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Case Report

An Unintentional Overdose: A Case Report

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ABSTRACT

The error prone processes of prescribing and administering medications is made even more dangerous when uncommon and potentially lethal medications are involved. This case report describes the admission of a patient who suffered an in-hospital theophylline overdose's subsequent critical care admission and resultant death. Included is a review of the most prevalent and recent evidence regarding this type of toxicity including extracorporeal removal and multidose activated charcoal as well as a reflection of how this multi-faceted fatal error occurred.

Keywords: Theophylline; Medication error; Seizure; CRRT; MDAC; Phenytoin; Toxicity; Overdose; ICU outcomes

INTRODUCTION

Overdoses, whether intentional or accidental, can occur from over ingestion of alcohol, over-the-counter and prescription medications. In hospital, in the processes of prescribing and administering medications, there are a multitude of opportunities for error. Some prescription medications have easily identifiable symptoms and reversal agents that are readily available in hospital while other toxicities have more subtle symptoms and no known reversal agents. Therefore, the prompt identification of these less common are all the more important since they are all the more difficult to treat. The following report will describe a patient's ward and intensive care unit admission and resultant demise from a preventable medication error.

CASE DESCRIPTION

A 73-year-old female presented to an emergency department one month after a carcinoma related right sided partial nephrectomy for which she had a prolonged recovery complicated by a urinoma which required stenting. She was complaining of chills, right flank pain, nausea, emesis, dysuria and reported oliguria. Other medical history included asthma/chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, arthritis, gastroesophageal reflux disease, anemia, and a previous cholecystectomy. She had been residing in an assisted living facility without homecare services and ambulated independently with a walker.

At this time, the nephrectomy site was indurated but no drainage or erythema was present and an infused CT abdomen showed the ureteric stent in good position with decreased perinephric fluid; therefore no cause of patient's flank pain was objectively identified. A midstream urinalysis was positive for ketones, blood and leukocytes, she was afebrile, her WBC was within normal limits - nonetheless urine and blood cultures were collected. She was subsequently admitted to a short stay unit with query pyelonephritis for intravenous antibiotics and her home medications reinitiated.

On admission day two, the urine culture returned positive for *enterococcus faecalis* and the blood cultures were negative; antibiotics were appropriately augmented. Nursing documentation was focused on patient's c-diff negative diarrhea, generalized abdominal pain, lack of appetite, lack of sleep, and family endorsed chronic nausea with vomiting. On admission day five, a physician documented that the patient had been "++ delirious" and agitated for two days and started the patient on scheduled quetiapine, no additional tests were ordered.

After a week in hospital, another urinalysis was performed that showed increased leukocytes which prompted a new urine culture to be collected and an infused CT abdomen repeated. The CT reported only a slight decrease in perinephric fluid prompting a stent exchange on admission day ten. The stent exchange was uneventful and the patient's foley catheter was removed the same day despite nephrology recommendations from it to remain in until discharge. Despite urology's involvement, the patient's doubled creatinine was not noted (Cr was 60 mmol/L on admission and then 120 a week later). Additionally, throughout the patient's stay, the patient's weight

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and intake/output (namely voided urine as well as emesis and diarrhea volumes) were also not documented.

On admission day eleven, the patient had a self-limiting one minute seizure for which she was loaded with phenytoin, had a nil acute uninfused head CT and EEG was to be arranged. Two days later, an EEG had yet to be performed, and a code blue was called for a witnessed tonic-clonic seizure. The seizure was again self-limiting, the patient adequately protected her airway, therefore the phenytoin dose was increased, lacosamide added and an MRI brain ordered. This seizure prompted the re-evaluation of the patient's suitability for the short stay unit and she was thereafter transferred to a general medicine ward.

Shortly after her arrival to the medicine ward, another code blue was called for consecutive prolonged tonic-clonic events for which the patient was no longer protecting her airway. She was orally intubated without difficulty and was promptly transferred to a closed medical intensive care unit. The admitting ICU nurse documented persistent right arm and leg clonus as well as decerebrate posturing and jaw clenching to stimuli. This nurse also noted that one of the patient's home medications, which had been continued while in hospital, was long-acting theophylline and that a serum level had not been checked during this admission or the surgical admission previous. The patient's serum theophylline level was drawn immediately and was toxic at nearly triple the therapeutic maximum.

