CASE REPORT

Phenytoin Overdose-induced Rhabdomyolysis: A Rare Case Report

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Abstract

Introduction: Phenytoin is the commonly used antiepileptic medication for abortive as well as maintenance therapy. Even though phenytoin is associated with various side effects, only a few cases of phenytoin-induced rhabdomyolysis have been reported so far. Most cases are either due to parenteral use for status epilepticus or hypersensitivity reaction to maintenance therapy.

Case description: We present an 18-year-old male, on regular treatment for a seizure disorder, who presented with altered sensorium following ingestion of 15–20 tablets of phenytoin (1500–2000 mg) and was found to have acute kidney injury (AKI) due to rhabdomyolysis secondary to phenytoin toxicity. The patient recovered completely with hemodialysis and supportive care.

Conclusion: Phenytoin overdose-induced rhabdomyolysis is a rare occurrence with high risk of acute kidney injury. Awareness of clinicians about this rare complication is helpful for early diagnosis and treatment.

Keywords: Acute kidney injury, Phenytoin, Rhabdomyolysis.

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Introduction

Phenytoin is one of the commonly used antiseizure medications for status epilepticus as well as maintenance therapy. Phenytoin use has been classically associated with a wide array of adverse reactions ranging from ataxia and nystagmus to drug reactions with eosinophilia and systemic symptoms syndrome. Phenytoin-induced rhabdomyolysis was first described four decades ago due to a hypersensitivity reaction.[1] We report the presence of an 18-year-old male who developed AKI and anuria secondary to rhabdomyolysis, which was later deduced to be secondary to phenytoin overdose.

Case Description

An 18-year-old male, who was on antiseizure medications [phenytoin 100 mg three times a day (TDS) and phenobarbitone 30 mg at night time (HS)] since 10 years of age, presented to our emergency with altered sensorium for one day. The patient had an alleged history of intake of 15–20 tablets of phenytoin (1500–2000 mg). At presentation, his Glasgow Coma Scale (GCS) was 8/15; pupils were equally reactive with no focal neurological deficits. His blood pressure was 100/70 mm Hg, his heart rate was 100/minute, and he had bilateral basal crepitations. Cardiac and abdominal system examinations were insignificant. The patient was started on mechanical ventilation with intensive monitoring in view of poor GCS and aspiration pneumonia. There were no episodes of seizures, but the patient developed anuria. His hemogram showed anemia with thrombocytopenia (hemoglobin 9.6 gm/dL and platelets 122,000/mm^3). Biochemical analysis revealed deranged renal function with hypoalbuminemia, elevated lactate dehydrogenase (LDH), and creatine kinase (CK) (urea 223 mg/dL, creatinine 13.97 mg/dL, albumin 2.11 g/dL, LDH 2571 U/L, and CK 67089 U/L). Myoglobin was detected in urine. He had hyponatremia with hyperkalemia (sodium 130 mEq/L and potassium 5.11 mEq/L). Erythrocyte sedimentation rate (59 mm/hour) and high sensitivity C-reactive protein (40.94 mg/L) were elevated. Prothrombin time (15.1 seconds and international normalized ratio of 1.3) and activated partial thromboplastin time (18.4 seconds) were normal. Electrocardiogram was normal. Abdomen ultrasound showed normal size kidneys with altered echotexture. The patient was diagnosed with AKI secondary to rhabdomyolysis and taken up for hemodialysis. Serum phenytoin and phenobarbitone levels were available after the first session of hemodialysis. The total phenytoin level was 17 µg/mL (therapeutic level 10–20 µg/mL), and the total phenobarbitone level was 9.2 µg/mL (therapeutic level 15–40 µg/mL). His tracheobronchial aspirate culture showed *Acinetobacter,* for which an appropriate antibiotic was given. The patient subsequently improved with alternate-day hemodialysis and vigorous intravenous (IV) hydration

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and was weaned off from mechanical ventilation after 2 weeks. Electroencephalogram (EEG) showed generalized slowing of waves in bilateral cerebral hemispheres, with no seizure activity. Magnetic resonance imaging (MRI) of the brain showed cerebellar atrophy. After 10 days patient had two episodes of generalized tonic–clonic seizures, which were controlled with levetiracetam 1500 mg twice a day (BD), valproate 500 mg BD, and clobazam 10 mg HS. The patient decannulated from tracheostomy to completely recover from renal injury in 3 weeks. The patient is currently seizure free and on regular outpatient follow-up.

Discussion

We conducted an exhaustive literature search, and tabulated the previous of phenytoin-induced rhabdomyolysis (Table 1). Three of these patients had developed rhabdomyolysis following IV administration of phenytoin for status epilepticus, while two patients were on an oral maintenance dosage. We report the first case of rhabdomyolysis following an acute phenytoin overdose. Unlike the previous case reports, our patient presented with high levels of CK (67089 U/L) with anuria and AKI requiring hemodialysis. Our patient also had a rare presentation of rhabdomyolysis, like anemia and thrombocytopenia.[2] He went on to require mechanical ventilation because of his poor GCS and multiple sessions of hemodialysis, ultimately attaining complete recovery after 3 weeks.

