LETTER TO THE EDITOR

To the Editor

Painful Proximal Weakness and HyperCKemia Related to Intravenous Loading of Phenytoin

Keywords: Neurology—adult, Epilepsy, Seizures, Myopathy, Muscle

Intravenous phenytoin is a commonly used antiepileptic drug for emergent treatment of seizures. Common side effects include ataxia, nystagmus, confusion, and nausea.[1] Rhabdomyolysis is a rare adverse effect of phenytoin. The first reported case of rhabdomyolysis associated with phenytoin was in 1976[2] and only a handful of cases have since been reported.[1,3,4] We present a case of acute painful proximal muscle weakness and markedly elevated creatine kinase (CK) levels in a 63-year-old woman immediately following intravenous loading of phenytoin that resolved rapidly with discontinuation of phenytoin.

Our patient initially presented to the emergency department by ambulance after she had a witnessed first generalized tonic-clonic seizure lasting <1 minute. In retrospect, she had a suspected first focal seizure with impaired awareness (5-10 minutes of expressive language difficulty) a few hours earlier. After arriving in the emergency department, she had a second witnessed generalized tonic-clonic seizure lasting <1 minute. She received a total intravenous phenytoin loading dose of 20 mg/kg, with a plan to continue oral phenytoin 300 mg each evening. Her history was significant for longstanding schizophrenia, which had been stable on treatment with clozapine for many years. There was no other significant past medical or surgical history. There was no history of alcohol or drug use.

The following morning upon assessment by the attending neurologist, she had a normal neurological exam with the exception of multidirectional nystagmus, appendicular ataxia, and negative myoclonus at the wrists that had the appearance of asterixis. Asterixis is a recognized but uncommon clinical sign of phenytoin toxicity.[5] Overall, her exam was consistent with phenytoin toxicity.

Her laboratory investigations on admission are detailed in Table 1 and were unremarkable. A plain CT head on the day of admission was normal. An electroencephalogram demonstrated diffuse background is slowing without lateralizing features or epileptiform discharges. An MRI brain was unremarkable. Two days following her intravenous phenytoin and after she had received another 300 mg orally the evening before, her phenytoin level was within the therapeutic range at 54 umol/L (40-80 umol/L).

On post-admission day 3 (PAD#3), she complained of myalgias and was found to have a proximal pattern of muscle weakness as follows (right/left): shoulder abduction 4−/4, elbow flexion 5/4+, elbow extension 4−/4, and hip flexion 3/3; with all more distal muscle groups in the upper and lower limbs graded as 5/5. Her reflexes were grade 2+ throughout and her plantar responses were flexor. Her CK level was found to be elevated at 23,661 U/L (PAD#3). Her phenytoin was stopped, and she was instead started on lamotrigine 25 mg daily with a plan for a slow upward titration. She was started on aggressive intravenous fluid resuscitation with normal saline for presumed rhabdomyolysis. Over the next 2 days, she regained full power. She did not develop acute kidney injury.

Her CK levels were retrospectively tested using previously collected serum samples. Her initial CK level on the day she presented (PAD#0) was 129 U/L (after her seizures but before her phenytoin load). This increased to 15,508 U/L by PAD#2. Her CK level peaked on PAD#4 (the day after her phenytoin was stopped) at 26,659 U/L and then began to trend downward (Figure 1). An MRI of the C-Spine was unremarkable. Electromyography/nerve conduction studies had been ordered but were cancelled due to the complete resolution of her weakness.

The patient was discharged from hospital after 1 week. She had no further seizure activity. Her CK level 5 days after discharge was 391 U/L. Despite the rarity of phenytoin-induced rhabdomyolysis, we believe that her acute onset myalgias, proximal weakness, and hyperCKemia was related to her exposure to phenytoin because of the close temporal correlation and pattern of weakness consistent with a drug-induced myopathy. Moreover, a causative role for phenytoin is further supported by the complete clinical and laboratory resolution following discontinuation of phenytoin. Similar cases of phenytoin-induced rhabdomyolysis have been reported in the literature that are similar to our patient's presentation without an associated hypersensitivity reaction.[1,3,4] Although seizure activity itself can be associated with elevated CK, the CK level in our patient was not elevated until PAD#2 and she had no further seizure activity in hospital. It is difficult to exclude the possibility that the patient's hyperCKemia could have been a delayed consequence of her initial seizure activity,[6] but such cases are usually associated with status epilepticus and dehydration and are not typically associated with a proximal pattern of weakness. Our patient had two very brief generalized tonic-clonic seizures and was immediately treated with intravenous fluids.

Clozapine overdose has also been reported to cause rhabdomyolysis,[7] but this was seen with a clozapine level 5× the upper limit of normal. Our patient had been stable on clozapine for years and there was no indication that she had overdosed. Her clozapine level was within the therapeutic window at 1575 nmol (1070-1835 nmol/L). Although both clozapine and phenytoin have been implicated in rhabdomyolysis, concurrent exposure to phenytoin (a potent CYP3A4 inducer) would be expected to decrease clozapine exposure and efficacy. Moreover, there were no clinical findings to suggest neuroleptic malignant syndrome in our patient.

The mechanism by which phenytoin could cause rhabdomyolysis is unclear. In theory, rhabdomyolysis could be precipitated by any drug that either impairs production of ATP, increases energy requirements beyond the rate of ATP production, and/or leads to accumulation of myoplasmic intracellular calcium.[8] Increased intracellular calcium initiates protease cascades that cause further cellular injury and further impairment of calcium homeostasis. The mechanism by which phenytoin might induce rhabdomyolysis is a topic that requires further research.

