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Atorvastatin induced rhabdomyolysis: A case report

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Background: Rhabdomyolysis is a clinical condition occurring due to direct or indirect injury to skeletal muscles. This condition is precipitated by a number factors like trauma, crush injury, strenuous exercise, etc. Some of the widely prescribed drugs like statins are known to induce rhabdomyolysis especially when coadministered with other drugs like fibrates, macrolide antibiotics, calcium channel blockers, aspirins, etc.

Case presentation: Here we present a case of rhabdomyolysis (creatinine phosphokinase 6250 IU/L) in a 58-year-old male following intake of atorvastatin, benidipine and aspirin. The patient was managed conservatively on outpatient basis with withdrawal of the offending drug and fluid therapy. He responded well with normalization of CPK (creatinine phosphokinase) level (125 IU/L) within one week. To conclude both family physicians and patients should be aware of this side-effect associated with statins.

Conclusion: As prompt identification of the symptoms and seeking medical attention on the patient's part is very important for the final outcome, besides prompt diagnosis and management, the family physicians must give importance to patient education while prescribing the drugs.

Key words: Creatinine phosphokinase (CPK), Rhabdomyolysis, Statin

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Introduction

Rhabdomyolysis is a pathological condition characterized by direct or indirect injury to the skeletal muscle and release of contents (myoglobin, electrolyte, and enzymes like creatine kinase, aldolase, lactate dehydrogenase, aspartate amino transferase) of myocytes in the circulation (Ferri, 2016; McPhee, Papadakis, & Rabow, 2010; Mohamed, Salameh, & Saeed, 2019; Porter, 2011). 40% of the total body mass is contributed by skeletal muscles and thus release of its intracellular contents can easily the excretory system of the body and result into acute kidney injury (AKI) (McPhee et al., 2010; Mohamed et al., 2019; Porter, 2011). Clinical presentation of rhabdomyolysis depends upon severity of the condition; in milder cases there is no symptoms, diagnosis is confirmed after laboratory investigation. But in severe conditions weakness, muscle pain, tenderness and swelling of the muscle can arise. Electrolyte disturbances are common presenting features due to release of myocyte contents. Other nonspecific symptoms are nausea, vomiting, confusion, coma, palpitation, etc. Due to excretion of myoglobin (myoglobinuria), urine has the typical appearance brown appearance ("tea coloured").

This clinical condition has long been documented; better understanding of the condition was achieved especially following natural disaster (the first scientific description appeared following 1908 earthquake) and during the World War II (Vanholder, Sever, Erek, & Lameire, 2000).

Besides direct injury (crush injury) other indirect causes of injury include excessive exercise, certain drug use including alcohol. Mortality rate of rhabdomyolysis is 1.6 per 100,000 person-year (McPhee et al., 2010; Mohamed et al., 2019; Porter, 2011). Cerivastatin was withdrawn from the market in the year 2001 following reports of several cases of rhabdomyolysis; for other statins the risk of rhabdomyolysis is 0.44 cases per 10,000 person-year (Dalugama, Pathirage, & Kularatne, 2018; Dybro, Damkier, Rasmussen, & Hellfritzsch, 2016; Maggini et al., 2004; Peringat, Manappallil, & Karadan, 2018).

The most important cause of statin induced rhabdomyolysis is pharmacokinetic type of drug interaction. Atorvastatin, 3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (HMG-CoA). Majority of the statins including atorvastatin is metabolised with CYP (cytochrome P450 system) 3A4; hence other drugs metabolised through this CYP system might increase the plasma concentration of statins and lead to rhabdomyolysis (Dalugama et al., 2018; Dybro et al., 2016; Peringat et al., 2018).

Creatinine phosphokinase (CPK) typically increases in rhabdomyolysis including statin induced cases. If its level is more than 5 times the upper limit of the normal range, statins are to be stopped completely. When the level of CPK exceeds 100 times the upper limit of the CPK range, diagnosis of rhabdomyolysis is confirmed (McPhee et al., 2010; Mohamed et al., 2019; Porter, 2011). Besides AKI, patients are also at risk of elevation of hepatic enzymes, electrolyte imbalance (hyperkalaemia, hypocalcaemia, and hyperphosphatemia), and elevated creatinine. Hypercalcemia can typically lead to sudden cardiac arrest and death (Mohamed et al., 2019).

Besides rhabdomyolysis other clinical conditions like acute myocardial injury, myocarditis, myxoedema, seizure, malignant hyperthermia, cerebrovascular accidents, pulmonary embolism, can increase the CPK level (Mohamed et al., 2019).

Among the imaging tools, magnetic resonance imaging scan (MRI) can localise the site of rhabdomyolysis with high sensitivity compared to ultrasonography (USG) and computerized tomography (CT scan).

