

Clinical perspectives on theophylline induced seizures and hyperglycemia: case study

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Abstract: *Theophylline is a phosphodiesterase inhibitor and an antagonist of adenosine receptor. It acts as a bronchodilator and is used to treat respiratory diseases. Theophylline poses challenges with its narrow therapeutic range and variable pharmacokinetics. Monitoring serum concentration is a crucial factor in avoiding its toxicity, mild toxicity can cause nausea and tachycardia in severe cases it may cause seizures and arrhythmias. Regular monitoring and dose adjustments ensure safe usage. This case report describes a 42-year-old male with a history of hypertension, type 2 diabetes mellitus, chronic kidney disease on hemodialysis, COPD, and recent smoking cessation. The patient presented with headache and involuntary movements of upper and lower limbs, progressing to generalized tonic-clonic seizures. Laboratory findings revealed hyperglycemia, anemia, and elevated lactate levels. Theophylline toxicity was suspected due to chronic use for COPD. Immediate management included the discontinuation of theophylline, stabilization of blood sugar levels, and treatment for seizures. The patient's condition improved over a seven-day hospital stay, and he was discharged with counseling on theophylline toxicity, medication adherence, and the risks of self-medication*

Key Words: *theophylline toxicity, seizures, hyperglycaemia, ciprofloxacin, COPD, patient counselling.*

1. INTRODUCTION:

Chronic medical conditions often necessitate complex therapeutic regimens involving multiple medications to manage various aspects of a patient's health. In this intricate landscape of polypharmacy, theophylline, a bronchodilator commonly used in the treatment of chronic obstructive pulmonary disease (COPD), presents a unique challenge due to its narrow therapeutic range and potential for adverse effects. Theophylline is a methyl xanthine bronchodilator used to treat airway diseases like asthma and COPD. Theophylline primarily acts as adenosine receptor antagonist and phosphodiesterase inhibitor. Theophylline is generally considered safe when used at normal therapeutic doses. Since inhaled beta agonists and corticosteroids are far more effective than theophylline its use has been limited and is now used for third line treatment in patients with poorly controlled therapy as add on drug ¹. A comparatively narrow therapeutic range and significant patient-to-patient pharmacokinetic variability complicate its clinical use. Age, disease condition and drug -interactions are additional variables that could increase chances for adverse effects and toxicities. Target plasma concentration is 10–20 mg/l, even slight elevation in serum concentration greater than 20 mg/l can show to effects, after initiation of therapy serum concentrations should be measured for every three to five days for dose adjustment and when maintenance dose is established theophylline levels can be monitored for every 6-12 months ². Signs of mild theophylline toxicity include nausea, vomiting and tachycardia whereas life-threatening symptoms of severe toxicity include seizures, ventricular arrhythmias ³⁻⁴.

2. CASE REPORT:

A 42 years male patient was admitted to the hospital with chief complaint of headache and involuntary movements of upper and lower limbs. Patient was apparently normal and illness started as involuntary movements of upper and lower limbs on 23/9/23 which is followed by generalized tonic clonic type seizures that lasted for 5mins, frothing of eyes and up rolling of eyes are observed by patients attendant. He has a history of hypertension & diabetic since 15 years, Telmisartan 20mg OD, Clonidine 0.1mg TID, Clinidipine 10mg BD are used for hypertension and he is using metformin 500mg BD for Type 2 diabetes mellitus. He is known to have chronic kidney disease and is undergoing haemodialysis since six months. Patient was chronic smoker and smoking cessation was done one week back. He has a history of COPD, for COPD 200mg of theophylline BD was used. Patient also has a habit of taking OTC medications recently he took ciprofloxacin 500mg BD for tooth infection. Patient's laboratory findings include a haemoglobin level of 9gms%, random blood sugar (RBS) of 430mg/dl, and a lactate level of 7.75mmol/L.

