Case Report

Status epilepticus associated with initiation of theophylline in an elderly patient with diabetic ketoacidosis

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An 80-year-old man with a history of Type 2 diabetes mellitus was hospitalized due to generalized convulsive status epilepticus. Initially, hyperglycemia and ketoacidosis were diagnosed, but his seizures were refractory to the medical treatment. Additionally, a high level of serum theophylline (29.1 µg/mL) was detected. Following detoxification of theophylline by oral activated charcoal, the patient regained consciousness and was free from seizures without antiepileptic drug treatment. Brain magnetic resonance imaging revealed subacute subdural hematomas at the bilateral occipital hemispheres. This case suggests that theophylline toxicity may be a predisposing factor for seizures in patients with a history of traumatic brain injury in spite of the presence of diabetic ketoacidosis that may have an anticonvulsant action.

Key words: Diabetic ketoacidosis, status epilepticus, subdural hematoma, theophylline

Introduction

Status epilepticus is a neurological emergency and its treatment should be focused on early seizure termination, identification of underlying etiology and prevention of recurrent seizures to minimize the related morbidity and mortality. Focal seizures or secondarily generalized tonic-clonic seizures (GTCS) may develop in patients of nonketotic hyperglycemia, but they are unusual in diabetic ketoacidosis (DKA) which may have an anticonvulsant effect. Herein, we describe a case of DKA suffering from generalized convulsive status epilepticus (GCSE) associated with theophylline intoxication under the circumstances of subacute subdural hematomas.

Case Report

An 80-year-old man was transferred to our emergency department with the diagnosis of DKA complicated with GCSE that had developed for one hour. Three weeks prior to his admittance, he had suffered a forehead contusion without medical management. Three days prior to this presentation, for productive cough, he began to take aminophylline 250 mg (Phyllocontin® Continus®, Bard, U.K.) orally twice daily since he had a history of chronic obstructive pulmonary disease. His medical history also included Type 2 diabetes mellitus for 20 years and he took gliclazide 60 mg daily and acarbose 100 mg twice daily. He had quit cigarette smoking for 10 years.

Upon arrival, the patient, weighted 78 kg, presented a stupor consciousness. Vital signs for blood pressure were 171/53 mmHg; pulse rate 120 beats/minute; respiratory rate 29 breaths/minute; and body temperature 37.2° C. The transfer chart displayed blood glucose, 608 mg/dL; serum osmolality, 301 mOsm/L; arterial blood gas, pH: 7.217, pCO2: 29.1 mmHg, pO2: 294.9 mmHg, HCO3: 11.4 mmol/L under the use of oxygen mask; and urine chemistry, specific gravity: 1.020, glucose: 3+, ketone bodies: 3+. He received intravenous infusion of 1,000 mL 0.9% saline, 30 units regular insulin, 5 mL 15% potassium chloride for DKA; as well as intravenous injection of 10 mg midazolam, 10 mg diazepam and infusion of 1,000 mg phenytoin for controlling convulsions. The noncontrast and contrast-enhanced computed tomography (CT) of his brain did not reveal remarkable lesions. He did not regain consciousness despite his blood glucose levels being reduced to 176 mg/dL. He was then referred to our hospital.

Subsequent laboratory findings were as follows: leukocyte 10,700/µL; hemoglobin 11.9 g/dL; platelet 181,000/µL; acetone negative; glucose 155 mg/dL; sodium 138 mmol/L; potassium 3.3 mmol/L; urea nitrogen 15 mg/dL; serum creatinine 0.8 mg/dL; alanine aminotransferase 12U/L; aspartate aminotransferase 24U/L and creatine kinase 1,518 U/L. Urine chemistry showed glucose ± and ketone bodies negative. An electrocardiography showed sinus tachycardia with rate 126 beats/minute. The chest film showed emphysematous changes. Serum theophylline concentration was analyzed by fluorescence

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polarization immunoassay (AxSYM® Theophylline II assay) and yielded 29.1 µg/mL above the therapeutic range (5-15 µg/mL). Gastric lavage with activated charcoal 40g was done every four hours for five times and theophylline level decreased to 2.9 µg/mL next morning. Furthermore, magnetic resonance imaging (MRI) revealed slim subacute subdural hematomas over the bilateral occipital lobes [Figure 1]. Lumbar puncture revealed no evidence of infection. An abdominal sonography showed normal without focal lesions. His HbA1c level was 14.0%, indicating poor glycemic control for months and insulin treatment was warranted. The patient regained full consciousness the following day with no recurrent seizures and therefore antiepileptic medications were discontinued.

Discussion

In patients with DKA, ketosis and intracellular acidosis are presumed to have an anticonvulsant action through elevating levels of γ-aminobutyric acid (GABA) by increasing activity of glutamic acid decarboxylase.[2] However, a hyperosmolar hyperglycemic state may trigger focal seizures or secondarily GTCS. The features of hyperglycemic-induced seizures include moderately severe hyperglycemia, moderate hyperosmolality and the cessation of seizure activity immediately following normalization of blood glucose.[3] It was hypothesized that hyperglycemia led to decrease of seizure threshold by increasing metabolism of GABA, accordingly decreasing its level.[4] In addition, reduction in regional cerebral blood flow during hyperglycemia was possible to trigger epileptic discharges in the area of a previously silent cerebral lesion.[5] In our case, the seizures were unresponsive to corrected hyperglycemia that may be related to infection, trauma, poor medical compliance of anti-diabetic drugs, dehydration or starving. His subdural hematomas were diagnosed by MRI scan that was sensitive to detect extracellular methemoglobin, the subacute nature of hemorrhage.[6]

The narrow therapeutic index of theophylline increases the occurrence of toxicities including hyperglycemia, hypokalemia, metabolic acidosis, cardiac arrhythmia and seizures that have been previously reported.[8] For patients with brain injuries, severe lung diseases, discontinuing tobacco use recently or even upper respiratory tract infection, we should pay attention to possible theophylline toxicities and its serum level should be maintained below 10-15 µg/mL.[8,9] There was more than one-third decrease in the clearance of theophylline in individuals who quit smoking for one week[10] and accumulation of theophylline due to renal insufficiency or heart failure also predisposes to its toxicities. In our case, the probability score for an adverse drug reaction was 6 based on Naranjo algorithm.[11] We do not think the case is strongly suggestive of theophylline toxicity due to other factors described in this patient. Although the mechanism of theophylline-induced convulsions has not been clearly elucidated, in vitro studies demonstrate that theophylline dose-dependently inhibits GABA_A receptors.[12] In an animal study, free radicals are possibly involved in theophylline-induced seizures in mice.[13] Oral activated charcoal is regarded as the mainstay of treatment of theophylline toxicity and the dose should be administered 30-40 g every four hours or in smaller doses more frequently.[14] It significantly enhances elimination of orally or parenterally administered theophylline and should be taken into consideration before more aggressive interventions such as charcoal hemoperfusion or hemodialysis.

This is a rare case of DKA who also suffered from GCSE precipitated by the synergistic effects of theophylline intoxication and traumatic brain injury. Furthermore, this case is suggestive of the need for physicians to be cautious in prescribing theophylline to aged patients with a history of recent traumatic brain injury.

References

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