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Case Report

Children Theophylline Toxicity: Case Report

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Introduction

Theophylline, a methylxanthine derivative, has historically been used as a bronchodilator for conditions like asthma and Chronic Obstructive Pulmonary Disease (COPD). However, its use has declined due to the availability of safer alternatives with lower toxicity profiles. Despite this decline, cases of theophylline toxicity, particularly in children, can lead to severe complications, including status epilepticus, hemodynamic instability and metabolic disorder.

Case Report

After ingesting 2000 mg of theophylline, a 5-year-old girl arrived at an external emergency department, reporting abdominal pain and vomiting that had persisted for one day, where they recommended outpatient monitoring and hydration with water. It is important to note that theophylline was a long-term treatment for her grandfather's COPD. A few hours after discharge, she experienced a generalized tonic seizure with eye rolling, without urination leakage, lasting 5 minutes, followed by her arrival at the emergency room 30 minutes later.

Upon admission to the emergency department, clinical assessment revealed a conscious patient with a Glasgow Coma Scale (GCS) score of 15/15, indicating full consciousness. The patient exhibited tachycardia with a heart rate of 179 beats per minute and hypotension, with blood pressure of 90/50 mmHg. Additionally, respiratory evaluation showed tachypnea at a rate of 49 breaths per minute, and oxygen saturation was 93% in ambient air. Signs of respiratory distress were observed; however, lung auscultation revealed clear breath sounds. The patient was afebrile and displayed no signs of dehydration. Blood sugar levels were noted at 2.14 mmol/L, with 3+ ketones detected in the urine. She presented with tachycardia and diabetic ketoacidosis and was thus admitted to the pediatric intensive care unit for theophylline

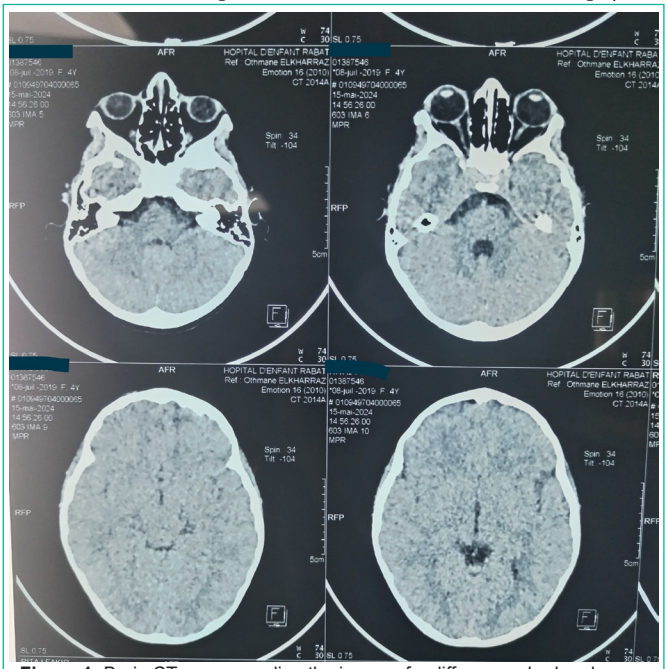

Figure 1: Brain CT scan revealing the image of a diffuse cerebral oedema.

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ingestion. In pediatrics, the toxic dose of theophylline may be as low as 7.5 mg/kg, although symptoms of toxicity typically occur when plasma concentrations exceed 20 µg/mL, about 1.2 mg/kg. Levels above 25 µg/mL, about 1.5 mg/kg, are commonly associated with severe toxicity [1-3].

On arrival at the Pediatric Intensive Care Unit, vital signs were temp 37.2°C, heart rate 210 bpm, blood pressure 155/8mmHg and respiratory rate 30/min. She was hyperventilating with an irregular respiratory pattern. her Glasgow Coma Scale was 7, with generalized tonic seizure with eye rolling.

midazolam (1 mg) was given. The patient underwent orotracheal intubation based on the neurological and hemodynamic criteria. As seizure activity continued, midazolam infusion was started at 1mg IV, followed by a second dose 1mg IV, after which we added gardenal 20mg IV and 20mg/kg/day with continuous infusion until cessation of clinical seizures.

Hemodynamic instability developed despite additional normal saline administration. noradrenaline was started at 10 mg/kg/min. Tachycardia continued.

Initial arterial blood gas showed pH 7.28, pCO2 37,5mmHg, pO2 275 mmhg on 35% oxygen.

a brain CT scan was performed, revealing cerebral oedema.

Some complications occurred during the stay in intensive care, the patient developed a fever, an infectious assessment was carried out objectifying: ECBU: E. coli, hemocuture: Pseudomonas aeruginosa. for which she was put on: tazocillin and amikacin.

