Phenytoin induced status epilepticus

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There is a growing body of literature that patients on antiepileptic drugs may experience worsening of seizure control such as increasing frequency, inducing new seizures, refractory seizures, and so forth. Phenytoin is used in all types of seizure except absence seizure and is the most commonly prescribed antiepileptic drug due to its cost and availability. Phenytoin is known for its side effects such as gingival hyperplasia, nystagmus, myopathy, and drug-induced lupus, but rarely causes seizures. Patients on phenytoin undergo frequent drug level monitoring. Status epilepticus could be precipitated by many etiologies such as metabolic, infections, CNS lesions, trauma, illicit drugs, alcohol toxicity, however, here we report a case of phenytoin toxicity induced status epilepticus.

A 28-year-old Saudi male, known case of post-traumatic seizure disorder for the last 20 years, presented to the Emergency Department with multiple generalized tonic clonic attacks every 7-10 minutes for more than one hour without gaining consciousness in between as witnessed by his brother. He was in his usual status of health walking with his brother, no history of trauma, no alcohol, or illicit drug ingestion, no fever, or neurological deficit. He was on phenytoin 300 mg once daily, levetiracetam 1500 mg BID, and valproic acid 500 mg BID. The valproic acid was stopped for an unknown reason 2 months earlier, and he is known to be incompliant with his treatment. On presentation, he was actively seizing, cyanotic, incontinent of stool and urine, moving all limbs, and pupils were reactive bilaterally. The respiratory, cardiovascular, and abdominal examination was unremarkable. He required diazepam 7 mg iv, Lorazepam 10 mg iv, and phenytoin 1 g over 30 minutes. Bloods were taken before iv treatment, and complete blood count, liver function test, electrolytes, urea, and creatinine were all normal. His albumin was 46 g/L, alcohol and toxicology screening were negative, and the phenytoin level was high at 30.3 mg/l (normal range 10-20). The arterial blood gases showed respiratory acidosis with a pH of 7.28. His ECG showed sinus rhythm, chest x-ray showed right upper lobe infiltrate due to aspiration pneumonia, CT head without contrast was unremarkable as compared with the previous scans. He stopped seizing but was agitated and vomiting frequently. He did not require intubation as he was maintaining his airway and able to cough with a positive gag reflex. He was transferred to the ICU for observation of his phenytoin level, which was monitored daily to be 34.3, 26.9, and 15.6 mg/l. He had no seizures during his hospital stay and was discharged after 4 days.

Phenytoin toxicity is defined as the clinical features of phenytoin toxicity caused by its toxic level. There are increasing reports of seizure cases induced by antiepileptic drugs. Phenytoin was one of the top 200 drugs prescribed in the United States in 2006, and it has a very narrow therapeutic range (10-20 mg/l). Absorption by oral ingestion is slow and variable with peak levels 3-12 hours after a single dose. The metabolism of phenytoin is capacity limited (dose dependent). At plasma concentrations below 10 mcg/ml, elimination is first order (a fixed percentage of drug metabolized per unit of time). However, at higher concentrations, including those in the therapeutic range (10-20 mcg/ml), the metabolic pathway may become saturated, and the elimination may change to zero-order kinetics (a fixed amount metabolized per unit of time). This means that a small increase in the dose will result in a higher drug level due to the saturation of the hepatic hydroxylation system. Most deaths from toxicity happen after rapid iv administration. With the per oral route, different individuals have different tolerance profiles. Early toxicity manifests as vestibular and cerebellar signs, such as nystagmus, dysdiadochokinesia, and ataxia, and a very high level is associated with seizure. Nystagmus on lateral gaze usually appears at the 20-25 mg/l levels, and ataxia and diplopia may occur at 30 mg/l. Although nystagmus and ataxia usually precede more severe symptoms, toxicity may remain unrecognized by the patient. When the blood concentration exceeds 30 mg/l dysarthria may be noted. A concentration greater than 40 mg/l may cause lethargy, drowsiness, and rarely asterixis. Extreme lethargy and occasional coma may occur with concentrations greater than 50 mg/l. A phenytoin induced seizure is usually brief and generalized, proceeded by other signs of toxicity and occurs after an acute overdose. In one study, which reviewed 96 cases that meet the criteria for phenytoin toxicity, 7 patients had seizures while toxic. However, in only 2 patients (2.1%) with serum concentrations of 93.2 and 69.7 was a causal relationship deemed highly probable. Seizures did not occur in most toxic epileptic patients with total serum phenytoin concentrations as high as 85.1, or in any of the nonepileptic patients with concentrations as high as 64.2. The lack of convulsant action of phenytoin in these patients suggests that seizure risk may be multifactorial and also that phenytoin is a weak anticonvulsant. In a case series of 3 patients with seizure with phenytoin levels of 34.5, 46.5, and 38.3, all were controlled by withdrawal of phenytoin, these toxic levels may or may not be accompanied by other features of phenytoin toxicity such as nystagmus. In another study of 50 patients with phenytoin intoxication, 5 of them had seizure, and the only factor that seemed to correlate with seizure was a phenytoin level >30 mg/l.
This case report highlights that the cause of status epilepticus, even with a level lower than the previous studies presented to the emergency department could be phenytoin itself, and emergency physicians should be aware of this issue. Status epilepticus has other etiologies such as sub-therapeutic levels of the anticonvulsants, cerebrovascular accident, illicit drug intoxication, hypoxia, alcohol withdrawal, and unknown etiology. But, to say that status epilepticus is secondary to phenytoin toxicity, one must establish a consistent temporal relationship between administration of a specific drug and specific epileptic type or syndrome. Other potential criteria include demonstrating that the exacerbation is observed soon after introduction of the antiepileptic drug, that seizure exacerbation is reversible when the dosage of the drug is reduced and recurs with rechallenge. Treatment of status epilepticus is preferred with 2 antiepileptic drugs if benzodiazepines are used, because of the time-dependant loss of potency at >30 minutes after seizure onset, and also status epilepticus is a heterogeneous disorder, and attacking 2 mechanisms of action might increase the chance of success. However, the emergency physician may be better to avoid phenytoin by using other second line drugs, for example, Phenobarbital, or only use half of the treatment dose in patients already know to take phenytoin while waiting for the phenytoin levels to come back.

References


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