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Rhabdomyolysis Following Initiation of Antiviral Therapy with Oseltamivir

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Conflict of interest: None declared

Patient: Male, 53
Final Diagnosis: Rhabdomyolysis with Oselatimivir therapy
Symptoms: Dark urine
Medication: Oseltamivir
Clinical Procedure: —
Specialty: Hematology

Objective: Adverse events of drug therapy

Background: Tamiflu (oseltamivir phosphate) serves as prophylaxis and treatment of upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) caused by viruses of the Orthomyxovirus family. Here, we present a patient with URTI and negative rapid influenza diagnostic testing (RIDT), who developed rhabdomyolysis after being started on oseltamivir.

Case Report: Our report describes a rare case of rhabdomyolysis after oseltamivir administration in a 53-year-old man with suspected influenza. We discuss the differential diagnosis for rhabdomyolysis to rule out other causes and review the literature on influenza-induced rhabdomyolysis.

Conclusions: Considering the serious consequences of rhabdomyolysis, care needs to be taken in routine prescription and use of oseltamivir. Although this is a rare adverse effect, our case highlights the need to be vigilant for uncommon adverse events with commonly used drugs.

MeSH Keywords: Orthomyxoviridae • Oseltamivir • Rhabdomyolysis

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Background

Prescribing oseltamivir as prophylaxis in patients with URTI has become a standard protocol, to the extent that the World Health Organization (WHO) has added it to the list of essential drugs [1]. Oseltamivir is used to treat acute influenza symptoms in patients more than 1 year old and any high-risk patient who tests positive for influenza [2–4].

Oseltamivir is a selective neuraminidase inhibitor. Neuraminidase prevents clumping of virions into a single particle and is responsible for release and spread of virions. On oseltamivir exposure, virions aggregate on the host cell surface, reducing viral spread, disease duration [5,6], and virulence. The duration of therapy is 5 days but can be extended in high-risk patients [6]. Oseltamivir is a prodrug which needs conversion to the active form, which is oseltamivir carboxylate by ester hydrolysis. It is absorbed from the gastrointestinal tract on oral administration, with a bioavailability of 80%. The active form of the drug carboxylates in the liver before distributing in the upper and lower respiratory tracts. Patients with hepatic dysfunction need no dose adjustment. The active metabolite has a half-life of about 6–10 h. Children ages 1–12 years need dose adjustments (increase to 2 mg/kg from the actual 1 mg/kg twice a day), as they excrete the drug faster than adults. Oseltamivir is excreted via the kidneys with no further metabolism and interaction with cytochrome P450 enzymes; therefore, there is less potential for drug interactions. Common adverse effects with the drug on initial days of treatment are mild to moderate nausea and vomiting. As less as 10% of people who use the medication experience rash, edema of face and tongue, or severe adverse events like toxic epidermal necrolysis, arrhythmias, worsening of diabetes, hepatic dysfunction, seizures, or delirium [6]. There are no reported cases of oseltamivir-related rhabdomyolysis in adults in the literature.

Rhabdomyolysis is a condition in which trauma or pharmacological injury to the sarcolemma of the myocyte causes release of intracellular ions, myoglobin, creatine kinase, and urate. The ramifications of this insult to the myocyte wall are acute renal failure, compartment syndrome, disseminated intravascular coagulation (DIC), and, in severe cases, multiorgan failure, mainly involving the pulmonary and hepatic systems [7]. We report our experience with a patient who developed rhabdomyolysis after treatment with oseltamivir.

Case Report

A 53-year-old man with a 5-year history of IgA smoldering multiple myeloma, presented to the emergency room (ER) with severe generalized body aches and dark urine. He did not experience any fever, chills, night sweats, weight changes, palpitations, shortness of breath, abdominal pain, nausea, or vomiting. There was no history of trauma and he denied use of illicit drugs or alcohol. He was prescribed oseltamivir for an upper respiratory tract infection at an urgent care clinic and had felt better after taking the drug for 2 days. On the third day, he developed myalgia and dark urine, for which he came to our center. Tamiflu was the only medication the patient was taking at the time of presentation, started for suspected influenza, which was stopped on admission.