The underlying etiology of rhabdomyolysis was initially unclear since the patient did not have any seizure episodes as witnessed by the attendee or any other cause of muscle trauma. There was no history of illicit drug abuse or signs of infection. Generalized slowing of EEG was suggestive of metabolic causes like uremia or phenytoin toxicity rather than nonconvulsive status epilepticus. Cerebellar atrophy in the MRI brain was suggestive of chronic phenytoin usage.

Our patient had a history of phenytoin overdose; however, the serum drug level obtained postdialysis was within the therapeutic level. Renal failure, hypoalbuminemia, and hemodialysis will affect the serum phenytoin levels. So, we have calculated the free phenytoin level as per Soriano's revised Winter–Tozer equation. The free phenytoin level in our patient was 3.2 µg/mL (normal therapeutic level—1–2 µg/mL). Besides hypoalbuminemia, configurational changes of albumin, along with the competition of uremic toxin for albumin binding site, reduce the affinity of phenytoin to serum albumin. These factors can lead to phenytoin toxicity despite normal therapeutic levels in patients with renal failure.[3] Our patient had renal failure along with hypoalbuminemia and a toxic level of free phenytoin, which resulted in rhabdomyolysis.

Phenytoin hypersensitivity as a cause of rhabdomyolysis was ruled out because of the absence of fever, rash, lymphadenopathy, and eosinophilia. Moreover, hypersensitivity reaction commonly occurs within 3 weeks to 3 months after initiation of treatment, which is also not in favor of hypersensitivity reaction in our patient.[4]

Prolonged immobilization due to drug intoxication, surgery of more than 4 hours, and trauma can lead to muscle compression, tissue ischemia, and myocyte injury.[5] Our patient also had immobilization for a day due to phenytoin overdose-induced depression of the central nervous system.

With the background of phenytoin overdose, EEG changes, renal failure, and hypoalbuminemia-induced alteration in the pharmacokinetics, the toxic level of corrected free phenytoin level and absence of other potential risk factors; phenytoin-induced rhabdomyolysis was concluded as the diagnosis. Prolonged immobilization as a cause of rhabdomyolysis cannot be excluded; it might have aggravated the rhabdomyolysis in our patient.

Our patient recovered completely with hemodialysis and was switched to alternative antiepileptics with levetiracetam 1500 mg BD, valproate 500 mg BD, and clobazam 10 mg HS.

The major limitations in our case were—serial measurement of CK was not done, which may have added to the prognostic value, and

Table 1: Phenytoin-induced rhabdomyolysis—earlier reports

Study author	*Diagnosis*	*Phenytoin dose and route of administration*	*Peak CKNAC levels*	*Diagnosis of phenytoin toxicity*	*Outcome*
Michael et al.,[1]	30 years/female, seizure disorder	Oral phenytoin and phenobarbitone for 1 month	500 IU/L	Clinical, serum phenytoin and phenobarbitone levels are not detectable	Favorable, no requirement for hemodialysis
Engel et al.,[6]	22 years/male, posttraumatic seizures	300 mg/day, oral for 3 months	242000 IU/L	Clinical and muscle biopsy, serum phenytoin level 9 mg/L	Favorable, no requirement for hemodialysis
Olaniran et al.,[4]	53 years/male, status epilepticus	20 mg/kg loading dose followed by maintenance dose (cumulative dose 2250 mg)	5447 IU/L	Clinical serum phenytoin level normal (0.4 µg/mL)	Favorable, no requirement for hemodialysis
Kim et al.,[7]	37 years/male, status epilepticus due to ruptured ACOM aneurysm	20 mg/kg IV loading dose followed by 150 mg BD oral dose	3825 IU/L	Clinical	Favorable, no requirement for hemodialysis
Zwaenepoel et al.,[8]	27 years/male, anoxic brain damage post cardiopulmonary resuscitation (cocaine intoxication)	IV phenytoin 750 mg loading dose followed by 500 mg/day	7769 IU/L	Clinical, serum phenytoin level 9.4 mg/L (subtherapeutic)	Persistent vegetative state, no requirement for hemodialysis

the serum drug levels were obtained only after the first hemodialysis instead of at the time of presentation due to logistic reasons.

Conclusion

We reported the case of a young male with an underlying seizure disorder who presented with low GCS and AKI due to phenytoin-induced rhabdomyolysis. We recommend maintaining a high index of clinical suspicion of this rare complication of phenytoin-induced rhabdomyolysis, especially for those who are on long-term antiepileptics, which may lead to depression and suicidal tendencies. We suggest periodic counseling for these kinds of patients to avoid this catastrophe.

Highlights

- Phenytoin-induced rhabdomyolysis is a rare complication.
- It has a good outcome with early diagnosis and management.
- A high index of suspicion is essential to prevent this entity.

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