Acute renal failure with preserved diuresis was diagnosed without recourse to hemodyalisis treated by saline solution.

the evolution was marked by the decrease in heart rate: from 200 beats per minute to 90 beats per minute; Metabolic abnormalities: hyperglycaemia, hypokalaemia has been corrected, the normalization of the renal assessment and the sterilization of the bacteriological samples.

Electroencephalogram was normal and on the CT scan was normal, and appearance of signs of awakening let us stop sedation and decide to extubate the patient.

Discussion

Theophylline, a methylxanthine derivative, has been utilized in the treatment of bronchospasm and other respiratory conditions for over 50 years. Its therapeutic effects are attributed to several mechanisms, including bronchodilation and anti-inflammatory actions, although the precise mechanisms remain a topic of debate.

Theophylline primarily functions as a bronchodilator by inhibiting phosphodiesterase enzymes, which leads to increased levels of cyclic AMP (cAMP) in smooth muscle cells. This results in relaxation of bronchial smooth muscle and improved airflow. Additionally, theophylline antagonizes adenosine receptors, which prevents bronchoconstriction caused by adenosine, and activates histone deacetylase, enhancing the anti-inflammatory effects of corticosteroids [4,5].

Theophylline is now generally considered a third-line treatment option, primarily used as an add-on therapy for patients with asthma or Chronic Obstructive Pulmonary Disease (COPD) who do not respond adequately to other treatments [4,6,7]. Recent guidelines have recommended against its use in acute exacerbations of COPD, citing the risk of adverse events [4,5].

Despite its long-standing use, theophylline is associated with a significant risk of toxicity. Studies indicate that up to 21% of patients on theophylline may experience toxicity, with mortality rates in some cases reaching as high as 10% [4]. In 1997 alone, there were 2,609 reported toxic exposures in the United States, resulting in 20 fatalities, with a notable number of these cases occurring in children [4]. Common side effects include nausea, vomiting, headaches, and at higher concentrations, serious complications such as cardiac arrhythmias and seizures [6,7].

Theophylline toxicity presents with a variety of clinical features affecting multiple organ systems. Main symptoms that come with theophylline toxicity:

Gastrointestinal symptoms are prominent in theophylline toxicity. Vomiting may occur in as many as 70% of children. Nausea and diarrhea often accompany vomiting [8,9]. Cardiovascular manifestations include non-sinus dysrhythmias, which may occur in approximately 22% of cases; these may include tachycardia, with potential life-threatening dysrhythmias such as atrial fibrillation. Hypotension may also occur and is most often the result of vasodilation or volume loss secondary to gastrointestinal symptoms [9,10]. Neurological symptoms include seizures, reported in 5-12% of cases, with status epilepticus occurring in about 0.8%. Notably, seizures in children can occur at theophylline levels below 70 mg/L, which is lower than typically observed in adults [11]. Other metabolic disturbances that may occur include hypokalemia, hyperglycemia, and metabolic acidosis. These abnormalities could theoretically result from the accumulation of lactic acid from tissue hypoperfusion or muscular hyperactivity [9]. Rarely, it has been associated with serious complications like rhabdomyolysis and acute renal failure [11].

These clinical features highlight the severe nature of theophylline toxicity and the need for keen observation and management in affected patients [4,7,9,10].

Treatment of theophylline poisoning is therefore mainly supportive, inclusive of gastrointestinal decontamination and symptomatic treatment in order to ensure the safety and recovery of the patient.

Gastrointestinal Decontamination

Activated charcoal is one of the cornerstones in the management of theophylline toxicity. Oral activated charcoal, 1 g/kg, is advisable in view of the fact that it greatly enhances the clearance of theophylline and reduces its gastrointestinal absorption by about sevenfold. This can reduce the half-life of theophylline by as much as 40-70% in severe cases and by 50% in patients receiving intravenous aminophylline. Contraindications, therefore, may be overlooked when multiple doses are used, especially in cases where serum levels exceed 60 mg/L, as repeated doses could further lower the body concentration of theophylline [10,12].

The cornerstone of the management of theophylline toxicity is supportive care. Airway, breathing, circulation, and hemodynamic status should be monitored continuously. In cases where there is severe respiratory distress, intubation and ventilatory support may be applied. Continuous cardiac monitoring is advised in all cases, especially in those with high presenting levels of theophylline [10].

Seizures due to theophylline toxicity can be resistant to control. Benzodiazepines are drugs of choice: lorazepam, midazolam, or diazepam. In seizures refractory to treatment, addition of phenobarbital or continuous infusion of propofol may be employed for better control.

