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Case Report

A Case Report of Severe Theophylline Poisoning: Management and Review of Literature

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ABSTRACT

Background

Theophylline poisoning leads to multisystem toxicity. Management of theophylline overdose is focused on stabilizing cardiovascular manifestations of arrhythmia and hypotension, correcting metabolic derangements, aborting seizures and removing the drug from the system. We present a case of refractory seizures and haemodynamic instability from theophylline poisoning and reviewed the literature to update the management of severe theophylline overdose.

Case Presentation

A 73-year-old Chinese gentleman presenting with chills and rigor was admitted for management of sepsis. While admitted suffered seizures which were refractory to benzodiazepine and anti-epileptic drugs. Based on his previous admission for theophylline overdose, serum levels were done confirming severe theophylline poisoning. He was resuscitated and subsequently started on haemodialysis following which seizures were eventually aborted when theophylline levels were successfully reduced.

Conclusion

Severe theophylline poisoning should be identified early and appropriate treatment initiated promptly. In the management of refractory hypotension, methylene blue and venoarterial-extracorporeal membrane oxygenation are reasonable rescue therapies to consider. Multi-dose activated charcoal and extracorporeal treatments for elimination of drugs should be administered in severe theophylline poisoning.

Keywords

Theophylline poisoning; Theophylline-associated seizures; Haemodialysis; Case report; Methylene blue; Venoarterial-extracorporeal membrane oxygenation; Multi-dose activated charcoal.

BACKGROUND

Theophylline is used to treat bronchospasm in asthma and chronic obstructive pulmonary disease (COPD) in adults. It blocks adenosine receptors and acts as a phosphodiesterase inhibitor, increasing beta-adrenergic effects and increases the release of catecholamines. Theophylline is a plant derived methyl xanthine compound that is similar to caffeine. It has up to 90% oral bioavailability and has a small volume of distribution of approximately 0.5 L/kg. It achieves peak serum concentration within 1 to 2-hours, although this is slowed in modified-release preparation. The half-life is approximately 8 to 11-hours with clearance lowered in overdose as elimination at high concentrations becomes zero-order.[1]

Acute theophylline toxicity manifestations can occur with doses from 7.5 mg/kg.[2] It presents with a constellation of clinical features that progress with severity as theophylline plasma concentration increases.[1] At lower toxic plasma levels, gastrointestinal features such as nausea and vomiting and neurological features such as headache, agitation and muscle tremor can occur.[3] With higher toxic plasma levels, more severe signs and symptoms such as hypotension, arrhythmia and seizures can occur. Metabolic derangements are more severe in acute toxicity and the ones commonly seen include hypokalaemia and hyperglycaemia.[4] In chronic theophylline intoxication, cardiovascular and neurological manifestation are more prominent. Risk of major toxicity resulting in morbidity correlates with serum theophylline levels in acute toxicity and extreme of ages in chronic toxicity.[5]

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The overall incidence of theophylline toxicity in Singapore is unknown. In America, the number of theophylline overdose reported to the American Association of Poison Control Centers (AAPCC) has decreased from 3100 cases reported in 1996[6] to 140 cases reported in 2019.[7] This is largely due to the decline in use of theophylline in the treatment of asthma and COPD with the emergence of other bronchodilator therapies. However, it still has a role in adult patients with asthma[8] and COPD as a third or fourth line therapy.[9]

The management of theophylline overdose is complex with life-threatening complications occurring across multiple systems in the body. The existing literature does cover the conventional management of theophylline overdose, however, there is a lack of information on further therapeutic measures that might need to be considered in the event of a severe theophylline overdose resulting in complications that are refractory to standard management. We aim to review the literature and provide an overview of the management of severe theophylline overdose.

