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Case Report

Pharmacology Section

Statin Induced Rhabdomyolysis with Non Oliguric Renal Failure: A Rare Presentation

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ABSTRACT

Statins are safe, well tolerated, efficient and time tested drugs for the management of hypercholesterolemia, and thus play a cardinal role in the management of patients with heart disease. Although safe in clinical practice, they are associated with adverse effects, clinically the most important and most severe being muscle related complications/myotoxicity. Rhabdomyolysis, though rare, is the most severe form of myotoxicity. The US Food and Drug Administration (USFDA) adverse event reporting system reports rate of statin induced rhabdomyolysis at 0.3-13.5 cases per 1,000,000 patients. We present a case of a 74-year-old male who presented with an acute coronary syndrome and was initiated on atorvastatin. However, patient developed atorvastatin induced rhabdomyolysis, with non oliguric renal failure, which subsequently improved on cessation of medication.

Keywords: Atorvastatin, Hypercholesterolemia, Myotoxicity

CASE REPORT

A 74-year-old male, known case of Type 2 diabetes mellitus and hypertension on treatment with metformin and amlodipine, was admitted with complaints of chest pain and breathlessness of two hours duration. Upon admission, blood pressure was noted to be 90/60 mmHG in the right arm in supine position, with heart rate of 112/min, and respiratory rate of 24/minute. Respiratory examination showed bilateral basal crepitations. ECG showed a right bundle branch block with diffuse ST depressions. A two dimensional echocardiogram revealed anterior wall hypokinesia with a left ventricular ejection fraction of 37%. A diagnosis of acute coronary syndrome was made and the patient was taken up for an emergency coronary angiography, which revealed 100% occlusion of the left main coronary artery. A Percutaneous Transluminal Coronary Angioplasty (PTCA) was performed to the left main coronary artery and a drug eluting stent was inserted. Post procedure, TIMI III flow was observed and the patient was initiated on double antiplatelets, aspirin 150 mg once daily per oral, ticagrelor 90 mg twice daily per oral along with atorvastatin 40 mg once daily at night, per oral. Patient's blood pressure was managed with amlodipine 10 mg once daily per oral, blood sugars were managed in hospital with short acting insulin given subcutaneously, and changed to metformin 500 mg twice daily per oral at discharge. N acetyl cysteine was given for three days after PTCA+DES to prevent contrast induced nephropathy. Pulmonary oedema was treated with intravenous furosemide as necessary.

One week following PTCA, patient developed severe pain associated with rapidly progressive weakness of both lower limbs. Neurological examination revealed cranial nerves 2-12 to be normal. Motor examination revealed 5/5 MRC power in the upper limbs, with intact deep tendon reflexes. Lower limbs had severe muscle tenderness in the proximal muscles, with a power of only 1/5 MRC; distal muscles had 3/5 MRC power. Lower limb deep tendon reflexes were preserved. Sensory examination revealed no objective deficits. A neurology opinion was sought, who considered the possibility of an anterior spinal artery syndrome. MRI whole spine was done which showed a normal study. Nerve conduction studies were performed, which were suggestive of amyopathic pattern. In addition, patient developed acute kidney injury. In view of the possibility of statin induced myopathy, serum Creatine Kinase (CK) levels were sent, which showed a trend as described in [Table/Fig-1]. Urine myoglobin was positive. On the basis of history, examination, and laboratory reports, a diagnosis of statin induced rhabdomyolysis was made. Atorvastatin was subsequently changed to rosuvastatin and after initiation of the same, creatinine and CK values decreased significantly [Table/Fig-1]. Urinary alkalization and intravenous fluids were initiated for management of rhabdomyolysis. Serum CK levels and creatinine levels were monitored serially till normal. Muscle power improved subsequently. Rest of his recovery course was uneventful. Patient's laboratory values were showing declining trend and clinically the patient was asymptomatic.

DISCUSSION

The term statin induced myopathy is commonly used to describe any muscle related complication arising as a result of statin therapy. Review of literature doesn't provide conclusive data regarding the relative incidence of statin related complications, partly as a result of improper and inconsistent nomenclature of the spectrum, and

Lab parameters/day of admission	Day 1	Day 11	Day 13	Day 16	Day 17	Day 19	Day 21	Day 23	Day 25	Day 26	Day 29
Creatine Kinase (U/L)	-	-	-	46,488	47,819	27,713	19,546	11,436	6551	3250	1058
Urea (mg/dl)	26	81	99	116	142	142	169	188	209	169	145
Creatinine (mg/dl)	1.4	1.8	2.1	2.1	2.5	2	2.4	2.7	3.4	2.8	1.7
Sodium (mmol/l)	136	134	128	132	137	142	128	128	130	130	136
Potassium (mmol/l)	3.5	3.3	4.1	5.4	3.9	3.8	3.7	3.2	3.2	3.8	3.8
AST (IU/L)	35	-	-	-	1125	-	-	-	166		102
ALT (IU/L)	57	-	-	-	314	-	-	-	108		82