In the ER, blood tests showed his hemoglobin was stable at 0.12 kg/L, CREAT was stable at 7.5e-6 kg/L, calcium (corrected for albumin) 0.089 kg/L, LDH 3600 U/L, and total proteins 0.063 kg/L. His liver function test results were elevated with alanine aminotransferase at 463 U/L (normal high 52) and aspartate aminotransferase at 1655 U/L (normal high 39). Renal function remained stable. Creatine kinase was elevated at >45 000 U/L (normal high <234). Urinalysis and microscopy were negative for toxins. Qualitative urine analysis revealed a large amount of blood and <5 RBCs per high power field. A viral panel for influenza A and B, influenza An H1N1, Parainfluenza1, 2, 3, Adenovirus, RSV, and Rhinovirus was negative. Serum and urine protein immunology were within baseline values for a history of IgA smoldering multiple myeloma (Table 1).

During his inpatient stay, the patient was on intravenous hydration and received a total of 3 liters per day. Given the rarity of rhabdomyolysis with oseltamivir, it was felt that there were other causes for this condition. Although myeloma can be a cause of rhabdomyolysis in rare instances, this was quickly ruled out due to stable para-protein levels for 5 years prior to the presentation and no other evidence of progression from the smoldering to active disease. An extensive autoimmune work-up to evaluate for myositis was negative (Table 2). CK levels were monitored daily with levels peaking at 45 000 units/L on the day of admission. Levels trended steadily down over the next few days, with 13 100 by day 16 of hospitalization and day 21 from the start of medication. Although these levels were higher than normal, the patient was doing well clinically and was discharged on day 16. Clinical follow-up 3 days later showed with normal CK levels (Figure 1).

Discussion

Oseltamivir, Zanamivir, and Peramivir are the 3 neuraminidase inhibitors licensed for use in the United States [8,6]. Oseltamivir was approved by the Food and Drug Administration (FDA) in 1999 [8]. In 2002 it was used for both prophylaxis and treatment in adults. A year later, pooled analysis of a 10 double-blinded randomized control trial (RCT) concluded that usage of oseltamivir reduces duration and virulence of lower

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Table 1. Laboratory Investigations on admission after Tamiflu administration.

All labs on admission	
Hematocrit	41.5%
MCV	80.6 fL
MCHC	0.262 kg/L
Platelet count	200 000 per µL
Differential count	
Neutrophil	56
Lymphocyte	36
Monocyte	6
Eosinophil	1
Basophil	0
Urinalysis	
Color	Light red
Clarity	Clear
Specific gravity	1.007
pH	6.5
Protein urine qualitative	200 mg
Glucose urine qualitative	Negative
Ketone urine qualitative	Negative
Blood urine qualitative	Large
WBC/HPF	<5
RBC/HPF	<5

All labs on admission	
Electrolytes	
Sodium	140 mmol/L
Potassium	4.2 mmol/L
Chloride	99 mmol/L
Carbon dioxide	33 mmol/L
Anion gap	8
Organic/Inorganic	
Glucose	0.0009 kg/L
BUN	0.00011 kg/L
Creatinine	1e-5 kg/L
BUN/Creat ratio	11
Albumin	3.9 g/dl
Bilirubin total	4e-6 kg/L
Total calcium	9.2e-5 kg/L
Phosphorus	3.2e-5 kg/L
Magnesium	2.1 mg/dl
Alanine aminotransferase	178 U/L
Alkaline phosphatase	46 U/L
Aspartate Aminotransferase	887 U/L
Creatine Kinase	>45 000 U/L

respiratory tract infections, antibiotic use, and rate of hospital admissions in both healthy and high-risk patients [9]. In 2006, a Cochrane review raised suspicion about the effectiveness of oseltamivir [10] and a systemic review and summary of regulatory comments suggested that oseltamivir does not reduce admission in hospitals nor decrease lower respiratory tract infections [11]. Despite this questionable benefit, it is commonly used in patients with suspected influenza.

