Case Report

Theophylline toxicity: a case report of an unusual mimicker of septic shock

Rehman Jinah[1], Jerrold Perrott[2,3]^, Vinay Dhingra[4]

[1]Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Department of Pharmacy, Vancouver General Hospital, Vancouver, BC, Canada; [3]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; [4]Division of Critical Care Medicine, Department of Medicine, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada

Correspondence to: Dr. Jerrold Perrott. Department of Pharmacy, Vancouver General Hospital, Vancouver, BC V5Z 1M9, Canada.
Email: jerrold.perrott@vch.ca.

Background: In cases of decompensated shock that fail to respond to initial resuscitative and supportive interventions, alternate causes should be explored, such as medication toxicity. Theophylline is an infrequently used treatment for chronic obstructive pulmonary disease (COPD) with a narrow therapeutic index and a toxidrome that can closely resemble septic shock. As it is cleared through both hepatic and renal mechanisms, acute alterations in organ function can lead to accumulation and symptomatic toxicity.

Case Description: We present a case of a 77-year-old woman who was admitted to the intensive care unit after a fall on the medical ward with symptoms suggestive of sepsis. She had an extensive work up for septic sources and pulmonary embolism, which were negative, and was ultimately found to have supratherapeutic theophylline serum levels. She was carefully managed in the intensive care unit with support from our regional toxicology service and with dialysis and supportive care, fully recovered.

Conclusions: We present this case report to remind clinicians to keep a broad differential diagnosis open when assessing a patient who fails to respond to initial measures and to advise therapeutic drug monitoring of theophylline for any patient who is unstable, demonstrates signs or symptoms of toxicity, or has alterations to renal or hepatic function in the setting of acute illness.

Keywords: Theophylline; toxicity; shock; case report

Received: 27 January 2022; Accepted: 14 April 2022; Published: 30 April 2022.
doi: 10.21037/jeccm-22-10
View this article at: https://dx.doi.org/10.21037/jeccm-22-10

Introduction

The management of a patient in decompensated shock requires rapid evaluation for probable causes and contributing factors. In cases where clinical improvement is not observed after providing targeted interventions against common inciting causes, such as volume replacement for hypovolemic shock and broad-spectrum antibiotics for septic shock, less common etiologies should be explored to further dictate management. We present a case of theophylline toxicity that mimicked the signs and symptoms of septic shock and describe the clinical course and management strategies for this patient.

Theophylline, part of the methylated xanthine family of drugs, is used for the management of chronic obstructive pulmonary disease (COPD) and asthma primarily for bronchodilatory effects, while in neonates it has been used to treat bradycardia and apnea (1,2). The mechanism of action of theophylline is contested, however, it can target phosphodiesterase receptors, adenosine receptors, and has some indirect stimulation of beta-1/beta-2 receptors (3,4). The drug is readily and rapidly absorbed through the gastrointestinal tract and can be affected by gastric

^ ORCID: 0000-0002-4341-1278.

Table 1 Signs and symptoms of theophylline toxicity (2)

System	Signs and symptoms
Behavioral	Agitation, irritability, restlessness
Neurological	Tremors, hallucinations, seizure
Cardiovascular	Sinus tachycardia, atrial fibrillation, ventricular tachycardia, hypotension, cardiac arrest
Respiratory	Tachypnea, acute lung injury, respiratory alkalosis
Gastrointestinal	Nausea, vomiting, abdominal pain

Table 2 Home medications

Indication	Medications
COPD/asthma	Salbutamol 5 mg four times daily as needed
	Ipratropium 0.5 mg four times daily
	Theophylline 600 mg daily
CHF/CAD	Ramipril 10 mg daily
	ASA 80 mg daily
	Atorvastatin 20 mg daily
	Amlodipine 5 mg daily
Osteoporosis	Alendronate 70 mg weekly
	Vitamin D 1,000 units daily
	Calcium carbonate (dose not specified)
GERD	Pantoprazole 40 mg daily
Pain	Acetaminophen with caffeine and codeine as needed

COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CAD, coronary artery disease; ASA, acetylsalicylic acid; GERD, gastroesophageal reflux disease.