CASE PRESENTATION

Our patient is a 73-year-old gentleman, with a past medical history of COPD, ischaemic cardiomyopathy, erosive esophagitis and seizure secondary to viral meningoencephalitis. He was brought into hospital *via* ambulance services with the presenting complain of chills and rigors of one day duration, with no recorded febrile temperature and occasional dry coughs for the past four-days. His wife provided further collaborative history and mentioned that he was alert, orientated and conversant during the episodes of rigors she had witnessed. The patient denied taking an overdose and his wife had not witnessed any attempt at poisoning. He arrived at the emergency department (ED) that evening with the following vitals: blood pressure (BP) of 83/54 mmHg, heart rate (HR) of 113 beats per minute, respiratory rate (RR) of 20 breaths per minute, oxygen saturation of 97% on room air. On examination, he was alert but noted to be breathless. There was scattered rhonchi heard bilaterally on examination of his lungs with no obvious crepitations. Notably, his right lower limb was swollen and red with pitting oedema. The rest of the physical examination was unremarkable. Electrocardiogram performed showed sinus tachycardia (HR 110, QTc 536 ms). Venous blood gas showed a pH of 7.4, serum bicarbonate of 19.8 mmol/L, normal anion gap acidosis with a corrected anion gap of 15, delta ratio 0.4 and lactate of 3.2 mmol/L. Renal and liver function tests were normal (serum potassium 4.2 mmol/L, serum glucose 8.2 mmol/L). Chest radiograph done to further evaluate his symptom of cough was unremarkable for congestion or consolidation. Serum theophylline, paracetamol and salicylate levels were sent in view of the recent history of theophylline poisoning.

His dyspnoea was initially attributed to COPD exacerbation and he was given intravenous (IV) hydrocortisone 100 mg and started on dry nebulisers. His hypotension and tachycardia on arrival was attributed to septic shock from a right lower limb cellulitis and he was started on IV Meropenem 1 g. After completing 500 mls of normal saline that was started by the paramedics, his blood pressure improved to 100/80 mmHg but he remained tachycardic at a PR of 130. Later that evening, he was noted to be increasingly dyspnoeic, with bibasal crepitations on lung examination and bilateral B lines seen on bedside ultrasound. There was now concern of a fluid overload state. Considering his dyspnoea and haemodynamic instability, he was admitted to a medical high dependency unit (HDU) for closer monitoring (Figure 1).

Figure 1. *Timeline Depicting the Main Progress During the First 7-Days of Admission*

