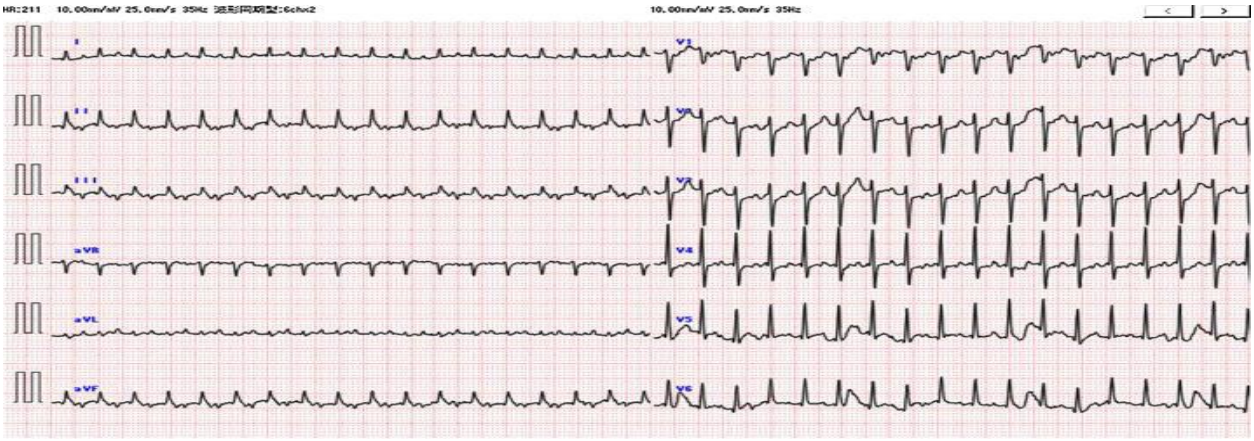

Figure 1: supraventricular tachycardia due to theophylline toxicity (**5**).

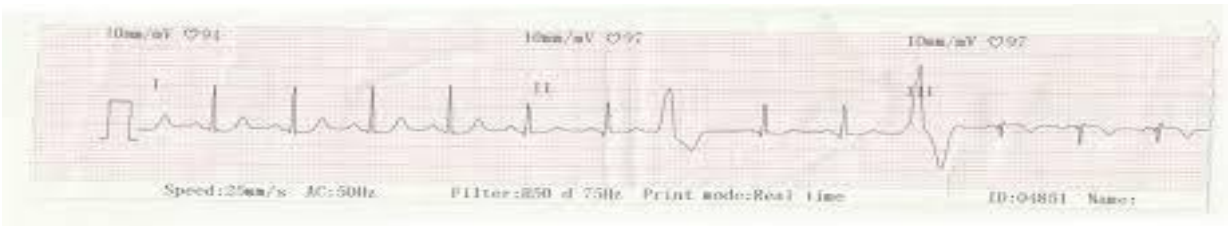

Figure 2: A photograph of ECG strip showing ventricular extrasystoles; in a theophylline intoxicated case{ note the braod bizarre QRS complexes among the normal sinus beats and the abnormal T waves (ORS complex is about 0.4 s)**(6**).

Neurological manifestations:

Neurological manifestations may include tremor, irritability, lethargy and seizures, including status epilepticus and non-convulsive status epilepticus **(4)**.

Seizures are major complication of theophylline toxicity, tend to be sever and recurrent and may be refractory to conventional treatment, they occur in chronic toxicity more than acute toxicity and occur more in extremes of age **(3).**

Theophylline stimulates the nervous system at various levels: the medulla (increased respiratory rate and sensitivity to carbon dioxide, nausea and vomiting), vagal effect (causing bradycardia), the cerebral cortex (restlessness, agitation, tremor, irritability, headache, seizures, difficulty in concentration), the hypothalamus (hyperthermia), and even the spinal cord (hyperreflexia). Furthermore, CNS effects of theophylline are mediated through increased cyclic-AMP concentration and blockage of adenosine receptors which results in CNS stimulation at various levels according to **Shannon (7).**

Gastrointestinal manifestations:

Gastrointestinal signs and symptoms are common in acute theophylline toxicity. Nausea and vomiting are generally present and occasionally are associated with hematemesis. Diarrhea has been observed **(8)**.