DISCUSSION

Theophylline is a methylxanthine, similar to caffeine, once frequently prescribed for bronchospasm in COPD and asthma. Generally, its use has decreased substantially due to its risk of toxicity and accidental ingestion, but remains in use as it is inexpensive, widely available, and there are ongoing studies on new potential indications for its use [1,2]. Therapeutic serum concentration is five to fifteen mg/L (27.5 to 82.5 mcmol/L) and there is considerable variability by age and comorbidities [3]. For example, theophylline clearance can be impaired by altered kidney or liver function, thyroid dysfunction and treatments, quinolone and macrolide antibiotics, some anti-virals and anti-fungals, and alkalinizing agents [3]. The manufacturer's monograph gives no recommendation for frequency of routine serum monitoring but it has been surmised that plasma concentrations should be checked routinely and even more frequently if there are any adverse effects, concerns regarding compliance, and/or any comorbidities or co-administered medications that are known to alter theophylline clearance [1,3]. Under steady state conditions, serum theophylline is best monitored 12 hours post dose [3], but if a patient is suspected to have deliberately overdosed or is exhibiting signs of toxicity a serum sample should be collected immediately (Table 1).

Table 1: Symptoms seen based on the classes.

Class	Symptom	Presence while on ward
Alimentary	Nausea	Noted to be chronic per patient's family, actual time frame is unknown
	Vomiting	Multiple episodes of emesis
	Abdominal pain	Present but was attributed to nephrectomy site
	Hematemesis	Thick vomitus was documented once by a ward nurse but colour was not documented
Cardiovascular	Sinus tachycardia	Was not noted due to active beta adrenergic blockade
	Ventricular arrythmias	Was not on cardiac monitoring while on short stay ward
	Hypotension	Blood pressure was at the lower range of normal but never profoundly hypotensive. Arguably, hypotension may not occur without tachycardia, [4] which was being masked by beta adrenergic blockade
Metabolic	Hyperglycemia	Not noted as was on gliclazide
	Hypokalemia	Received a total over 300 mmol of potassium replacement over thirteen days
	Acid/base disturbance	Blood gases were not drawn until after the patient intubated
	Rhabdomyolysis	Plasma myoglobin and creatinine kinase were drawn on admission to ICU. Myoglobin was >400 mcg/mL and CK was 62 units/L on admission to ICU. CK increased to 130 units/mL on the follow-up bloodwork seven hours later. Urine output in ICU was documented as dark amber.
Neurological	Restlessness	Documented as agitated delirium and treated with haloperidol (also for nausea) and quetiapine
	Convulsion/seizure	Present on multiple occasions. Rationale for intubation and ICU management.

In a literature review conducted in 1988, the most common clinical manifestations of theophylline toxicity were nausea, vomiting, tachycardia, and seizures among other neurological symptoms.5 In both the overdose and iatrogenic groups of this study, hypokalemia, hyperglycemia, hypophosphatemia, acidosis, and rhabdomyolysis also occurred often [5,6]. Since then, gastrointestinal disturbances are consistently documented in the literature as the early sign of acute toxicity, [2,7] which may be explained by phosphodiesterase inhibition [1].

Treatment recommendations

Theophylline is one of the only causes of true toxin-induced status epilepticus, due to adenosine antagonism [2]; the exact serum threshold of theophylline to induce seizures is unknown. Seizures related to theophylline should be treated with IV diazepam or lorazepam PRN, IM midazolam PRN if unable to obtain IV access, and phenobarbital if unable to suppress seizures benzodiazepines alone [6]. Continuous infusions of midazolam and propofol can be used in addition to phenobarbital [8]. Electroencephalography (EEG) of these patients typically show periodic lateralized epileptiform discharges or similar activity [9], but EEG should not be used to differentialize theophylline-induced seizures from other potential causes.

No specific antidote for theophylline exists therefore supportive care is the biggest component towards survival, followed by extracorporeal removal and bowel decontamination. Additionally, endotracheal intubation should be performed if there is any concern for airway protection and should be anticipated related to the respiratory depression caused by antiepileptics.