pH and contents (4). Theophylline is distributed within extracellular fluid and can be bound to albumin (50%). The liver metabolises up to 90% of the parent drug and the metabolites are eliminated through the urine (4). The half-life of theophylline ranges between 6 and 13 hours in adults and can be heavily influenced by hepatic function, renal impairment, and congestive heart failure (CHF) (2). The therapeutic serum levels of theophylline are 55 to 110 µmol/L (10 to 20 µg/mL) and toxic levels are above 110 µmol/L (2). It should be noted that toxicity can occur within the therapeutic range and that severe toxicity, including dysrhythmias, seizures, and death can occur at levels of 440 to 550 µmol/L (2). Other common symptoms of toxicity are detailed in *Table 1* (2). We present the following case report in accordance with the CARE reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-10/rc).

Case presentation

Our patient was a 77-year-old woman with severe COPD (FEV1 of 27%), asthma, mild CHF, coronary artery disease (CAD), osteoporosis with compression fractures, and gastroesophageal reflux disease (GERD) who presented via ambulance to the emergency department with an acute exacerbation of COPD (AECOPD) on October 2nd 2018. Her home medications are presented in *Table 2*.

She was initially admitted to the clinical teaching unit under the Internal Medicine Team who initiated standard therapy for an AECOPD with supplemental oxygen, corticosteroids, bronchodilators, and antibiotics targeted to community acquired pneumonia. Home medications were continued, including theophylline. Over the first week in hospital, she continued to have dyspnea and orthopnea which slowly improved. Her course was complicated by a mild rise in her serum creatinine. Detailed laboratory findings are presented in *Table 3*.

On day 9 of her hospital stay, she was found down next to her bed and a "code blue" was called, bringing the Intensive Care Team to her bedside. Collateral from her nurse reported that she was eating breakfast with a care aid 5 minutes prior and was behaving normally without any neurological symptoms or concerns. The patient was placed in a c-spine collar with a frontal laceration present indicating she had fallen from her bed. She was hypertensive (187/100 mmHg), tachycardic (160 bpm), and tachypneic with increased work of breathing initially. She was also agitated and was given hydralazine, haloperidol, and ketamine. A head CT was obtained which ruled out any acute intracranial process. She quickly became hemodynamically unstable and there were concerns for her

