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Case Report

STATINS RELATED ACUTE RHABDOMYOLYSIS IN EMERGENCY DEPARTMENT STOPPING OR CHANGING STATIN DECISION

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Abstract

We report the case of a 72-year-old female patient, type IIB dyslipidemia, admitted in the ED for flu-like diffuse muscle pain, recently installed, progressive, apparently without a clear cause. For 3 months, the patient was being treated with gemfibrozilum and atorvastatin. The patient had suffered a myocardial infarction three years ago and right adrenalectomy as a cure for secreting adenoma.

Rhabdomyolysis and important metabolic acidosis led to the decision to replace the statin and dynamic supervision of the iatrogenic myopathy. After 10 days, the clinic was improved without further reported incident.

The rhabdomyolysis trigger event seems to be, apparently, associated with adding gemfibrozil to the treatment, statin being previously tolerated without incidents.

However, keeping gemfibrozilum and changing the statin type, the myopathy showed short-term improvement, which raises the issue of whether changing the treatment scheme is urgently needed or just observation might be enough.

Conclusions:

Type of calcium channel blockers associated with the treatment should be considered when choosing a statin.

Routine monitoring renal function, muscle damage biomarkers, and serum potassium level should be considered in this circumstances

It seems preferable for ED to recommend changing the statin, management, and myopathy follow up, against stopping statin administration.

It is likely that the interaction between these two classes of drugs to be influenced by the previous adrenalectomy and low muscle glycogen reserves due to diabetes.

Keywords: statins, myopathy, rhabdomyolysis, emergency department, biomarkers

Introduction

Iatrogenic muscle damage associated with lipid-lowering therapy, although widely recognized[1-3], doesn't have unanimously accepted incidence, etiology, and treatment guidelines, furthermore for emergency departments do not exist reports with the incidence of patients presenting myopathy symptoms, or management guidelines. Thus, 1.2 per 10000 people/year (C.I 95% 0.3-4.7) are treated with statins (3-hydroxy-3-methyl-glutaryl-CoA(HMG-CoA) reductase inhibitors)[4], and for hospital treated patients, the average incidence per 10000 people/year for monotherapy with atorvastatin, pravastatin or simvastatin was 0.44 (0.20 to 0.84) and for cerivastatin was 5.34 (1.46 to 13.68) [5].

In these circumstances, it is quite possible that given the expansion of treatment recommendations with statins, or other lipid-lowering therapy for management of dyslipidemic syndromes, many cases with unclear symptoms are underdiagnosed in emergency departments or omitted entirely from diagnosis, while symptoms are misinterpreted and assigned to other diseases.

Not lastly, threshold value of biomarkers which usually show the severity of myopathy may already be altered in the presence of heart failure[6], kidney or liver failure, sepsis[7], acute coronary or lung artery thrombosis[8], ventricular apical ballooning, implanted cardiac pacemaker, which can make muscle damage difficult to diagnose and monitor.

In the presence of patient having muscular pain, myopathic syndrome or rhabdomyolysis, the emergency physician must decide if the disease is iatrogenic, if it is life-threatening[9] and also recommend a strategy to control the myopathy, without increasing cardiovascular risk, usually without being assisted in this decision by a pharmacologist.

Materials And Methods

We present the case of a 72-year-old female patient, admitted to the emergency department for diffuse muscle pain, with flu-like character, without an apparent cause. Medical history shows that for three months the patient is treated with gemfibrolizum, in addition to atorvastatin for type IIb dyslipidemia (Frederickson), and having cholesterol level >250 mg/dl, and VLDL cholesterol >450 mg/dl (mixed – severe hyperlipidemia, according to European Association of Atherosclerosis)[10].

Medical history also shows that the patient has type 2 diabetes, with blood glucose levels maintained under control with treatment (no any hypoglycemic event), she suffered an anteroseptal myocardial infarction 3 years ago, for which she did not achieve reperfusion procedures, and 4 years ago right adrenalectomy as a cure for secreting adenoma. The patient does not have renal or liver failure.

Laboratory exams showed severe rhabdomyolysis, elevated levels of creatin kinase-Mb, CK-Mb >500ng/ml and myoglobin >1000ng/ml, mild metabolic acidosis (pH =7,230), BE=-11,1 HCO_3^- =14,2, respiratory compensated (pCO_2=37,1), initial potassium level 5.4 mEq/dl, decreasing to 4.9 mEq/dl after 2 hours of treatment. Blood glucose level =231mg/dl. Cholesterol and triglycerides levels were lower than the previous evaluation (2 months ago), but still not decreasing enough to reach target levels of 50% off the initial value[11].

Results And Discussion

Although it is not uncommon that a female patient, elder, with medical history of diabetes, with long-term treatment with cytochrome P-450 3A4 inhibitor statins, in medium/high doses, in association with fibrate therapy, to present iatrogenic myopathy, of variable severity[12-15], the presentation of the patient to an emergency department and a series of clinical issues

makes the case particular in the direction of medical emergency decision.

The first challenge was to identify the etiology and severity of the myopathy and differentiate it from other causes of rhabdomyolysis[16] (flu and trichinosis were taken into consideration, given the fact that in winter time consumption of pork meat or venison meat increases, also fever, infection or seizures.)

We consider that adding gemfibrozil to treatment is the trigger event of myopathy, although it is possible that the trigger event might be related to the administration of high dose (60 mg/day) for long time (over 2 years) of atorvastatin, since the average time until the symptoms onset is 6.3 (DS 9.3) months, with minimum of one to four weeks[17].