Nausea and vomiting should be treated with non-sedating antiemetics [10]; ondansetron, metoclopramide, and prochlorperazine if warranted [6]. Hypokalemia can be attributed to beta adrenergic receptor-mediated intracellular shift and gastrointestinal losses, and should be judiciously replaced [2].

Phenytoin has been found to be ineffective at terminating theophylline seizures independently in a case review [5], and in a study in mice it was shown to perhaps increase mortality [11]. Both of these studies, published in the same year, did not take into account phenytoin levels and the then unknown relation that phenytoin induces theophylline metabolism, which in turn reduces circulating phenytoin [12], lessening phenytoin's serum concentration and ability to have clinically useful effects.

Hypotension may be precipitated by tachycardia or secondary to benzodiazepines and/or phenobarbital use. Initial fluid resuscitation with lactated ringers is recommended over normal saline to prevent further acidosis [10]. Hypotension resistant to isotonic fluids may require vasopressors with predominantly alpha-agonistic activity, eg. phenylephrine, norepinephrine [6]. Some dated studies recommend the use of short-acting beta-adrenergic receptor antagonists to improve cardiac output and blood pressure by prolonging diastole and increasing stroke volume [4,10].

Extracorporeal removal of theophylline is recommended with when a patient is experiencing seizures, life threatening dysrhythmias, hemodynamic compromise, and/or a theophylline level greater than 100 mg/L (555 mmol/L) in acute exposure [2]. Greatest theophylline clearance is obtained via charcoal hemoperfusion which comes at a higher cost and is rarely available [2]. In adults, hemoperfusion and CRRT are less effective but acceptable alternatives with hemoperfusion having a higher recommendation based on the limited data available regarding CRRT and theophylline likely as CRRT's popularity was increasing as the use of theophylline was decreasing in the 1990s [13].

Lastly, gut decontamination with multi-dose activated charcoal (MDAC) is recommended to enhance theophylline clearance concurrent with extracorporeal removal [2,10]. There is no evidence that MDAC independently lowers serum theophylline levels but it is recommended as an adjunctive therapy to prevent ongoing absorption in chronic toxicity involving modified release preparations and acute ingestion [2]. MDAC must be administered with caution as it may be associated with aspiration in patients with CNS depression and is further limited by those with the symptom of intractable vomiting [2,10].

ICU stay and outcome

Upon ICU admission, midazolam and ketamine infusions were initiated and increased until visible clonuses had been supressed, which resulted in the patient requiring low dose norepinephrine. An MRI brain was obtained and the results were unremarkable. A lumbar puncture was performed and the CSFs colour, protein, glucose and chloride were all within normal limits. An EEG was then conducted and confirmed non-convulsive status epilepticus (NCSE) and a propofol infusion was subsequently introduced.

The patient's initial theophylline level was 43.2 mg/L followed by 27.9 mg/L nineteen hours later without any extracorporeal intervention; the patient had however received three additional doses of phenytoin which is known to decrease half-life and increase clearance of theophylline [3]. Phenytoin was subsequently discontinued due to the misinterpretation that it would decrease theophylline clearance, despite the impressive decrease since it was introduced.

Nephrology was then consulted and noted that the patient's serum theophylline had already slowly improved 'on its own' but agreed that dialyzing the patient to enhance its clearance would be reasonable; MDAC was not considered. CRRT was subsequently initiated using CVVHDF mode, tight pre-filter heparin anti-coagulation and an ST 150 filter with an average delivered effluent dose of 50 mL/kg/h.

An EEG nine hours after CRRT initiation showed continued NCSE for which the patient's levetiracetam dose was increased and phenobarbital added. Twelve hours after CRRT initiation, the patient's theophylline level had dramatically decreased to 7.2 mg/L followed by 1.4 mg/L at hour 29. CRRT was subsequently discontinued at hour 41 and a third EEG revealed stimulus induced rhythmic, periodic or ictal discharges (SIRPDs) amidst pharmacologic induced heavy burst suppression patterns.

The following day, theophylline levels were undetectable and the nephrology consult signed off. Following a fourth EEG, neurology commented that the patient remained in super refractory NCSE and given the rarity of theophylline overdoses that there were few reports to help predict the typical length of seizure activity.

