CASE REPORT

A Rare Adverse Event Induced by Theophylline: Epilepsy

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INTRODUCTION
Theophylline, which is a methylxanthine derivative, is being widely used for the treatment of chronic obstructive pulmonary disease (COPD) for a long time both for its low cost and high bronchodilator activity [1].

Theophylline binds to plasma proteins, mainly to albumin, by 40-50%. The rate of theophylline binding to proteins is decreased in the third trimester of pregnancy, in premature babies, new-borns elderly, and in patients with renal or hepatic disease; thus, distribution volume of theophylline is increased. Since serum theophylline concentrations may show sudden increases accordingly, toxicity symptoms may be encountered [2].

Decrease in theophylline clearance particularly in patients over the age of 60 years causes an increase in serum concentrations. The rate of binding to proteins may decrease with the decrease in albumin concentrations in elderly and accordingly, serum theophylline concentration increases. Considering multiple drug use in the geriatric group, dose adjustment is of great importance in patients over the age of 60 years [3,4].

The most frequently reported toxicity symptoms related to theophylline include headache, nausea, vomiting, abdominal distension, and irritability. These usually occur due to the inhibition of phosphodiesterases. These might be accompanied by increase in acid secretion, gastroesophageal reflux (GER) and diuresis. Convulsions, epilepsy-like seizures, cardiac arrhythmia, and death, which are encountered with higher concentrations, are thought to usually result from adenosine receptor antagonism. Such serious adverse events occur with serum theophylline concentrations higher than 20 µg/mL [5-7].

CASE PRESENTATION
A 67-year-old female patient underwent neurological examination at neurology outpatient clinic due to complaints of tremor in the right hand. Her medical history revealed Parkinson’s disease for 4 years and COPD for approximately 6 months. She had no history of head trauma. On her neurological examination, there was resting tremor in the right upper extremity and mild rigidity in the right wrist and elbow joints. She had mild bradykymia and walking in slight anteflexion posture. Laboratory findings were as follows, complete blood count: normal, erythrocyte sedimentation rate: 53 mm/h and troponin I and CK-MB, which are among cardiac markers, within normal range. With regard to biochemical test results, postprandial blood glucose concentration was 119 and albumin level was 3.4. Among other biochemical analyses, hepatic function tests, renal function tests and electrolyte levels were within normal ranges (Urea: 17, Creatinine: 0.58, aspartate aminotransferase (AST): 23, alanine transaminase (ALT): 12, sodium (Na): 137, potassium (K): 5.1, chloride (Cl): 101, and calcium (Ca): 9.3).

Since she reported wheezing and shortness of breath after treatment for Parkinson Disease had been arranged, consultation was requested from Chest Diseases Emergency Unit. Detecting low oxygen saturation by pulse oximeter, in addition to dyspnea and diffuse ronchi in both lungs, intravenous theophylline therapy was planned. Theophylline was diluted in normal saline and administered at a dose not exceeding 25 mg/minutes. Beginning from the 2nd minute of treatment, tonic and clonic contractions were observed in the right upper extremity. The patient, who was conscious, was considered to...
have a partial seizure and 10mg diazepam was administered as slow infusion in 5 minutes by intravenous route, considering the risk of diazepam-induced respiratory depression. The seizure stopped after approximately 15 minutes. On blood gas analysis, it was determined that potential hydrogen (Ph) was 7.44, partial carbon dioxide pressure (PCO₂) was 32, bicarbonate (HCO₃) was 21.7, and oxygen saturation was 96%. The patient was transported to the neurology clinic and electroencephalography (EEG) was performed. EEG demonstrated spike wave activity originating from the left parietal region and extending also to the right hemisphere (Figure 1a, b).

Seizure-free period of the patient lasted for 3 hours. As the epileptic seizure recurred, sodium valproate therapy (1000 mg/day) was commenced. The seizure was taken under control and maintenance therapy with oral sodium valproate was commenced at a dose of 1000 mg/day.

Electrocardiography (ECG) and transthoracic echocardiography (ECHO) were normal. Seizure did not recur on clinical monitoring and the patient was discharged from the hospital with valproate to be received at the same dose. The patient was evaluated after 2 weeks at the outpatient clinic and seizure-free status was on-going. The consent of the patient was obtained for this adverse event to be presented as a case report.

DISCUSSION

The use of theophylline during exacerbations of chronic obstructive pulmonary disease, even though not used frequently today, requires attention particularly in elder patients. In order to avoid adverse events, theophylline should be used by monitoring the serum concentrations of the drug after precise evaluation of current concomitant diseases, medications and serum albumin concentration of the patient.

Cases with theophylline-induced epileptic seizure are not less common. In a case report in 2010, high body temperature and pleocytosis was reported in a 70-year-old male patient following the seizure, which occurred after theophylline therapy and lasted for approximately 2 hours [8].

Theophylline can cause seizures in patients regardless of the presence of epilepsy and this might be associated with drug dose, infu-
REFERENCES