It is also questionable the role of calcium channel blocker which the patient was receiving (amlodipine 10 mg/day), in triggering and maintenance of rhabdomyolysis and the risk of myocardial vulnerability to endogenous catecholamines[18], is a fact that Ca2+ channel blockers increase the bioavailability of statins (decreased metabolism by inhibiting CYP3A4 enzyme, which interacts with glycoproteins liver) and decrease statins clearance. All this is relevant due to the fact that the patient was receiving statin – atorvastatin – that interact with cytochrome P450 3A4[19], even if many studies fail to acknowledge as significant the interaction of amlodipine-atorvastatin (no effect on C_{max} of atorvastatin, but the increased AUC by 18%)[20].

We focused the management of acute rhabdomyolysis in emergency department on of acute renal failure prevention (ensuring proper renal plasma flow by 500 ml saline solution infusion)[21] and alkalizing with caution[22] (0,5ml/kg of 8,4% sodium bicarbonate, during 1 hour), in terms of left ventricular outflow of 30-35% which can be further depressed by alkalizing, having risk for left ventricular failure), and treatment of electrolyte imbalance. It is interesting that the level of potassium is almost normal, despite severe rhabdomyolysis and acidosis, which can be explained by the inadequate level of mineralocorticoid (after adrenalectomy) or polyuria (diabetes) associated with depletion of potassium after administration of an anti-aldosterone diuretic.

Severe rhabdomyolysis, on the other hand, demanded several etiological treatment options: stop both lipid-lowering drugs, stop the only statin vs. decreasing the statin dose, and statin replacement with another statin[23,24].

Cardiovascular safety for patients with very high cardiovascular risk (in this case the patient had a significant coronary event) in which high dose statin therapy should begin very early (even during hospitalization for acute coronary syndrome)[25], must be maintained by combined therapy[26] to target level of lipids recommended by guidelines (LDL-cholesterol recommended is <1.8 mmol/L or <70 mg/dL, or a decrease of LDL-cholesterol by 50% when the target level can't be obtained – level of recommendation IA)[27]. So for keeping coronary risk stable, we decided, in consensus with the cardiologist, to replace the statin in use, lipophilic, acting on cytochrome P450 3A4 (CYP3A4) with a hydrophilic statin – pravastatin. We analyzed DECREASE-IV study which demonstrated benefit association of perioperative statins and beta-blockers on the incidence of non-fatal myocardial infarction and death at 30 days after surgery (using fluvastatin)[28]. We have taken into consideration that fluvastatin is also a lipophilic statin which is metabolized also in the liver, although in cytochrome P450 2C9 (CYP2C9), while pravastatin is metabolized in the kidney. In addition, there are studies about using fluvastatin at patients who experienced an adverse reaction from another statin[28], so the final decision was to replace atorvastatin with fluvastatin in

therapy. When choosing a different statin we considered that could be helpful to choose a statin from the same class of solubility, but with different P450 action, contrary with choosing a statin from another solubility class.

Since the average time which muscular symptoms persist after stopping statin treatment are known to be 2.3 (DS 3.0) months, with minimum between one to four weeks[29], we recommended to the patient a follow up of symptoms and markers of muscular damage, for the next 3 months every 2 weeks, in the event of myopathy recurrence to this statin. Only the first follow up (after 3 weeks) results are available – after 10 days, the clinic was improved without further reported incident, normalization of creatin kinase-Mb level (CK-Mb 5,8 ng/ml), and decreasing myoglobin level (130ng/ml).

Our department's decision was if there can be identified or reported a pattern to myopathy recurrence to another statin[30], a solution might be to ask to the cardiology department a standard model of modifying therapeutic strategy, which the emergency medicine doctors could use in safe conditions, with a low cardiovascular risk.

Even if rhabdomyolysis seems to be associated with adding gemfibrozil to statin treatment, changing the type of statin may improve myopathy, so the benefit of lipid-lowering therapy is preserved and cardiovascular risk remains acceptable.

A challenge in this direction is establishing a reference level and dynamic follow up of rhabdomyolysis in the evolution of management, considering side effects of lipid-lowering therapy, the persistence of biomarkers of muscular destruction in circulation, and any intercurrent illness, especially infectious, frequently to immunosuppressed patients, such as diabetic patients.

Rhabdomyolysis in emergency department represents a potentially severe metabolic impairment, that can trigger or aggravate or cardiac, renal failure or leading to missing or confusing differential diagnosis.

Calcium channel blockers associated with the dyslipidemia treatment is important in the interaction with cytochrome P450 and statin, so the type of calcium channel blocker should be considered when choosing a statin and routine monitoring renal function, muscle damage biomarkers and serum potassium level should be considered when atorvastatin and gemfibrozil added to a lipophilic, statin acting on cytocromeP450 3A4 (CYP3A4), to a diabetic patient, eventually with kidney function impairment.

Even if in literature there are no guidelines for emergency doctors to decide, it seems acceptable that, in emergency departments, to recommend changing the statin, management of hyperpotassemia, acidosis and referring to a cardiologist for the myopathy follow up, against stopping statin treatment and increase cardiovascular risk for a period of time. Local protocols between the emergency department and cardiology department should be implemented to decide the level of impairment at which it is necessary to ask for the cardiologist or admission directly from the emergency department.

Aknowledgements

All authors have equally contributed to this work. Authors declare that there are no any conflict of interest issues.

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