Fluid replacement therapy is the mainstay of management along with alkalization of urine, mannitol therapy and in severe cases dialysis.

Here, we present a case of rhabdomyolysis most probably precipitated by atorvastatin use along with other drugs like aspirin and benidipine.

Case presentation

A 58-year-old male attended the family medicine outpatient department with the chief complaints of pain in the muscles, joints, chest, and back along with malaise and fatigue for a period of one month; the symptoms especially muscle and joint pain aggravated during the last one week. The pain typically occurs during night time.

His drug history revealed that the patient started taking atorvastatin 15 days before the onset of the symptoms. He also revealed that earlier he was prescribed statins but due to unknown reasons he discontinued the drug for the last one year. However this time within 15 days of starting the drug he developed the aforementioned symptoms.

Besides pain the patient complained of darkening of urine in the past week without reduction in urine volume. The patient also complained of burning sensation during urination.

Initially the patient attended a different hospital; however as his symptoms persisted he attended our OPD.

There were no history of fever, loss of appetite, cough, nausea, vomiting, diarrhoea, and constipation. Also the patient did not have any known drug allergy. There were no history of intake of herbal remedies and substance abuse.

He was a known hypertensive, and diabetic (type 1, managed with insulin) with impaired kidney functions (diabetic kidney disease). The patient also had a history of atrial fibrillation and flutter, congestive heart failure, chronic renal disease, and dyslipidaemia (mixed hyperlipidaemia).

The patient was taking irbesartan 300mg/day, linagliptin 5mg/day, clopidogrel 75mg/day, benidipine hydrochloride 4mg/day, atorvastatin 40mg/day, and low dose aspirin (100mg/day).

On physical examination, the patient was conscious, oriented and his general condition was good with stable vital signs. Systemic examination including nervous system was within normal limits.

Blood pressure was 170/80 mm of Hg, respiratory rate was 17/min, SpO2 was 98% while breathing room air, and heart rate was 80 beats per minute. He was overweight with a body mass index of 28.8 kg/m2.

Investigations done in the previous hospital revealed following findings of high creatinine phosphokinase (CPK) 7.400 IU/L (normal range, 20-171 IU/L), creatinine 2.65 mg/Dl (normal range, 0.5-1.17 mg/dL)

levels, AKŞ 154 mg/dL(normal range, 74-106 mg/dL), potassium 5.8 mmol/L (normal range,3.5-5.3 mmol/L), HBA1c 6.7 % (normal range, 4.5-6.3 %), cholesterol 304 mg/dL(<200 mg/dL normal), triglyceride 312 mg/dL(<200 mg/dL normal), LDL 199 mg/dL(<150 mg/dL normal), and HDL 43 mg/dL(normal range, 0-40 mg/dL).

Other parameters like urea, D-dimer, Ferritin, C-Reactive protein, rheumatoid factor (RF), ALT, AST, ALP, LDH, albumin, TSH, sT4, sodium, calcium, WBC, haemoglobin were within normal limits.

Urine analysis (urine dipstick) revealed leukocyte ++, and blood ++. There were 10-12 leukocytes and myoglobinuria on microscopic examination.

The patient was informed about these abnormal laboratory findings; however, he was not ready to accept treatment in the previous hospital. Once the symptoms aggravated, he attended our hospital. Certain blood parameters like CPK (6250IU/L; normal range, 20-171 IU/L)), CK-MB (174 IU/L; normal range 0-25 IU/L), and creatinine (2.63 mg/dL; normal range, 0.5-1.17 mg/dL) were high like the previous occasion.

No ultrasound (USG) scan for KUB (kidney, ureter, and bladder), magnetic resonance imaging scan (MRI scan) and electromyography (EMG) were ordered.

On the basis of history, clinical examination, and laboratory findings, the patient was diagnosed with rhabdomyolysis (RML).

He was managed on outpatient basis. Statin was stopped and fluid therapy was done on OPD basis

After 1 week, the patient's CPK value returned to normal level (125 IU/L; normal range, 20-171 IU/L); however all other parameters remained almost the same.

Discussion

In our patient the most probable cause of rhabdomyolysis is concomitant use of statin (atorvastatin) with aspirin and calcium channel blocker (benidipine). In many patients of rhabdomyolysis might not have muscle pain; however, in our case muscle pain was one of the predominant complaints.

Besides characteristic drug history and symptoms, laboratory investigations especially elevated CPK level confirms the diagnosis of rhabdomyolysis as in our case (Kahanov, Eberman, Wasik, & Alvey, 2012; Mendes, Robles, & Mathur, 2014; Mrsić, Rasić, Smiljanić, & Turcić, 2008; Torres, Helmstetter, & Journal, 2015). In our patient myoglobinuria another finding in rhabdomyolysis was also present.