Vomiting occurs in 75% of acutely poisoned cases, only 30% of chronic toxicity cases, and when occurs it is usually severe and may be difficult to be controlled by potent antiemetics **(3).** Gastrointestinal symptoms occur

most often as a result of a central effect of an excessive serum theophylline concentration on the medulla rather than because of a local irritative effect on the stomach **(9).**

Pulmonary manifestations

Theophylline stimulate respiratory center causing increase in respiratory rate so in overdose it may cause hyperventillation, respiratory alkalosis, respiratory failure, respiratory arrest, and acute lung injury **(10).**

Musculoskeletal manifestations

Theophylline increase striated muscle contractility, it also increase muscle oxygen consumption and increase the basal metabolic rate **(10).** Skeletal muscle excitation includes fasciculation, hypertonicity, myoclonus, or even rhabdomyolysis all may occurs in theophylline overdose **(3).**

Mechanisms by which rhabdomyolysis may result include increased muscle activity, particularly from seizures, and direct cytotoxicity from excessive sequestered intracytoplasmic calcium **(10).**

Metabolic changes:

In significant theophylline overdoses, various laboratory abnormalities can be observed. Hypokalemia is often due to a combination of factors, including transcellular shifts and gastrointestinal losses. Hyperglycemia arises from increased catecholamine activity. Metabolic acidosis is typically linked to elevated lactic acid, which may result from tissue hypoperfusion or muscular hyperactivity. Respiratory acidosis may occur in patients with central nervous system depression **(4)**, while respiratory alkalosis is explained by hyperventilation which may be due to direct stimulation of respiratory center **(11)**.

Evaluation

Workup should include the following:

-Serum theophylline level: Therapeutic serum levels range from 10 to 20 mcg/mL. Toxic levels are considered to be 20 mcg/mL or higher. However, toxic effects can be seen within therapeutic levels as well. Cardiac dysrhythmias, seizures, and death can be seen with 80 to 100 mcg/mL levels. Chronic toxicity can be seen at levels of 40 to 60 mcg/mL **(1).**

Table1: Theophylline level (**12**).

LEVEL (MICROMOL/L)	LEVEL (MG/L)	TOXICITY
55 – 110	10 – 20	Therapeutic
110 – 220	20 – 40	Minor toxicity
220 – 440	40 – 80	Moderate toxicity
440 – 550	80 – 100	Severe toxicity
>550	>100	Usually fatal without intervention

- Serum glucose: for Hyperglycemia (**13**).

-Complete metabolic panel: for Hypokalemia and metabolic acidosis (**10**).

-Complete blood count (CBC): White blood cells can be elevated due to increase catecholamine release **(14)**.

- Creatine kinase: Evaluation for rhabdomyolysis (**3**).

-Liver function tests: Evaluation of liver dysfunction as the liver metabolizes theophylline (**14)**.

-ECG to evaluate arrhythmias, ischemia, or other toxic ingestions. Consider CT Head: Evaluation of other potential causes of altered mental status or seizures **(14).**

Treatment

Stabilization

In cases of large theophylline ingestions, immediate resuscitation may be required. Endotracheal intubation should be considered if there is a risk of losing airway reflexes. Hypotension should be managed aggressively with fluid resuscitation. Lactated Ringer's solution is preferred over normal saline, as the latter can lead to hyperchloremic acidosis, potentially worsening the wide-gap acidosis associated with theophylline toxicity **(4).**

Decontamination

If patients present shortly after ingestion and there are no contraindications, single-dose activated charcoal (SDAC) should be given. Whole-bowel irrigation may also be considered, particularly after ingestion of a sustained-release product, but it likely offers no additional benefit over SDAC **(15).**

Elimination

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**.** However, there is no clear evidence that MDAC improves outcomes and it may be associated with aspiration in patients with CNS depression **(4)**.

Due to its small volume of distribution (0.5 L/kg) and moderate protein-binding, theophylline can be effectively removed by hemodialysis. The Extracorporeal Treatments in Poisoning workgroup advises intermittent dialysis in certain situations following an acute theophylline overdose **(16)**. If intermittent dialysis is not feasible for the patient, continuous renal replacement therapy (CRRT) or hemoperfusion can be used, though they are less effective alternatives **(4)**.

Indications for intermittent hemodialysis following acute theophylline overdose:

Theophylline level >100 mg/L, presence of seizures, shock, life-threatening dysrhythmia, rising theophylline level or clinical deterioration despite optimal care **(16)**.