Rhabdomyolysis is a severe consequence of muscle necrosis that can lead to complications such as acute kidney injury. Fortunately, an elevated CK was found quickly in our patient and she responded well to prompt cessation of phenytoin and

Table 1: Initial patient laboratory investigations on the day of admission with associated normal values and units

Lab test	Value	Normal range	Units
Hematology			
Hemoglobin	125	120-160	g/L
Hematocrit	0.37	0.36-0.48	L/L
RBC	4.0	4.0-5.6	10E12/L
MCV	91	82-100	fl
MCHC	342	320-360	g/L
RDW	13.4	11.0-16.0	%
Platelet count	255	150-400	10E9/L
WBC	10.6	4.0-11.0	10E9/L
Neutrophils	8.5	2.0-9.0	10E9/L
Immature granulocytes	0.3	0.0-0.0	10E9/L
Lymphocytes	1.2	0.5-3.3	10E9/L
Monocytes	0.4	0.0-1.0	10E9/L
Eosinophils	0.2	0.0-0.7	10E9/L
Basophils	0.0	0.0-0.2	10E9/L
INR	1.0	0.9-1.1	–
General chemistry			
Sodium	135	133-145	mmol/L
Potassium	4.1	3.3-5.1	mmol/L
Chloride	99	98-111	mmol/L
CO_2 content	24	21-31	mmol/L
Creatinine	66	40-100	mmol/L
eGFR	86	≥60	ml/min/1.73 m^2
Urea	2.6	2.5-8.5	mmol/L
Calcium	2.26	2.10-2.55	mmol/L
Phosphate	0.86	0.80-1.50	mmol/L
Magnesium	0.84	0.65-1.05	mmol/L
Glucose	10.7	3.3-11.0	mmol/L
CK	129	0-170	U/L
LD	252	100-235	U/L
Protein	58	63-80	g/L
Albumin	32	33-48	g/L
Bilirubin total	4	0-24	umol/L
Bilirubin direct	2	0-7	umol/L
ALP	54	30-145	U/L
ALT	25	1-40	U/L
GGT	23	8-35	U/L
Lipase	30	0-80	U/L
TSH	4.02	0.20-4.00	ml U/L

ALP = alkaline phosphate; ALT = alanine aminotransferase; CK = creatine kinase; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyltransferase; INR = international normalised ratio; LD = lactate dehydrogenase; MHHC = mean corpuscular hemoglobin concentration; MVC = mean corpuscular volume; RBC = red blood cell count; RDW = red blood cell distribution width; TSH = thyroid stimulating hormone; WBC = white blood cell count.

supportive therapy. Drug-induced rhabdomyolysis may be overlooked due to a subclinical presentation without common features.[9] Although rare, phenytoin-induced rhabdomyolysis should be considered when a patient develops myalgias, proximal muscle weakness, or has increased CK levels despite adequate seizure control.

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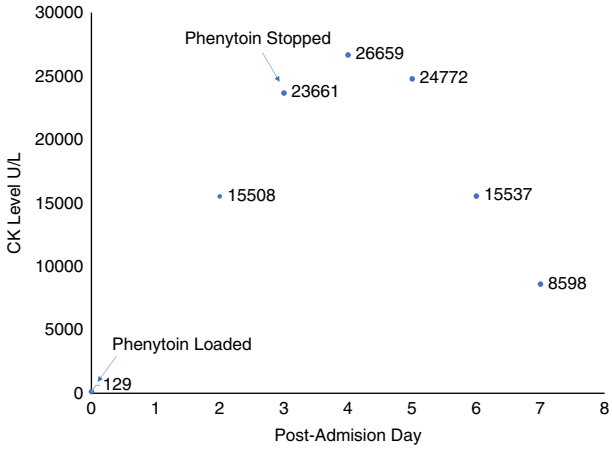

Figure 1: *Creatine kinase (CK) levels at various days over the patient's hospital admission. Phenytoin initiation and stop dates are indicated. Creatine kinase levels peaked at 26,659 U/L and quickly trended downwardly after cessation of phenytoin and aggressive supportive therapy.*

Disclosure

The authors have nothing to disclose.

Statement of Authorship

RM contributed to drafting the manuscript and clinical information on the case. TB contributed to critical revision of the manuscript and clinical information on the case.

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References

1. Kim H, Jo S, Park KW, Han S, Lee S. A case of phenytoin-induced rhabdomyolysis in status epilepticus. J Epilepsy Res. 2016;6: 36-8.
2. Michael JR, Mitch WE. Reversible renal failure and myositis caused by phenytoin hypersensitivity. JAMA. 1976;236:2773-5.
3. Santos-Calle FJ, Borras-Blasco J, Navarro-Ruiz A, Plaza Macias I. Unsuspected rhabdomyolysis associated with phenytoin. Int J Clin Pharmacol Ther. 2005;43:436-40.
4. Olaniran K, Keshishyan S, Assallum H. Phenytoin-induced rhabdomyolysis. J Case Reports Med. 2015;4, Article ID 235849, https://doi.org/10.4303/jcrm/235849.
5. Chi WM, Chua KS, Kong KH. Phenytoin-induced asterixis – uncommon or under-diagnosed? Brain Injury. 2000;14:847-50.
6. Mishra A, Dave N. Acute renal failure due to rhabdomyolysis following a seizure. J Family Med Primary Care. 2013;2(1): 86-7.
7. Jansman FGA, Crommelin HA, van Hout FJAH, Meulenbelt J. Rhabdomyolysis in clozapine overdose. Drug Saf Case Rep. 2015;2(1):9.
8. Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis – an overview for clinicians. Critical Care. 2005;9(2):158-69.
9. Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. Curr Opin Pediatr. 2004;16:206-10.

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