Case Report

Theophylline use—a conundrum in modern medicine: a case report

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Background: The theophylline toxidrome presents with multisystemic involvement that includes cardiovascular, neurologic, metabolic, musculoskeletal, and gastrointestinal manifestations. Considering such a varied spectrum of presentations, it is often difficult to ascertain the diagnosis of this particular toxidrome. Review of home medications is an important step when working with a patient presenting as a toxidrome.

Case Description: The case report is about a 69-year-old female patient who was brought to the emergency room in status epilepticus and atrial fibrillation with rapid ventricular response. She had a prolonged state of drowsiness following an initial antiepileptic therapy and a toxicologic screen positive for toxic levels of theophylline at 59.7 mcg/mL. Emergent dialysis was performed leading to improvement of her overall clinical status. We suspect the patient had built up toxic levels of theophylline due to evolving drug interactions after she discontinued many of her routine home medications following her husband's death.

Conclusions: Theophylline is a methylxanthine derivative medication that is used sparingly in the treatment of airway diseases. It has become less favorable over the years due to its narrow therapeutic index and potential for development of toxicity. Monitoring serum drug levels and adjusting the dose frequently to maintain a therapeutic range is essential to prevent toxicity related to theophylline. There is emerging evidence that the drug might have anti-inflammatory properties to aid in treating many chronic airway disorders and pharmacovigilance is necessary for its continued use.

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Introduction

Theophylline is a methylxanthine derivative medication with smooth muscle relaxant properties commonly used historically to treat airway diseases such as bronchial asthma and chronic obstructive pulmonary disease. The drug's therapeutic effects are achieved by inhibiting phosphodiesterase enzymes, leading to increased intracellular cyclic adenosine monophosphate (cAMP) levels and subsequent bronchodilation. At the same time, metabolism primarily occurs in the liver via CYP1A2 (major) and CYP2E1 (minor) enzymes (1). Factors such as liver disease, drug interactions, age, smoking, and renal function can significantly affect its clearance, potentially leading to toxicity. Toxicity with this compound commonly

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manifests as a clinical spectrum relating to the stimulant properties of theophylline on account with its narrow therapeutic index. The stimulant activity of theophylline is used to treat bradycardia, apnea in premature newborns and life-threatening cheyne-stokes respiration (2). Serum theophylline levels are monitored regularly to avoid toxicity since the adverse effects of theophylline are directly related to its plasma concentration. Lower toxic plasma levels can cause neurological symptoms like headache, agitation, tremors, and gastrointestinal symptoms like nausea and vomiting (3). More severe clinical features, including hypotension, arrhythmia, and seizures, can appear with higher toxic plasma levels. Despite declining use over recent years, the occurrence of theophylline toxicity is still quite frequent and with significant morbidity and mortality of about 140 cases reported in the year 2020 (4,5). We report the case of a patient who presented with established convulsive status epilepticus and atrial fibrillation with rapid ventricular response attributed to theophylline toxicity. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-111/rc).

Case presentation

A 69-year-old female with past medical history of bronchial asthma, breast cancer on chemotherapy, anxiety disorder, prior stroke, and long-standing atrial fibrillation presented to the emergency room in status epilepticus. The patient had two episodes of seizures enroute to the hospital and received two doses of diazapem by the emergency medical services crew. Upon arrival at the hospital, the patient was drowsy and had two more episodes of seizures in the emergency room that required to be abated with two doses of lorazepam and a loading dose of levetiracetam 1 gm infusion. She was also tachycardic with the rhythm of atrial fibrillation with a rapid ventricular rate but hemodynamically stable with a blood pressure of 130/80 mmHg. Routine labs showed normal cell counts and hypokalemia with a potassium level of 2.7 mmol/L. Computed tomography scan of the head was unremarkable. On further assessment, the patient progressed to a semi-comatose state following the cessation of seizures indicating intubation for airway protection. The patient had been to the emergency room 4 days earlier with nausea, vomiting, loss of appetite, and diarrhea for which she was managed conservatively and discharged home. Home medications included albuterol inhaler as needed, apixaban 5 mg twice daily, trazodone 100 mg twice daily, oxycodone-acetaminophen 10–325 mg every 6 hrs as needed, gabapentin 300 mg thrice daily, oxybutynin 5 mg twice daily, theophylline-extended release tablet 300 mg once daily, metoprolol tartrate 50 mg twice daily, allopurinol 300 mg once daily, intramuscular fulvestrant injections 500 mg once monthly, and omeprazole 40 mg once daily. A serum theophylline level was drawn and was at a supratherapeutic level of 59.7 mcg/mL (therapeutic range 10–20 mcg/mL). She followed up with her primary care physician in the outpatient clinic and had normal therapeutic serum theophylline levels until the current presentation. Poison control was contacted for recommendations and advised continuous hemodynamic monitoring with control of the rapid heart rate and initiating hemodialysis for detoxification. Activated charcoal was not given as the patient was in altered mental status on presentation and there was less degree of suspicion for acute toxicity since she was seen in the emergency room 4 days prior for gastrointestinal symptoms which related to early features of theophylline toxicity. The patient placed in the intensive care unit on mechanical ventilation. A nasogastric tube was placed, and a dark-colored output was noted which was probably an occult upper gastrointestinal mucosal bleed. Nephrology consult was placed to evaluate for emergent hemodialysis. A temporary dialysis catheter was placed, and the patient underwent two rounds of hemodialysis on consecutive days to prevent rebound toxicity from tissue redistribution. The rapid ventricular rate occurred intermittently and did not respond to any rate and rhythm control medications

Highlight box

Key findings

- In this case report, we present a case of theophylline-related systemic toxicity that presented as an excitoxic syndrome.