Antidote

There are no antidotes to reverse the toxic effects of theophylline; therefore, therapy is focused on enhancing its elimination **(17).**

Supportive and symptomatic treatment

Some sources suggest using beta-adrenergic receptor antagonists to manage hypotension by producing a negative chronotropic effect through β1 receptor blockade. This slows the heart rate, prolongs diastolic filling time, and consequently increases stroke volume and cardiac output **(18).** However, some patients may experience sudden decompensation, and beta blockers could worsen pulmonary conditions in individuals taking theophylline **(4).**

Additional treatments involve managing seizures and symptoms, as well as replacing electrolytes. Benzodiazepines or other GABA agonists are recommended for seizure control. Hypokalemia should be corrected

with potassium and magnesium supplements. Nausea and vomiting should be managed with non-sedating antiemetics **(4)**.

Differential Diagnosis (1)

- Alcoholic ketosis
- Amphetamine intoxication
- Anticholinergic poisoning
- Atrial fibrillation
- Bipolar disorder
- Cocaine intoxication
- Carbon monoxide toxicity
- Diphenhydramine toxicity
- Delirium tremors
- Diabetic ketoacidosis
- Encephalitis
- Hypercalcemia
- Hyperthyroidism
- Hyponatremia
- Hypoxia
- Iron toxicity
- Monoamine oxidase inhibitor toxicity
- Salicylates toxicity
- Sepsis
- Status epilepticus
- Ventricular tachycardia

Chronic toxicity

The major difference between acute and chronic toxicity is the duration of exposure to the drug. Chronic theophylline toxicity typically occurs in the setting of therapeutic use. Patients chronically receiving theophylline have higher total body stores and they may develope toxicity with a smaller amount of additional theophylline **(19).**

Patients with a chronic theophylline overdose often present with nonspecific gastrointestinal symptoms, which can result in misdiagnosis for a variety of gastrointestinal conditions. Convulsions that may be fatal can occur as a result of a theophylline overdose **(20)**.

The relationship between the intensity and severity of clinical signs of theophylline intoxication and actual serum theophylline concentrations is unclear in cases of chronic poisoning. Older patients are more likely to experience life-threatening events due to chronic theophylline poisoning, and it is impossible to infer the extent of clinical signs based on peak serum theophylline concentrations. Adults older than 75 years are 16.7 times more likely to be severely affected than those younger than 25 years, regardless of serum theophylline concentration **(21).**

Recommendations for treatment of theophylline toxicity occurring in patients as a result of chronic overdosage are similar to those for acute overdosage with the following caveat: young patients tolerate acute overdosage much better than older patients, who most often are suffering from chronic overdosage. Serious adverse events are more likely to occur at lower serum concentrations in the chronic overdose situation, and therefore, more aggressive measures are indicated in this setting. In patients older than 60 yr, seizures may occur at levels lower than 30 µg/mL, and therefore, prophylactic anticonvulsive therapy should be instituted earlier than in the young individual suffering from acute theophylline overdosage **(9).**

Acute on top of chronic toxicity

Acute-on-chronic toxicity can occur with acute overdoses in adults already being treated with therapeutic theophylline. Life-threatening theophylline toxicity remains a concern throughout treatment duration, especially in the elderly due to potential alterations in theophylline pharmacokinetics, increase in interacting medications, and/or improper adherence to treatment which results in overdosing **(17).**

Acute on top of chronic theophylline toxicity can present with a wide array of clinical manifestations, ranging from mild gastrointestinal complaints to potentially lethal cardiac arrhythmias and seizures. Its non-specific symptom presentations require a high level of suspicion **(22).**

Due to its narrow therapeutic index, prescribing theophylline should be strongly reconsidered, and if prescribed, the risk and benefits should be thoroughly discussed with the patient with routine drug level monitoring in long-term therapy and in acute exacerbations **(17)**.

Enhancing Healthcare Team Outcomes

Theophylline toxicity is best managed in an interprofessional fashion. The key to theophylline toxicity is prevention. First, healthcare providers should avoid prescribing this agent for asthma when other safer drugs are available. All patients should be educated about the dangers of theophylline. Parents should be told to store theophylline in a safe place away from the reach of children. For those who intentionally overdose on the drug, a mental health consult is recommended before discharge **(23).**

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