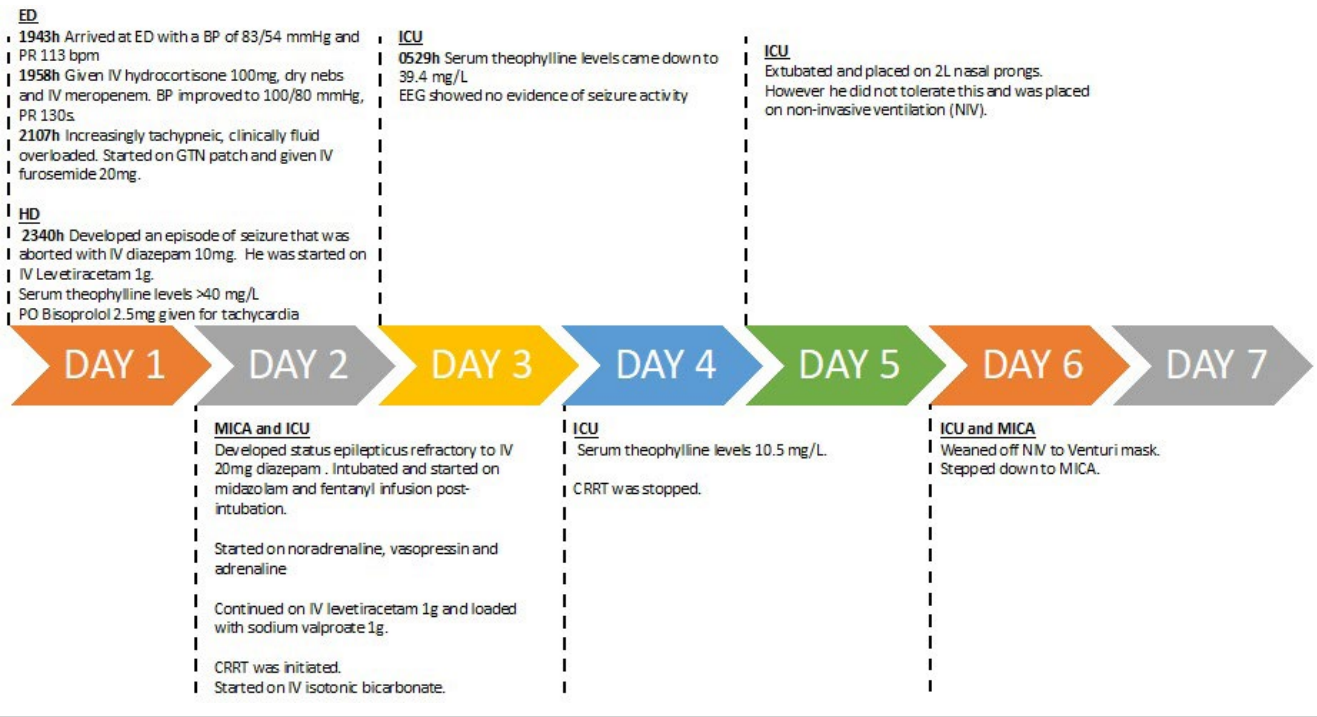
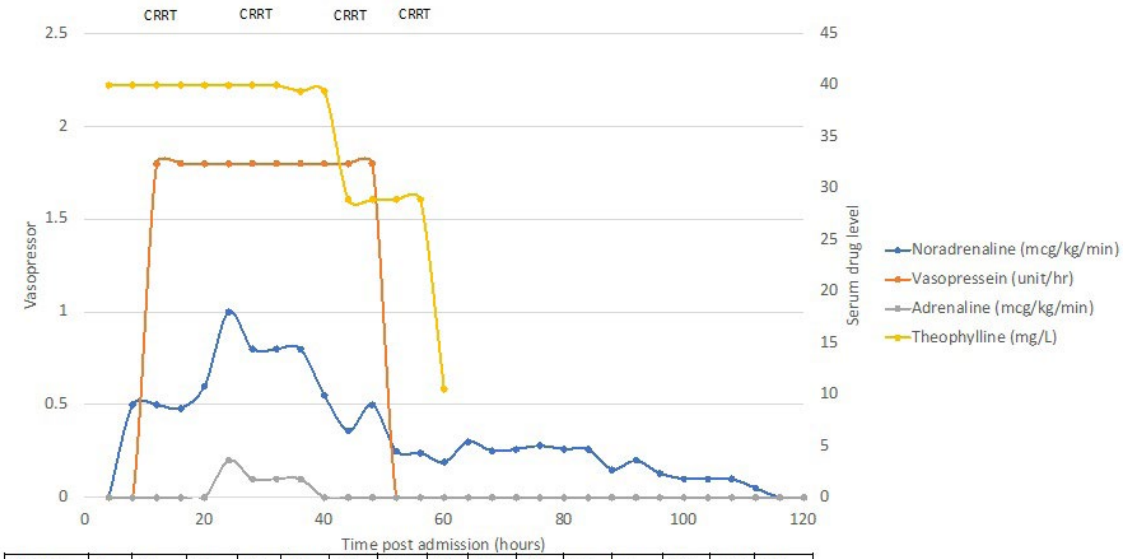


Figure 2. *Line Graph of Vasopressor Support and Serum Theophylline Levels Post Admission with CRRT as an Intervention*



Time (h)	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120
BP (mmHg)	84/50	105/54	97/48	115/67	98/57	112/54	115/53	72/67	105/74	101/65	98/58	113/56	107/54	151/71	164/79
HR (bpm)	117	106	106	121	109	84	104	85	82	84	94	86	83	100	103