3. OUTCOME AND FOLLOW-UP:

The management of this complex case involved a multidisciplinary approach addressing the diverse medical issues presented by the patient. Due to the complex circumstances surrounding theophylline toxicity like severe hyperglycemia, and generalized tonic-clonic seizures, a combination of pharmacological interventions and supportive care was implemented to stabilize the patient's condition. After suspecting the condition and considering the patient's history of chronic kidney illness, also its tendency to build up in renal impairment, terminating the medication was essential to avoid further harm. Immediate management focused on stabilizing blood sugar levels as patient's severely elevated blood glucose levels (RBS: 430mg/dl) demanded immediate intervention. Intravenous insulin therapy (Inj. human actrapid 40units @ 6ml/hour) was initiated to achieve glycemic control and prevent further complications associated with hyperglycemia. Regular monitoring of glucose levels allowed for adjustments in insulin dosages based on the patient's response. For treating seizures the patient received an injection of 100 mg of phenytoin in 100 ml of normal saline three times a day. During the patient's hospital stay, this antiepileptic medicine was used to manage seizures and stop them from happening again. Tab. Folic acid 5mg was given once a day to treat anemia. The patient's clinical presentation raised concerns about potential dehydration, likely exacerbated by theophylline use and the recent seizure activity. To restore fluid balance, 2 pints of normal saline were administered intravenously. Throughout the hospital stay, the patient's vital signs, neurological status, and laboratory values were closely monitored. This included regular assessments of blood glucose levels, ensuring the efficacy of insulin therapy. Adjustments to medication dosages and fluid management were made based on the patient's response and evolving clinical condition. Follow-up during the seven-day hospital stay allowed for continuous assessment of the patient's progress and facilitated timely modifications to the treatment plan.

Table 1. GRBS monitoring at regular intervals

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
12:00am	432mg/dl	357 mg/dl	283 mg/dl	232 mg/dl	191 mg/dl	163 mg/dl	145 mg/dl
4:00am	408 mg/dl	323 mg/dl	267 mg/dl	218 mg/dl	183 mg/dl	150 mg/dl	130 mg/dl
8:00am	375 mg/dl	304 mg/dl	242 mg/dl	209 mg/dl	275 mg/dl	182 mg/dl	126 mg/dl
12:00pm	342 mg/dl	270 mg/dl	221 mg/dl	181 mg/dl	152 mg/dl	122 mg/dl	108 mg/dl
4:00pm	319 mg/dl	254 mg/dl	206 mg/dl	164 mg/dl	136 mg/dl	116 mg/dl	90 mg/dl
8:00pm	288 mg/dl	231 mg/dl	184 mg/dl	142 mg/dl	118 mg/dl	90 mg/dl	115 mg/dl

Patient exhibited improvement in both clinical and laboratory parameters during the hospitalization period. He got discharged on September 30 2023, laboratory values reflected positive changes with Hb levels increased to 10.3gms%, RBS levels reduced to 98mg/dl, and lactate levels normalized to 1.64mmol/L. Patient counselling was provided to him on the warning signs and symptoms of theophylline toxicity, patient was counselled on the significance of regular blood glucose level monitoring, emphasizing the need for adherence to prescribed medications for diabetes and hypertension. Follow-up appointments were scheduled to ensure ongoing monitoring of the patient's health status and to address any emerging concerns promptly. Importantly, counselling extended to the risks associated with self-medication, given the patient's history of taking over-the-counter medications. The patient was educated on the potential consequences of unsupervised medication use, emphasizing the importance of consulting healthcare professionals before initiating any treatment.

4. DISCUSSION:

Theophylline is used to treat respiratory diseases like asthma and COPD as it is a narrow therapeutic drug, elevated serum theophylline levels can cause adverse effects like seizures and hyperglycaemia⁵. Literature suggests that concomitant administration of ciprofloxacin and theophylline can inhibit CYP3A4 enzyme activity as a result theophylline clearance is reduced which in turn increase serum theophylline concentrations⁶⁻⁷. Elevated levels of serum theophylline cause an increase in cyclic adenosine monophosphate, which facilitates the mobilization of calcium and causes an imbalance between GABA and N-MDA neurotransmitters, ultimately leading to the onset of seizures⁸. Elevated serum theophylline concentrations can also cause hyperglycaemia because high serum theophylline levels affect the pancreas and inhibit insulin release, which in turn causes hyperglycaemia. They also influence on the liver and parasympathetic nervous system, increasing gluconeogenesis⁹.

5. CONCLUSION:

This case illustrates the complex difficulties in treating patients with comorbidities. Theophylline-induced seizures and hyperglycemia are rare adverse events. Theophylline is a narrow therapeutic drug so health care professionals should closely monitor patients who are administered theophylline cautiously and take proactive steps to reduce any potential adverse effects. This case study also emphasizes importance of individualized patient care, where factors such as medical history, concomitant medications, and underlying conditions must be carefully considered.

Patient consent: Yes

Conflict of interest: The authors declare no conflict of interest

Abbreviations:

BD	- Twice daily
COPD	-Chronic obstructive pulmonary disease
CYP3A4	-Cytochrome P 3A4 enzyme
GABA	-Gamma aminobutyric acid
GRBS	-Gradient random blood sugar
Hb	-Haemoglobin
NMDA	-N-methyl-D-aspartate
OD	-Once a day
OTC	-Over the counter
TID	-Thrice in a day

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