That night, the patient had a steady increase in vasopressor requirements prompting a new pan-culture and additional antibiotics given for probable hospital acquired infection. Norepinephrine was increased to 1.0 mcg/kg/min while the patient experienced sinus bradycardia which decompensated into a third degree heart block shortly before an asystolic arrest. ACLS guidelines were followed for a bradycardic ROSC requiring transcutaneous pacing followed by the prompt insertion of a transvenous pacemaker. The patient subsequently experienced multiple asystolic arrests resulting from loss of capture likely related to her profound acidosis. CRRT was briefly restarted at this time to attempt to manage the acidosis but despite the aggressive support provided, the patient passed away that day in the presence of family.

Due to the patient's sudden and catastrophic hemodynamic collapse, bradycardia, and high anion gap metabolic acidosis despite successful theophylline clearance, the critical care attending attributed her death to propofol related infusion syndrome (PRIS) and no autopsy was performed.

During this patient's admission, her series of adverse events were preceded by textbook signs and symptoms of theophylline toxicity. Instead of being further investigated, her symptoms were separately attributed to delirium, chronic nausea and post-operative complications from her nephrectomy. Since it had been established in the emergency department that this patient's primary issue was pyelonephritis, the following providers were biased by that perspective and did not see the whole clinical picture. In fact, prior to her nephrectomy, the patient's chronic nausea, vomiting and loss of appetite could have been the early signs of mild theophylline toxicity [3,14]. If any provider had done a thorough independent review of the entire narrative during either of her admissions, perhaps they could have recognized the pattern of her symptoms and perhaps saved her life.

Additionally, this patient situation illuminates a common clinical conundrum – whose clinical responsibility should it have been to identify theophylline toxicity as a potential post-operative complication for this patient? What was happening to this woman slipped by multiple physicians, nurses, and specialist consults who were each independently competent enough to have determined what was actually occurring, but each only evaluated a specific piece of the puzzle. Unfortunately, the necessary divisions of labour and specialization in addition to exponentially increased workloads in medicine have generated the unintended consequence of destructive and inevitable disconnections such as this. This silo mentality is pervasive in medicine, from technology to treatments, and can be deadly. In order to begin to bridge the silos that have been created in healthcare, each additional individual involved with a patient must take the opportunity to critically examine the issues and attempt to not make any assumptions based on other practitioners' evaluations.

The manner by which medications are ordered through to being administered in-hospital is an error-prone process. The stages of this process include ordering, transcribing and verifying, dispensing, administering, monitoring and/or reporting-all of which leave plenty of opportunity for error from illegible handwriting to the wrong route or time. Preceding these stages, there is evidence that indicates that over 30% of medication errors can be attributed to lack of knowledge about the medication or the patient [15]. And although nurses are increasingly challenged with the demands of a high workload and in turn have much less time to critically think, they remain to be the last defence before a patient receives an inappropriate medication.

This patient's ICU admission, and ultimately her demise, were directly related to this multi-faceted medication error despite the critical care attending physician's determination that her death was solely related to PRIS. Under provincial law, a person's death should be reported to the medical examiner if it results from any type of poisoning which would include PRIS as well as theophylline toxicity. After this case review was conducted, a posthumous critical incident report was submitted by this author and is being investigated by the patient safety officer for the facility.

CONCLUSION

Furthermore, given the substantial decrease in serum theophylline following a loading dose and four additional doses of phenytoin, perhaps its efficacy as a theophylline clearance agent should be further studied. Phenytoin could potentially have a place in acute or chronic overdoses in a patient that may or may not have experienced seizures and is hemodynamically stable (i.e. acute on chronic exposure) and could have a significant cost-savings effect in the context of hemodialysis nurse utilization and/or intensive care unit admission. Further, phenytoin has the possibility of becoming an additional adjunct to extracorporeal removal and MDAC.

This report illuminates the need for robust independent analysis by every member of the health care team regarding each intervention in every patient. Even the interventions that seem mundane and routine, like continuing a long-term home medication, can ultimately lead to patient deaths. All of us need to be vigilantly inquisitive to keep our patients safe and report all events that have or could affect patient safety.

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