On arrival at the medical HDU he was noted to have seizure with right gaze preference, tonic-clonic jerking movements of his right upper limb, left upper limb and bilateral lower limbs stiffening. His seizure was aborted with IV diazepam 10 mg. He was loaded with IV levetiracetam 1 g. Serum theophylline levels were >40.0 mg/L (laboratory could not provide exact level) and salicylate and paracetamol levels not elevated. He was also given oral bisoprolol 2.5 mg for his sinus tachycardia (Figure 2).

In the early hours of the next day, he developed status epilepticus that was refractory to 2 doses of IV diazepam 10 mg. He was intubated for ongoing status epilepticus, a depressed GCS of E4V1M3 and haemodynamic instability. He was subsequently transferred to the intensive care unit (ICU). Post-intubation, he was started on midazolam and fentanyl infusion. He became haemodynamically unstable with hypotension post-intubation and was started on noradrenaline and vasopressin. He was reviewed by the neurologist and placed on regular IV levetiracetam 1 g twice daily and was loaded with a second anti-epileptic sodium valproate of 1 g and maintained on 400 mg twice daily after. He was reviewed by the renal physicians and continuous renal replacement therapy (CRRT) was initiated. He was also started on 500 mls of IV isotonic bicarbonate. Meropenem was stopped due to possible interactions with sodium valproate and his antibiotics was switched to piperacillin tazobactam. Later that evening, he was started on a third vasopressor adrenaline as blood pressure was persistently borderline.

On day 3 of admission, serum theophylline levels came down to 39.4 mg/L. He was weaned off adrenaline. Electroencephalography conducted later that day showed no evidence of seizure activity. Sodium valproate was held off and he was placed on levetiracetam 1 g every 8-hours due to deranged liver function tests.

On day 4 of admission, serum theophylline levels were now in the normal range of 10.5 mg/L and CRRT was stopped. He was subsequently extubated on day 5 and stepped down to medical HDU two days after. No further seizure episodes were observed during his hospital stay. An alert was raised in his electronic medical records to avoid further theophylline prescriptions. He was transferred to a subacute hospital for rehabilitations 55-days after admission with an outpatient neurology and respiratory follow-up.

DISCUSSION

Theophylline poisoning leads to multisystem dysfunction with high risk of serious cardiovascular instability and neurological complications. The immediate management of theophylline overdose is often that of its life-threatening complications.

Management of Theophylline Induced Cardiovascular Instability

Hypotension in theophylline overdose occurs as a result of beta 2 adrenergic stimulation and phosphodiesterase inhibition leading to vasodilation. Besides intravascular isotonic fluid boluses, vasoactive, predominately alpha adrenergic acts such as noradrenaline and phenylephrine[10] and beta adrenergic antagonists such as propranolol or esmolol[11] are used in theophylline induced hypotension. Common cardiac arrhythmias in theophylline poisoning, such as SVT, should also be addressed as they contribute to cardiovascular instability. Although adenosine is recommended by