Viral infections can be a cause of rhabdomyolysis and have been reported previously. A report by Tanaka et al. identified influenza virus as the implicated agent in nearly 33% of cases of known viral-induced rhabdomyolysis. The earliest recognition of the syndrome was called “myalgia cruris epidemica” or “benign acute childhood myositis”, which describes an acute myopathy during the convalescent phase of viral respiratory infections in children, characterized by bilateral calf pain and tenderness, with resultant difficulty in ambulation. It was usually benign and without significant complications. There are 42 cases of virus-induced rhabdomyolysis documented in the English-language and Japanese-language literature, and influenza accounted for 14 of 42 (33%) of these reported cases [12]. However, our patient tested negative for influenza by RIDT (rapid influenza diagnostic testing) and he did not have any significant viral infection, being totally asymptomatic from an infection perspective on admission. Indeed, the Naranjo algorithm applied gave a score of 3, suggesting a possible adverse drug reaction, supporting that oseltamivir was a more likely cause than any underlying infection [13].

Rhabdomyolysis is a molecular injury of the striated muscle cells with release of myocyte content into the plasma. It is diagnosed by a more than 5-fold rise in creatinine kinase levels (above upper limit of normal). In addition, we found abnormal levels of serum electrolytes, serum calcium, renal function, urine dipstick and microscopy for myoglobin, and blood and urine myoglobin levels. Management with rigorous intravenous hydration is sufficient, although some physicians

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Table 2. Viral studies and autoimmune workup to rule out other probable causes of rhabdomyolysis.

Viral studies	
HIV antigen/antibody	Negative
Influenza A	Negative
Influenza H1N1	Negative
Influenza B	Negative
Respiratory syncytial virus A	Negative
Respiratory syncytial virus B	Negative
Parainfluenza 1	Negative
Parainfluenza 2	Negative
Rhinovirus	Negative
Parainfluenza 3	Negative
Metapneumovirus	Negative
Adenovirus	Negative

Autoimmunity studies	
Anti SSA 52(Ro) antibody	Negative
Anti SSA 60(Ro) antibody	Negative
Anti U1 RNP antibody	Negative
Anti Jo 1 antibody	Negative
Anti Mi 2 antibody	Negative
Anti PL 7 antibody	Negative
Anti PL 12 antibody	Negative
Ant I P155/140 antibody	Negative
Anti Ku antibody	Negative
Anti U2 RNP antibody	Negative
Anti EJ antibody	Negative
Anti SRP antibody	Negative
Anti OJ antibody	Negative
Anti PM/Scl ANTIBODY	Negative