Isotonic saline can be used to restore circulating volume for the management of hypotension. In refractory hypotension despite fluid resuscitation, alpha agonists such as phenylephrine or norepinephrine are recommended to stabilize the blood pressure.

Nausea and vomiting are some of the common complications that may make the management of toxicity complicated. There is a recommendation for drugs such as ondansetron to be used in controlling the complication for better patient comfort and adherence to treatment protocols.

Extracorporeal Therapies

When theophylline levels are severely elevated, greater than 100 mg/L, or in the case of seizures, life-threatening dysrhythmias, and clinical deterioration despite optimal therapy, extracorporeal treatments such as hemodialysis may be indicated. Hemodialysis is more desirable compared to hemoperfusion because it is generally more effective at removing theophylline from circulation [4].

These treatment modalities place into perspective an integrated approach to the management of theophylline toxicity for the assurance of timely and effective treatment of patients suffering from this condition to avoid serious complications.

In our case, the patient came into the ED long past the window for administration of activated charcoal and thus did not receive this treatment. Nevertheless, the tachycardia is explained by the toxicity of theophylline itself, coupled with the hypokalemia. Once the potassium levels were corrected and theophylline was removed from her system, the tachycardia resolved. As for the status epilepticus that developed, treatment was done on two fronts: infusion of midazolam and phenobarbital, with deep sedation but within recommended dosages. An urgent EEG could not be carried out; hence, a follow-up EEG was done and turned out normal. However, an anticonvulsivant treatment was kept under the control of a pediatric neurologist. The development of acute renal failure was, however functional, and did not necessitate hemodialysis, especially with the conservation of diuresis. Generally speaking, at least the maintenance of stable hemodynamic status is necessary to provide better renal perfusion through sufficient fluid resuscitation.

Conclusion

In conclusion, prevention, especially keeping the medication out of the reach of children, remains the best treatment for theophylline toxicity. Management should be prompt and efficient for exposures to toxic amounts of theophylline in order to stabilize the patient's hemodynamic, respiratory, and neurological status. Early interventions include the administration of activated charcoal if the patient presents within an appropriate time frame, which reduces the absorption of theophylline from the gastrointestinal tract.

Management of these patients is based on effective hemodynamic and respiratory monitoring for vital parameters. Besides this, seizures, if occurring due to theophylline toxicity, should be treated with extreme caution in view of the propensity of children for status epilepticus. The management should also cover the treatment for different complications that may occur along with the condition.

In general, an approach that emphasizes prevention as much as possible, timely treatment, and careful monitoring goes a long way in enhancing prognosis for theophylline toxicity.

References

1. Yaman A, Kendirli T, Ödek Ç, Azapağası E, Erkol H, Pişkin İE, et al. Severe theophylline poisoning treated with continuous venovenous hemodialysis in a child. Turk J Pediatr. 2016; 58: 297-300.
2. Douglas Baker MDM. Theophylline toxicity in children. J Pediatr. 1986; 109: 538-42.
3. Greene SC, Halmer T, Carey JM, Rissmiller BR, Musick MA. Theophylline toxicity: An old poisoning for a new generation of physicians, Turkish Journal of Emergency Medicine. 2018; 18: 37-39.
4. Scurek M, Brat K. A narrative review of theophylline: is there still a place for an old friend?. Journal Of Thoracic Disease. 2024; 16: 3450-3460.
5. Nicolae S Bodor, Kenneth B Sloan, Yu-Neng Kuo. Method for synthesizing certain selected pro-drug forms of theophylline. US Patent US4000132. 1956.
6. Barnes PJ. Theophylline. Am J Respir Crit Care Med. 2013; 188: 901-6.
7. Jilani TN, Preuss CV, Sharma S. Theophylline.. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2024.
8. Goh JW, Thaw MM, Ramim JU, Mukherjee R. Theophylline Toxicity: A Differential to Consider in Patients on Long-Term Theophylline Presenting with Nonspecific Symptoms. Cureus. 2023; 15: e48480.
9. Greene SC, Halmer T, Carey JM, Rissmiller BJ, Musick MA. Theophylline toxicity: An old poisoning for a new generation of physicians. Turk J Emerg Med. 2018; 18: 37-39.
10. Journey JD, Bentley TP. Theophylline Toxicity. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2024.
11. Kong A, Ghosh S, Guan C, Fries BL, Burke FW. Acute on Chronic Theophylline Toxicity in an Elderly Patient. Cureus. 2021; 13: e13484.
12. Goldberg MJ, Park GD, Berlinger WG. Treatment of theophylline intoxication. J Allergy Clin Immunol. 1986; 78: 811-7.