Common risk factors of statin induced rhabdomyolysis include advanced age, being male and presence of other comorbidities like renal, hepatic dysfunctions, hypothyroidism, diabetes, hypertension, and concomitant intake of drugs fibrates, nicotinic acid, macrolide antibiotic, verapamil, amiodarone, alcohol abuse (Kahanov et al., 2012; Mendes et al., 2014; Mohamed et al., 2019; Mrsić et al., 2008; Torres et al., 2015).

Our patient was a known diabetic, hypertensive, and had diabetic kidney disease. He also took several other drugs besides statin which significantly increase the risk of statin induced rhabdomyolysis.

Laboratory findings typically revealed CPK elevation in our case; initial CPK level was 7400 IU/L which became 6250 IU/L; in cases of rhabdomyolysis rise of CPK exceeding more than 100 times the upper limit of the normal range (20-171 IU/L) is diagnostic of rhabdomyolysis.

Pharmacokinetic drug interaction (interfering with CYP 3A4 mediated metabolism of statins) of statins with other concomitantly administered drugs is the main cause of statin induced rhabdomyolysis (Kahanov et al., 2012; Mendes et al., 2014; Mrsić et al., 2008; Thompson, Panza, Zaleski, & Taylor, 2016; Torres et al., 2015). In our patient due to his many ailments, he took several other drugs besides statins; of these drugs aspirin, and benidipine (calcium channel blocker) are well known to increase the risk of statin induced rhabdomyolysis.

Other risk factors for statin induced rhabdomyolysis like hypothyroidism, history of strenuous exercise, and physical trauma were absent in our patient (Kahanov et al., 2012; Mendes et al., 2014; Mrsić et al., 2008; Torres et al., 2015).

However, he had certain known clinical conditions predisposing to statin induced rhabdomyolysis like hypertension, dyslipidaemia, diabetes mellitus, and impaired renal function (diabetic renal disease).

Comprehensive review of 112 case reports (between 1999 and 2013) of statin induced rhabdomyolysis published by Mendes P and her colleagues documented that simvastatin and atorvastatin were responsible for most of the cases; the most commonly reported doses of the drugs were 40 mg/day and 10 mg/day, respectively (Mendes et al., 2014). In our case the patient was taking atorvastatin at a dose of 40mg/day.

As per the study published by Mendes P et al, usually the time interval between starting statin therapy or increasing its dose or concomitant drug intake and the onset of rhabdomyolysis range between 1 and 60 days (Mendes et al., 2014). In our patient, symptoms of rhabdomyolysis appeared after 15 days of starting atorvastatin at a dose of 40mg/day.

Also affected people usually recover from symptoms and signs (normalisation of CPK level) and resume normal activities between 7 days and 6 months following withdrawal of the offending drug and treatment (Mendes et al., 2014). In our patient CPK level was normalised with disappearance of symptoms within 1 week.

Although the evidence is not conclusive, still because of ease of performing and quick result, urine dipstick test is used as a screening tool for detection of AKI due to rhabdomyolysis in suspected cases (Alavi-Moghaddam, Safari, Najafi, & Hosseini, 2012; Grover, Atta, Eustace, Kickler, & Fine, 2004; Rodríguez-Capote et al., 2009; Thompson et al., 2016).

In our patient, dipstick test showed ++ for blood; as there were no normal erythrocytes (as in haematuria), ghost or hollow erythrocytes (as in haemoglobinuria), diagnosis of myoglobinuria was confirmed.

Our patient responded satisfactorily following withdrawal of the offending drug and OPD based fluid therapy.

In our patient onset of symptoms within a short span (15 days) of initiation of atorvastatin therapy, significant elevation in CPK levels without other causes, and rapid normalisation of CPK level following withdrawal of drug and fluid therapy confirmed the diagnosis of statin induced rhabdomyolysis.

To conclude, family medicine practitioners should suspect statin induced rhabdomyolysis in patients with known comorbidities taking statin with other drugs known to precipitate rhabdomyolysis, perform regular monitoring both clinically and with laboratory investigations and manage promptly.

Patient education in this regard is also very important as patient should seek immediate medical help with the onset of typical symptoms like muscle pain and passage of "tea coloured" urine.

List of Abbreviations:

CPK: creatinine phosphokinase

AKI: acute kidney injury

HMG-CoA: 3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors

CYP: cytochrome P450 system

MRI: magnetic resonance imaging

USG: ultrasonography

EMG: electromyography

RML: rhabdomyolysis

Consent for publication

All participants gave written consent to the study including publication of results.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Competing interests

The authors declare that they have no competing interests.

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