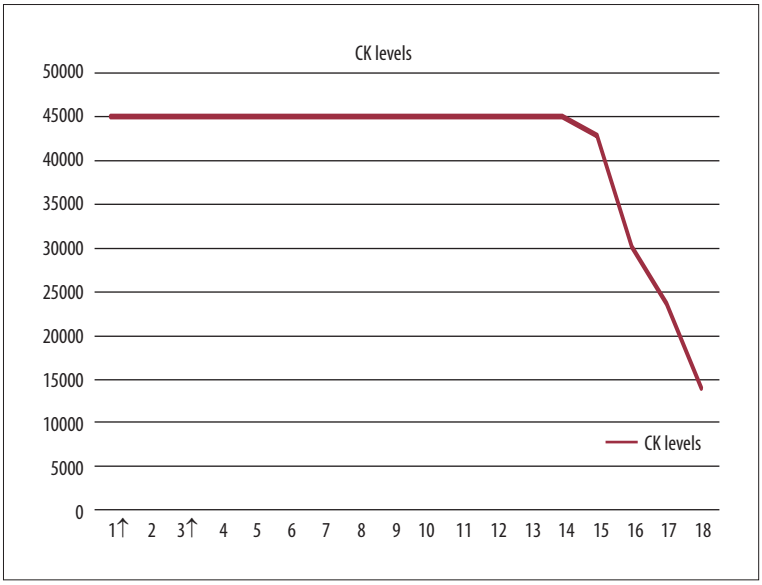

Figure 1. CK levels plotted against time in days (Day 1 indicating start of Tamiflu and Day 3 the day of hospital admission with rhabdomyolysis). This line chart depicts the tracking of creatine kinase levels (usually >45000U/L since day1 of Tamiflu therapy) and how it downgraded after its cessation and hydration therapy. On the x-axis day 1 represents introduction of Tamiflu to the patient by urgent care physician. Day 3 was when he started observing the symptoms of rhabdomyolysis. The creatine levels started decreasing from day 16 and the patient was discharged on day 18.

prefer to combine it with diuretics. In addition, urine alkalization may be performed, as myoglobin toxicity increases with acidic urine, but some protocols suggest limiting its use due to the risk/benefit ratio. If the patient is anuric and/or unresponsive to hydration, hemodialysis may also be required [7,14,15].

Conclusions

To the best of our knowledge, this is the first reported case of a patient with rhabdomyolysis caused by oseltamivir therapy in adults. Considering the serious consequences of rhabdomyolysis, care needs to be taken in routine prescription and use of oseltamivir. Although this is a rare adverse effect, our case highlights the need to be vigilant for uncommon adverse events with commonly used drugs.

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References:

1. World Health Organization: WHO model list of essential medicines: 17th list; 2011
2. Stiver G: The treatment of influenza with antiviral drugs. CMAJ, 2003; 168: 49–56
3. CDC Recommendations for Influenza Antiviral Medications Remain Unchanged. 2014 Apr 10 [cited 2018 Jan 1]. Available from: URL: *https://www.cdc.gov/media/haveyouheard/stories/influenza_antiviral2.html*
4. Davies BE: Pharmacokinetics of oseltamivir: An oral antiviral for the treatment and prophylaxis of influenza in diverse populations. J Antimicrob Chemother, 2010; 65(Suppl. 2): ii5–10
5. Fiore AE, Fry A, Shay D et al: Antiviral agents for the treatment and chemoprophylaxis of influenza [published erratum appears in MMWR Morb Mortal Wkly Rep, 2011; 60: RR01: 1–24]. MMWR Morb Mortal Wkly Rep, 2017; 66: 707
6. Khan FY: Rhabdomyolysis: A review of the literature. Neth J Med, 2009; 67: 272–83
7. Chatzizisis YS, Misirli G, Hatzitolios AI, Giannoglou GD. The syndrome of rhabdomyolysis: complications and treatment. Eur J Intern Med, 2008; 19: 568–74
8. US Food and Drug Administration. Tamiflu (Oseltamivir Phosphate) Capsule. 2001 Mar 30 [cited 2018 Jan 1]. Available from: URL: *https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21087_Tamiflu.cfm*
9. Kaiser L, Wat C, Mills T et al: Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med, 2003; 163: 1667–72
10. Jefferson T, Jones M, Doshi P, Del Mar C: Neuraminidase inhibitors for preventing and treating influenza in healthy adults: Systematic review and meta-analysis. BMJ, 2009; 339: b5106
11. Jefferson T, Jones M, Doshi P et al: Oseltamivir for influenza in adults and children: Systematic review of clinical study reports and summary of regulatory comments. BMJ, 2014; 348: g2545
12. Fadila MF, Wool KJ: Rhabdomyolysis secondary to influenza a infection: A case report and review of the literature. N Am J Med Sci, 2015; 7: 122–24
13. Naranjo CA, Busto U, Sellers EM et al: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther, 1981; 30: 239–45
14. Splendiani G, Mazzarella V, Cipriani S et al: Dialytic treatment of rhabdomyolysis-induced acute renal failure: Our experience. Ren Fail, 2001; 23: 183–91
15. Department of Health and Human Services. One-Year Post Pediatric Exclusivity Postmarketing Adverse Events Review Drug Oseltamivir phosphate. 2005 Aug 24 [cited 2018 Jan 1]. Available from: URL: *https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_06_01_Tamiflu%20AE_reviewed.pdf*

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