What is known and what is new?

- Theophylline has a narrow therapeutic index and can result in toxicity if the serum drug levels are not monitored closely.
- Theophylline is still being used as an anti-inflammatory compound when treating patients with airway disease. It is important to consider theophylline toxicity especially in patients presenting with an undifferentiated excitogenic toxidrome.

What is the implication, and what should change now?

- Close consideration of a patient's comprehension of the drug toxicity before using this medication for treatment.
- Review of home medications serves as an important clue in the recognition of such toxidromes.

and ultimately, she had to be cardioverted back to sinus rhythm on day four of the hospital course. Her mental status improved gradually over the next three to four days, pointing towards the slow recovery of cerebral tissue toxicity. Following the initial period of stabilization, the patient was placed in a step-down unit for further monitoring. Mentation improved gradually and her oral diet was slowly advanced after a swallow study screen. She had an aspiration event two days later after starting solid food intake and developed a severe bilateral pneumonia that did not respond to antibiotics. She underwent bronchoscopy and was found to have a mass at the division of the main stem bronchus which was likely metastatic disease considering her history of breast cancer. The patient's medical condition continued to decline, and she was placed on comfort care measures. The patient passed away from sepsis secondary to severe bilateral pneumonia seventeen days into admission.

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki declaration (as revised in 2013). Written informed consent for publication of this case report was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

The bronchodilator effect of theophylline can be seen at serum concentration of 5–8 µg/mL. Theopylline related toxicity can be variable and relatively minor at serum concentrations below 15 µg/mL but become more consistent and more serious at and above 20 µg/mL. Based on this data, the therapeutic range has been established at 10–20 µg/mL with 10–15 µg/mL being optimal (6). Considering this narrow therapeutic index, some controversy exists with establishing the toxicity threshold. The clinical response of theophylline appears to correlate with its log plasma concentration in most cases, but some authors claim the clinical aspects should precede determination of serum concentrations for dose corrections (7). The metabolism of theophylline is determined by multiple factors and varies based on a person's metabolism rate, co-existent illnesses and medications, age, body weight, and social factors like smoking.

Theophylline toxicity commonly manifests with nausea, vomiting, diarrhea, gastrointestinal hemorrhage, hypokalemia, metabolic acidosis, seizures, arrhythmias, and hypotension. Toxicity can occur in an acute setting from an intentional or inadvertent overdose or chronically with worsening renal function and addition of any new CYP-450 inhibitor medications or discontinuation of any CYP-450 system inducers (5,8). Our patient stopped taking her usual medications besides the theophylline and had reduced intake of her regular diet at home following her husband's recent death. We think that might have been a contributory factor to her developing theophylline toxicity. We also suspect the seizures were related to theophylline toxicity rather than just medication non-complaince as she did not respond to multiple doses of lorazepam, the first-line therapy for status epilepticus but later was stabilized with an infusion of levetiracetam. Levetiracetam is very effective in suppressing methylxanthine-excitotoxicity-related seizures in mice (9).

The mainstay of treatment for theophylline toxicity is supportive care. In patients presenting with acute toxicity and with good mentation, multiple doses of activated charcoal (MDAC) can be administered. Gastrointestinal toxicity with protracted nausea and vomiting can make oral means of decontamination difficult to perform necessitating extracorporeal means to clear the drug toxicity. Extracorporeal clearance with either charcoal hemoperfusion or hemofiltration (HF) is a rapid method of detoxification if plasma theophylline levels are greater than 100 mg/L in an acute overdose, greater than 60 mg/L in chronic toxicity (10), or in patients presenting with seizures or cardiac arrhythmias necessitating pharmacologic intervention, regardless of the serum theophylline concentration (11). Theophylline is readily cleared by extracorporeal means because of its low volume of distribution and minimal protein binding. High-flux, high-efficiency hemodialysis is more effective in removing theophylline than charcoal hemoperfusion and is associated with fewer side effects. Continuous venovenous HF can be used but requires a more sustained period of treatment (2).

The process of hemofiltration involves the flow of blood across a semipermeable membrane which allows for the movement of water and solutes of a molecular weight; up to 40,000 Da by convection, similar to glomerular filtration (12). The rate of this filtration process is proportional to the concentration of the solutes and not dependent on their size (12). Hemofiltration is also favored over hemoperfusion due to its better tolerance with hemodynamically unstable patients, its ability to filter solutes of relatively larger molecular mass (up to approximately 15,000 Da), accessibility in the hospitals, and lower cost. These solute clearance properties theoritically support the idea of using

hemofiltration in patients presenting with theophylline toxicity. Theophylline is noted to have a molecular mass of 180 Da, distributes mostly to the intravascular compartment, is not heavily protein bound (~40%), and has a lower rate of endogenous clearance (<4 mL/min/kg) (12).

Due to the limited availability and impact of tenuous hemodynamics associated with charcoal hemoperfusion, many physicians prefer using hemofiltration in combination with oral activated charcoal; provided the patient is conscious and can take the antidote orally.

Conclusions

Theophylline was an essential medication in the management of airway diseases in the twentieth century and due to the narrow therapeutic index and the development of better medications with local action effects, it has fallen out of favor to be used by most physicians. However, some physicians still prefer using it due to patients' feeling of satisfaction and its anti-inflammatory effect on the airways (13). It is essential to monitor serum theophylline levels in patients on this medication and dose titration to be accordingly. Our case points to difficulty with the use of such medication, especially in the independent elderly population who might not be vigilant with their self-care and can develop toxicity, especially in the setting of physiological and psychological stressors.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-111/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-111/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki declaration (as revised in 2013). Written informed consent for publication of this case report was not obtained from the patient or the relatives after all possible attempts were made.

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