advanced cardiac life support (ACLS) guidelines for treatment of supraventricular tachycardia (SVT), it has a high incidence of therapeutic failure when given in the setting of theophylline poisoning. This is the result of the short half-life of adenosine and the potent and profound adenosine receptor agonism of theophylline. A selective beta 1 antagonist such as esmolol is a good alternative as it can effectively terminate SVT and can be titrated to maintain this effect as a continuous infusion. It can be safely used in the setting of patients with asthma or heart failure.[12] If hypotension persists and is refractory to these standard treatment, other treatments can be explored. Vasopressin and its analogues can be considered an added on therapy to current vasoactive agents. It has been used in vasoplegic shock states in sepsis and after cardiac surgeries,[13] and has been used in drug overdosed states namely caffeine and calcium channel blockers[14,15] Methylene blue has also been used to treat vasoplegic shock[16] arising from a variety of settings such as septic shock,[17] cardiac surgery[18,19] and liver transplantation.[20] Data on the use of methylene blue in drug-induced vasoplegic shock have varied outcomes.[21] Further studies are required to determine the mortality benefit of using methylene blue in drug-induced vasoplegic shock. For now, methylene blue could be considered a form of rescue therapy in refractory vasoplegic shock that is unresponsive to conventional treatment. The last potential therapeutic option for refractory hypotension is the use of venoarterial-extracorporeal membrane oxygenation (VA-ECMO). VA-ECMO has been used in treatment of cardiogenic shock as a bridge to recovery of myocardium or until definitive treatment with heart transplant can be ascertained.[22] The use of VA-ECMO in drug-induced cardiogenic shock has been shown to improve haemodynamic and metabolic status in patients who do not respond to conventional medical treatment,[23] providing them the support they need until the toxic agent can be broken down or removed. VA-ECMO can be considered for use in drug-induced cardiogenic shock that is refractory to conventional therapy or in cardiac arrest.[24]

Management of Theophylline-Associated Seizures

Another serious complication of theophylline poisoning is theophylline-associated seizures (TAS), which can be intractable to first line seizure therapy with benzodiazepine, leading to status epilepticus.[25] Theophylline's antagonistic effect on adenosine receptor A2 and its inhibition of gamma-aminobutyric acid receptors are some of the proposed mechanism of theophylline's interaction with benzodiazepine, rendering it less useful in aborting TAS.[26] Hence, it is important to initiate early alternative therapy with anti-epileptic drugs (AED).[27] In the treatment of toxin-related seizures, pyridoxine[28] and propofol should be considered 2nd and 3rd line therapy after benzodiazepines.[29] There are however limited studies on the treatment of TAS specifically. In animal studies, the use of diazepam, clonazepam, phenobarbital or valproic acid increases threshold for theophylline-induced seizures[30] while phenobarbital is more effective than phenytoin in the termination of theophylline induced seizure.

Decontamination and Enhanced Elimination

Gastrointestinal decontamination with activated charcoal can be given if patients present early. In addition, the use of multi-dose activated charcoal (MDAC) can also be considered in patients who have ingested life-threatening amounts of theophylline.[31] Whole bowel irrigation might not be as effective in theophylline poisoning, as it reduces the capacity of charcoal to bind to theophylline. Recent clinical studies have substantiated the lack of improvement in the poisoned patient.[32] Extracorporeal treatments (ECTRs) enhance theophylline elimination with severe poisoning. It is indicated for use in acute overdose with theophylline serum levels >100 mg/L and in chronic overdose with serum theophylline level >60 mg/L or >50 mg/L if the patient is less than 6-months-old or more than 60-years-old. It is also indicated in presentations of severe toxicity, including seizures, life-threatening dysrhythmias, and shock. Rising serum theophylline levels despite optimal therapy should also prompt the use of ECTRs. As per the extracorporeal treatments in poisoning (EXTRIP) workgroup's recommendation, ECTRs should continue until clinical improvement or serum theophylline level is below 15 mg/L. The preferred form of ECTRs is intermittent hemodialysis, with hemoperfusion and CRRT being reasonable alternatives.[33] Exchange transfusion and peritoneal dialysis clearance rate seldom exceeded 15 ml/min which was deemed clinical significant only in newborns.[34]

CONCLUSION

In conclusion, severe theophylline poisoning should be identified early and appropriate treatment initiated promptly. In the management of refractory hypotension, methylene blue and VA-ECMO are reasonable rescue therapies to consider. MDAC and ECTRs should also be considered and administered in severe theophylline poisoning.

DECLARATIONS

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

Availability of Data and Materials

Not applicable.

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Authors Contributions

ZJ and RP are major contributors in writing the manuscript. IH collated and summarised the information used in writing up the manuscript. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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