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Case Report

Phenytoin-Induced Rhabdomyolysis

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Abstract *Summary.* A 53-year-old Hispanic male with a history of seizure disorder was admitted for acute kidney injury (AKI) and rhabdomyolysis due to status epilepticus. He was managed with IV fluids and IV phenytoin. No breakthrough seizures occurred on admission and AKI quickly resolved. Twenty-four hours after therapeutic levels of serum phenytoin were reached, serum creatine kinase (CK) levels peaked again despite adequate IV fluid administration and in the absence of any other cause of rhabdomyolysis or CK leak. CK levels dropped acutely after phenytoin was discontinued. *Discussion.* The correlation between the second peak in CK and peak phenytoin levels provides significant evidence of this rare adverse effect. This is confirmed by the acute drop in serum CK levels upon discontinuation of phenytoin. *Conclusion.* Further cases need to be collated and compared in order to ascertain specific risk factors for this adverse reaction as well as any possible relationship to dosage.

Keywords phenytoin; rhabdomyolysis; creatine kinase and drug reaction

1. Introduction

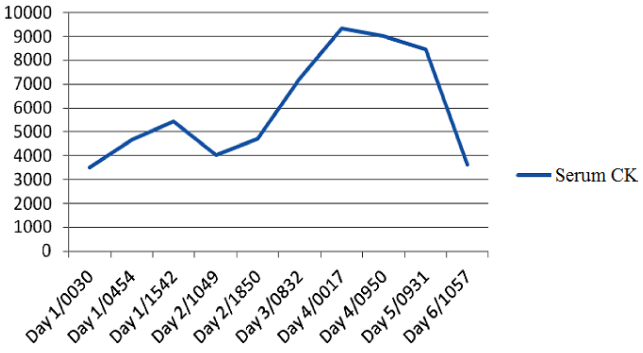
Phenytoin is one of the most widely used drugs for treating seizure disorders and has been a first-line medication since its introduction. It has well-known adverse and toxic effects. There are only a few reported cases of phenytoin-induced rhabdomyolysis. In our case, despite the appropriate treatment, there was a second peak of creatine kinase (CK) levels suggesting ongoing muscle injury or a new cause of rhabdomyolysis.

2. Case presentation

A 53-year-old Hispanic male was admitted for status epilepticus. The patient has a past medical history of seizure disorder, alcohol dependence, alcoholic liver cirrhosis without decompensation or portal hypertension and nonadherence to antiseizure medication which at the time was phenytoin. On admission, the patient was alert and fully oriented. A small occipital scalp laceration obtained as a result of falling at the onset of seizures was found. There were no residual neurological deficits. The patient was not in respiratory distress and there were no tongue lacerations. Blood alcohol level was less than 3 and serum phenytoin level was 0.4 mcg/mL. Serum CK was significantly elevated at 3,504 U/L. Also of note was his albumin level which was 2.8 g/dL and AST 165 U/L, with a normal ALT and PT. Urine toxicology was positive for cocaine and methadone. Serum creatinine was 1.3 mg/dL, well above patient baseline, thus indicating acute kidney injury (AKI). Vital signs were stable. Using the hospital's standardized score for alcohol withdrawal, the patient was not in withdrawal. The patient was managed with aggressive IV hydration and loaded with IV phenytoin, which was subsequently changed to oral phenytoin. AKI quickly resolved and phenytoin levels were therapeutic by day 2 at 13.3 mcg/mL, corrected for hypoalbuminemia to 20.2 mcg/mL. Serum CK levels peaked at 5,447 U/L in 24 h. After trending down, serum CK peaked again on day 4 at 9,335 U/L. Phenytoin was discontinued while continuing IV fluids and starting levitracetam. Subsequently, serum CK trended down. Total phenytoin administered was 2,200 mg. An assessment of phenytoin-induced rhabdomyolysis was made. Total fluids administered till discharge was 20 L. The patient was discharged home two days later with serum CK continuing to trend down.

3. Discussion

Creatine kinase is a molecule commonly found in the skeletal muscle, myocardium, and brain. As it is found in the inner mitochondrial membrane and cytoplasm, it can be released into the blood through cell membrane disruption and cell death. Tonic-clonic seizures are a well-known cause of rhabdomyolysis leading to elevated serum CK levels [1]. The usual pattern associated with a single nonrecurring episode of musculoskeletal insult is rising serum CK which peaks and then gradually declines to normal levels with appropriate IV fluids in the setting of normal renal function [2]. In our case, appropriate hydration was provided and the AKI rapidly resolved. In spite of this, our patient had a second serum CK peak. We hypothesize this is due to a rare reaction to phenytoin [3]. Note that the second serum CK peak occurs after therapeutic levels of phenytoin are attained. When corrected for low albumin, phenytoin is



Graph 1.

not supratherapeutic and therefore not at toxic levels. Also, the decline after the second peak has a high gradient after the half-life of phenytoin has been exceeded (see Graph 1). Our patient had persistent muscle soreness and this may be considered evidence of ongoing muscle breakdown [4, 5]. Therefore, an ongoing musculoskeletal insult must have caused the second peak as opposed to reduced clearance of serum CK as may occur in AKI [6] or cirrhosis which our patient had evidence of. However, our patient's renal function returned to normal by the end of day 1 and although he developed asterixis treated with lactulose, cirrhosis is not known to cause a rising CK level [7]. In addition to this, there were no further reported seizures on admission. There was no prolonged immobilization due to postictal state on admission as the patient ambulated to and from the bathroom without incident. Prolonged immobilization has been known to cause muscle breakdown [8].