[Table/Fig-1]: Table showing various laboratory investigation across different days of hospitalization.
AST= Aspartate transaminase, ALT= Alanine transaminase

partly as a result of under reporting [1-4]. The clinical spectrum itself ranges from asymptomatic rise in CK levels, myalgias, myositis, up to rhabdomyolysis [1,2]. Various studies define asymptomatic rise in CK levels as an absolute serum CK level of not more than 10 times the upper limit of normal. Since baseline CK levels are rarely tested prior to initiation of therapy, majority of these cases are unreported. Myalgias are the most common presentation of statin induced myotoxicity, with patients typically presenting with predominantly proximal muscle pain and tenderness, with or without weakness; the weakness and tenderness can be exaggerated by exercise. [1,2]. Serum CK levels may or may not be elevated in patients with myalgias, based on the severity of presentation. Patients with myositis have similar complaints, but have an associated absolute elevation of serum CK levels. Rhabdomyolysis consists of severe muscle pain, tenderness, weakness, with serum CK levels in thousands, along with renal insufficiency, as a consequence of myoglobin induced nephrotoxicity.

The duration between initiation of statins and presentation with statin induced myopathy ranges between 1-60 days [3-5]. Risk factors associated with statin induced myotoxicity include both exogenous and endogenous factors [1-3]. Exogenous factors include a high dose of statins, concomitant treatment with cytochrome inhibitors and simultaneous treatment with other lipid lowering agents. Studies also suggest lipophilic statins (atorvastatin, simvastatin, lovastatin) are more likely to precipitate toxicity. Endogenous factors include personal or family history of muscle disease, pre-existing liver or kidney disease, and hypothyroidism. Incidence is higher in the female gender, and in those with a low body mass index. Drug responses can be affected by genetic variants of metabolizing enzymes.

The precise mechanisms by which statins cause myotoxicity are unknown [1-4]. Statins inhibit the synthesis of mevalonate by inhibiting the action of HMG CoA reductase. Mevalonate, apart from being a precursor of cholesterol, is also a component of many other intracellular pathways and downstream signals. The mitochondrial theory suggests decreased cellular levels of mevalonate reduce cellular levels of Coenzyme Q, (CoQ) an important component of the Electron Transport Chain (ETC). Aberrant ETC functioning may alter cellular respiration which may precipitate muscle death. Other mechanisms proposed include direct actions on the myocytes causing an increase in sarcoplasmic calcium by increasing mitochondrial and cell membrane permeability, which in turn causes mitochondrial membrane depolarization with consequent abnormal cellular energy cycles. Studies have also shown statins to precipitate the apoptotic processes in myocytes, as well as disruption of regenerative and reparative pathways, by direct modulation of gene expression, as an extension of their pleotropic actions.

As per the Naranzo scale for determining association and probability of adverse drug reactions, we got a score of 6 which suggested probable adverse drug reaction. Giving a placebo was not considered because of the temporal association of atorvastatin administration and rhabdomyolysis, and as the patient suffered from an extreme form of rhabdomyolysis, re-challenge with atorvastatin was not considered feasible as it could have been life threatening. In our patient, changing the statin used led to a resolution of symptoms; patient was completely asymptomatic at the time of discharge. In a true sense the patient qualified for a definite Adverse Drug Reaction (ADR) (more than 9 points).

Thorough review of literature about statin induced rhabdomyolysis reveals only a few case reports, further emphasizing the extreme rarity of the condition [5,6]. Ambapkar SN et al., recently described a case of statin induced rhabdomyolysis in a patient with hypothyroidism, two weeks after the initiation of atorvastatin [5]. Schreiber DH et al reported statin induced rhabdomyolysis following therapy with simvastatin [6].

Evidence regarding management of statin induced myopathy is limited due to the reasons aforementioned [2]. Mainstay of management is change of statin used, or complete cessation of statin use, with use of non-statin lipid lowering agents. Bile acid resins and ezetimibe are available options. Chinese red rice yeast has been used therapeutically; it contains lovastatin, and is tolerated by those unable to with stand standard statin dosing [7].

CONCLUSION

This case highlights how even medications used on a daily basis can sometimes present with life threatening complications and the need for monitoring and vigilance for potential side effects, however rare their occurrence.

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