Table 3 Laboratory findings

Test	Reference	03-Oct	04-Oct	09-Oct	11-Oct (06:28)	11-Oct (10:15)	11-Oct (12:25)	11-Oct (14:10)	11-Oct (15:45)	11-Oct (17:05)	11-Oct (18:00)	12-Oct	13-Oct	14-Oct	15-Oct	16-Oct
Hematology																
WBC	4×10^9–$1^1\times10^9$/L	11.7	9.6	14.6	–	30	–	–	–	37.6	–	20.8	16.2	18.7	19.3	18.7
Hb	120–155 g/L	138	125	133	–	122	–	–	–	115	–	104	92	86	96	93
Platelets	150×10^9–400×10^9/L	257	253	289	–	259	–	–	–	244	–	193	129	125	141	153
Chemistry																
Sodium	135–145 mmol/L	136	137	134	129	131	–	–	–	134	–	137	139	137	136	137
Potassium	3.5–5 mmol/L	3.2	3.4	3.1	4.7	4.4	–	–	–	4.0	–	4.2	4.1	4.5	2.9	4.7
Chloride	95–107 mmol/L	99	99	95	94	96	–	–	–	102	–	107	106	103	102	104
Bicarbonate	22–31 mmol/L	28	23	28	24	22	–	–	–	16	–	24	28	29	29	28
Anion gap	8–16.5 mmol/L	12	18.4	14.1	15.7	17.4	–	–	–	20	–	10.2	9.1	9.5	9.9	9.7
Creatinine	40–95 μmol/L	89	76	100	168	171	–	–	–	117	–	51	90	56	100	62
Lactate	0.5–2.2 mmol/L	–	1.6	1.7	–	3.2	–	–	–	–	–	–	–	–	–	–
Calcium (ionized)	1.10–1.30 mmol/L	–	–	–	–	0.96	–	–	–	–	–	1.29	0.71	0.63	0.89	0.71
Phosphate	0.8–1.45 mmol/L	–	–	–	–	1.6	–	–	–	–	–	0.95	0.76	0.95	0.84	0.85
Magnesium	0.7–1.1 mmol/L	–	–	–	–	0.58	–	–	–	–	–	–	–	–	–	–
ABG																
pH	7.32–7.43	–	–	–	–	7.25	7.19	7.21	7.20	–	–	7.43	7.45	7.46	7.46	–
pCO_2	35–45 mmHg	–	–	–	–	47	46	43	41	–	–	36	38	41	39	–
pO_2	>80 mmHg	–	–	–	–	224	171	104	98	–	–	92	93	91	113	–
Bicarbonate	22–29 mmol/L	–	–	–	–	20	17	17	15	–	–	23	26	29	27	–
Enzyme/protein chemistry																
GGT	10–55 U/L	–	14	–	–	242	–	–	–	–	–	–	–	–	–	–
AP	30–160 U/L	–	62	–	–	131	–	–	–	–	–	–	–	–	–	–
ALT	10–45 U/L	–	20	–	–	33	–	–	–	–	–	–	–	–	–	–
AST	10–38 U/L	–	16	–	–	51	–	–	–	–	–	–	–	–	–	–
LDH	90–240 U/L	–	221	–	–	446	–	–	–	–	–	–	–	–	–	–
Troponin	<0.10 μg/L	–	–	–	–	0.14	–	–	–	1.18	–	0.42	–	–	–	–
BNP	<168 ng/L	–	–	46	–	–	–	–	–	–	–	–	–	–	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Test	Reference	03-Oct	04-Oct	09-Oct	11-Oct (06:28)	11-Oct (10:15)	11-Oct (12:25)	11-Oct (14:10)	11-Oct (15:45)	11-Oct (17:05)	11-Oct (18:00)	12-Oct	13-Oct	14-Oct	15-Oct	16-Oct
Drugs																
Salicylate	0.3–2.1 mmol/L	–	–	–	–	–	–	–	–	0.1	–	–	–	–	–	–
Theophylline	55–110 mmol/L	–	–	–	–	–	–	–	–	176	–	33	–	–	–	–
Endocrine																
TSH	0.38–4.85 mIU/L	–	0.62	–	–	–	–	–	–	–	–	–	–	–	–	–
Cortisol	80–620 nmol/L	–	–	–	766	–	–	–	–	–	–	–	–	–	–	–

WBC, white blood cell count; ABG, arterial blood gas; GGT, gamma glutamyl transferase; AP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase; BNP, brain natriuretic peptide; TSH, thyroid stimulating hormone.

maintaining her airway and she was therefore transferred to the ICU.

In the ICU she became progressively more hypotensive despite volume resuscitation and required vasopressor support to maintain her mean arterial pressure greater than 65 mmHg. Her initial bloodwork was significant for a leukocytosis, a mildly elevated troponin, a lactate of 3.2 mmol/L, an acute kidney injury (AKI) and an arterial blood gas with an anion gap metabolic and respiratory acidosis (as detailed in *Table 3*). Her initial working diagnosis was aspiration/hospital acquired pneumonia leading to septic shock and she was commenced on meropenem and vancomycin. A CT scan of her chest was obtained which demonstrated only small bilateral subsegmental pulmonary embolisms and no evidence of pneumonia. Other septic work up, including microbiology of sputum and blood, was negative for evidence of bacterial infection.

Despite significant fluid resuscitation and vasopressor support (vasopressin and norepinephrine), she remained hemodynamically unstable (hypotensive and tachycardic) and had a progressive increase in her anion gap. This lead our team to broaden our differential diagnosis to other etiologies and theophylline toxicity was postulated as a potential contributor. At this time, her serum theophylline level was measured to be 176 µmol/L, supporting the diagnosis of theophylline toxicity.