None of our patient's other medications (thiamine tablets, multivitamin tablets, folic acid tablets, subcutaneous heparin) are associated with elevated serum CK or drug-induced myopathy apart from methadone. However, the dose of methadone remained constant throughout admission. Although frequent intramuscular injections are associated with a rise in serum CK levels [9], our patient only received subcutaneous (SQ) injections throughout his admission and therefore there is no correlation with the second CK peak. Again there is no evidence that SQ injections even cause elevations in serum CK. The patient's chronic alcoholism and cocaine use could be a cause of elevated serum CK [10, 1], however this would only explain the first peak as there was no evidence the patient had access to either alcohol or cocaine and physical findings did not correspond with their recent use. Cocaine and opioids can cause direct damage by inducing muscle breakdown [10, 11]. As a consequence of the patient's chronic alcoholism, he required frequent replacement of electrolytes including potassium. Hypokalemia is a well-known cause of rhabdomyolysis [2]. But this usually occurs with severe hypokalemia at serum levels below 2 mEq/L. Our patient never registered a serum potassium below 3.4 mEq/L. Our patient also had macrocytic anemia from chronic alcoholism and his hemoglobin remained stable. There was no evidence of hemolysis. Hemolysis would not usually produce the degree of CK elevations witnessed in this patient. Of note is that he developed a fever of 102 °F on day 4 after an influenza injection. Although high fever up to 104 °F with chills are known to cause rhabdomyolysis [12], there was no correlation between the patient's fever and his second elevation in serum CK.

As phenytoin drug-induced myopathy is rare, it is uncertain whether the dose of phenytoin plays a role in myopathy. Our patient received a total of 2,200 mg IV. A prior case report demonstrated a total dose of 3,059 mg [13]. This would suggest that there is no relationship to dose but further data must be collated. There were no other similar comorbidities between our patient and the subject of the prior case report. Also of interest is the normal absolute eosinophil count in our patient. Phenytoin hypersensitivity with eosinophilia is a severe and often life threatening disorder associated with multiple organ involvement and may result in elevated CK levels. Our patient's presentation did not correlate with this picture.

4. Conclusion

We have presented a rare case of phenytoin-induced rhabdomyolysis. Although this is an uncommon adverse effect, knowledge of this is important in general practice to enable prompt identification and corrective measures to be taken. Further data must be collated to determine risk factors for and dose relationship to phenytoin-induced rhabdomyolysis.

Conflict of interest The authors declare that they have no conflict of interest.

References

[1] R. Vanholder, M. S. Sever, E. Erek, and N. Lameire, *Rhabdomyolysis*, J Am Soc Nephrol, 11 (2000), 1553–1561.

[2] F. Y. Khan, *Rhabdomyolysis: A review of the literature*, Neth J Med, 67 (2009), 272–283.

[3] J. N. Engel, V. G. Mellul, and D. B. Goodman, *Phenytoin hypersensitivity: A case of severe acute rhabdomyolysis*, Am J Med, 81 (1986), 928–930.

[4] W. Tan, B. C. Herzlich, R. Funaro, K. Koutelos, M. Pagala, B. Amaladevi, et al., *Rhabdomyolysis and myoglobinuric acute renal failure associated with classic heat stroke*, South Med J, 88 (1995), 1065–1068.

[5] M. M. Ward, *Factors predictive of acute renal failure in rhabdomyolysis*, Arch Intern Med, 148 (1988), 1553–1557.

[6] A. L. Huerta-Alardín, J. Varon, and P. E. Marik, *Bench-to-bedside review: Rhabdomyolysis – an overview for clinicians*, Crit Care, 9 (2005), 158–169.

[7] D. Pateron, P. Beyne, T. Laperche, D. Logeard, P. Lefilliatre, P. Sogni, et al., *Elevated circulating cardiac troponin I in patients with cirrhosis*, Hepatology, 29 (1999), 640–643.

[8] D. Szewczyk, P. Ovadia, F. Abdullah, and R. Rabinovici, *Pressure-induced rhabdomyolysis and acute renal failure*, J Trauma, 44 (1998), 384–388.

[9] F. J. Montero Pérez, J. Muñoz Avila, A. Berlango Jiménez, M. Durán Serantes, J. M. Calderón de la Barca Vázquez, L. Jiménez Murillo, et al., *Increase of blood levels of creatine kinase following intramuscular injection* (Spanish), Med Clin (Barc), 107 (1996), 649–654.

[10] B. Z. Horowitz, E. A. Panacek, and N. J. Jouriles, *Severe rhabdomyolysis with renal failure after intranasal cocaine use*, J Emerg Med, 15 (1997), 833–837.

[11] J. C. Klock and M. J. Sexton, *Rhabdomyolysis and acute myoglobinuric renal failure following heroin use*, Calif Med, 119 (1973), 5–8.

[12] G. Efstratiadis, A. Voulgaridou, D. Nikiforou, A. Kyventidis, E. Kourkouni, and G. Vergoulas, *Rhabdomyolysis updated*, Hippokratia, 11 (2007), 129–137.

[13] F. J. Santos-Calle, J. Borrás-Blasco, A. Navarro-Ruiz, and I. Plaza Macias, *Unsuspected rhabdomyolysis associated with phenytoin*, Int J Clin Pharmacol Ther, 43 (2005), 436–440.