With her AKI, unstable hemodynamics, and evidence of theophylline toxicity, and in consultation with a regional toxicology specialist from the British Columbia Drug and Poison Information Centre, we commenced continuous renal replacement therapy (CRRT) (Baxter PrismaFlex system) configured to provide continuous veno-venous hemodiaultrafiltration. Additionally, she was commenced on an infusion of unfractionated heparin for the pulmonary embolism and her antibiotics were narrowed and ultimately stopped as infection was deemed less likely her cause of decompensation. She demonstrated rapid clearance of her serum theophylline while on CRRT (see *Table 3*) and her hemodynamics normalized over the following 3 days. Overall, she stayed in ICU for 5 days before being transferred back to the clinical teaching unit team on day 14 of her admission. From there she was ultimately discharged back to her home at her prior baseline level of function.

She provided informed consent for the publication of this case report and the need for research ethics approval was waived by our affiliated hospital and university research ethics boards. All medical care and procedures performed were in accordance with the ethical standards of our

institution, ethics review boards, and with the Helsinki Declaration (as revised in 2013).

Discussion

This case is presented to demonstrate an uncommon, but important mimicker of septic shock. Our patient was admitted to hospital for a COPD exacerbation and went on to develop respiratory distress, altered mental status, hemodynamic instability requiring vasopressor support, tachycardia, leukocytosis, and an elevated lactate. Whether you apply the traditional Systemic Inflammatory Response Syndrome (SIRS) criteria (5) or Sequential Organ Failure Assessment (SOFA) score (6), this patient fit a picture of septic shock with a hospital acquired pneumonia as a probable source, whereas her ultimate diagnosis was determined to be theophylline toxicity.

We wanted to raise awareness other common sepsis mimickers to keep on the broad differential, such as hypovolemia, pulmonary embolism, pancreatitis, diabetic keto acidosis, and adrenal insufficiency (7). In 2017, Long and Koyfman, published a review looking at this topic and further identify anaphylaxis, aspiration, bowel obstructions, thyroid storm, intestinal ischemia, vasculitis, withdrawal, and spinal cord injuries as potential sepsis mimics (8). Moreover, they recognized that toxic ingestion, without specific mention of theophylline, can similarly mimic a septic patient (8).

Although COPD management has changed over the last several decades with the introduction of more effective inhaled medications and reduced utilization of systemic theophylline, it is still occasionally used in select patient populations. With an aging population, stable chronic medications can present with unexpected toxicity as the patient becomes more susceptible to therapeutic effects and potentially has altered function of organs of elimination leading to accumulation. We suspect that our patient experienced chronic theophylline toxicity due to accumulation related to her AKI.

The pearls that we want readers to take from this case presentation are that theophylline toxicity can mimic the signs and symptoms of septic shock and that the local toxicologist is an important ally in the management of suspected toxic ingestions whether they are acute or chronic. Additionally, our case supports the practice of conducting therapeutic drug monitoring of theophylline on any patient who is unstable, decompensating, or displaying any potential signs of systemic toxicity.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-10/rc

Peer Review File: Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-10/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-10/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 medical care and procedures performed were in accordance with the ethical standards of our institution, ethics review boards, and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Weinberger M, Hendeles L. Theophylline use: an overview. J Allergy Clin Immunol 1985;76:277-84.
2. Journey JD, Bentley TP. Theophylline Toxicity. In: StatPearls. Treasure Island, FL, USA: StatPearls Publishing, 2021.
3. Hendeles L, Massanari M, Weinberger M. Update on the

pharmacodynamics and pharmacokinetics of theophylline. Chest 1985;88:103S-11S.
4. Rosenal TW. Uses and abuses of theophylline. Can Fam Physician 1987;33:2575-9.
5. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
6. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754-8.
7. Cunha BA. Sepsis and septic shock: selection of empiric antimicrobial therapy. Crit Care Clin 2008;24:313-34, ix.
8. Long B, Koyfman A. Clinical Mimics: An Emergency Medicine-Focused Review of Sepsis Mimics. J Emerg Med 2017;52:34-42.

doi: 10.21037/jeccm-22-10
Cite this article as: Jinah R, Perrott J, Dhingra V. Theophylline toxicity: a case report of an unusual mimicker of septic shock. J Emerg Crit Care Med 2022;6:19.