Simvastatin-induced rhabdomyolysis: a case study on clinical-decision making based on the evidence-based medicine approach

Konstantinos Koskinas[1], Thrasyvoulos G. Tzellos[2], Kyriakos Gougoulias[1], Georgios Gougoulias[1], Christos Papakonstantinou[1], Dimitrios Kouvelas[2]

[1]Department of Internal Medicine-Pneumonology, General Hospital of Halkidiki, Greece
[2]Department of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Greece

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Corresponding author:
Dimitrios Kouvelas, MD, PhD
Associate Professor of Pharmacology
School of Medicine
Aristotle University of Thessaloniki
P.O.Box 1532, 54006
Thessaloniki, Greece
Phone/fax: +30 23 199 93 35
E-mail: kouvelas@auth.gr

Abstract

A case of a woman diagnosed to have rhabdomyolysis is presented. It was attributed to simvastatin she had been receiving for 1 year. Based on pathogenesis and medical examination, the diagnosis of statin-induced rhabdomyolysis was made. Simvastatin was discontinued with concomitant clinical improvement followed by serum creatine kinase decrease. Future course of therapy was decided after reviewing the literature using evidence-based medicine tools. The purpose of this case report is to share our experience so that physicians are reminded of the potential of rhabdomyolysis related to statin use and illustrate the value of evidence-based medicine in clinical practice.

Key words: case report, rhabdomyolysis, simvastatin, statin safety, evidence-based medicine.

Introduction

Rhabdomyolysis is defined as an acute increase in serum concentrations of creatine kinase to more than five folds the upper normal limit, provided that myocardial infarction has been excluded as a cause (creatine kinase MB fraction less than 5%) [1]. It is a clinical condition which is characterized by dissolution of striated muscle fibres, resulting in leakage of muscle enzymes, myoglobin, potassium, calcium, and other intracellular constituents, accompanied by a critical increase in sarcoplasmic calcium and intracellular damage by activation of proteases and phospholipases. It can potentially result in dramatic, even life threatening, consequences [1, 2].

The immediate consequences of rhabdomyolysis include electrolytic disorders, namely hyperkalaemia, which may cause fatal cardiac arrhythmia and hypocalcaemia due to calcium binding by damaged muscle proteins and phosphate. Major complications include acute renal failure, cardiac abnormalities and compartment syndrome [3]. Acute renal failure represents a common complication resulting from the combination of intraluminal myoglobin cast formation, haem protein nephrotoxicity and renal vasoconstriction. Visible myoglobinuria (tea or cola coloured urine) occurs when urinary myoglobin concentration exceeds 250 ng/mL (normal <5 ng/mL),

corresponding to the destruction of more than 100 g of muscle. Myoglobinuria can be inferred by a positive urine dipstick test for haem, in the absence of red cells on microscopic examination of urine.

The causes [1, 2] of rhabdomyolysis include infections (viral, bacterial, or other), metabolic and electrolytic disorders, myotoxic drugs, or physical factors such as compartment syndromes, ischaemia, reperfusion (including surgical procedures), or pressure from hard surfaces in comatose patients. The risk of statin-related rhabdomyolysis in particular [4] can be exacerbated by several coexisting parameters, including impaired hepatic and renal function, hypothyroidism (clinically apparent or even occult), diabetes mellitus, and concomitant medications, either myotoxic or involved in statin metabolism. Other risk factors for statin-induced myopathy include consumption of grapefruit juice (more than 1 L per day), a personal or family history of hereditary muscle disorders, previous myotoxicity with lipid lowering drugs (statins or fibrates), a history of alcoholism and being of Chinese or Japanese descent.

An extensive evidence base exists [5] for the use of statins in both primary and secondary prevention. Statins are of particular concern because of their widespread and increasing use. Currently, statins are being used extensively and more aggressively for the treatment of hypercholesterolemia. As more data gets pooled from newer trials, the threshold for statin use has been lowered and the potential for adverse events therefore has probably increased.

Although treatment benefits of statin use is a fact, the adverse effects which have been attributed to statins can not be ignored when prescribing the above drug category. Myotoxicity associated with statins, ranging from mild myopathy or elevated serum creatine phosphokinase (CPK) levels to rhabdomyolysis, is one of the well documented dose related adverse effects a clinician might have to cope with. Data concerning safety of statins are generally gathered from cohort studies, randomized controlled trials and voluntary notifications to national regulatory authorities of adverse events and published individual case reports. Regarding the widespread use of this particular class of drugs as well as their rare but potentially life-threatening adverse effects, it is worth sharing even individual cases of statin-induced rhabdomyolysis with the scientific community. Herein we present a case of rhabdomyolysis in a patient receiving simvastatin, which lead us to fully review the evidence-base regarding statins, especially a very recent meta-analysis. Our future course of therapy was decided according to this review.

Case report

We describe the case of a 70-year-old woman who presented complaining of diffuse myalgia, especially affecting the upper and lower extremities, for the past few days. The patient had a history of type 2 diabetes mellitus, dyslipidemia, hypertension, smoking and mild chronic obstructive pulmonary disease. Medications at that time were simvastatin (40 mg), valsartan (40 mg), and metformin (850 mg) daily. She had been under treatment with simvastatin, for about 1 year.

The patient started feeling weak and excessively fatigued and also started to have dull aches in the proximal muscles of the upper and lower limbs. She also complained of exacerbation of the pre-existing lower extremities oedema, which had previously been attributed to chronic venous insufficiency. These symptoms were accompanied by reported paroxysmal dyspnoea and due to her history of obstructive pneumonopathy (currently under no medication) she was admitted to the pneumonology emergency room, where laboratory tests revealed a markedly elevated CPK level (9658 U/L), while CK-MB fraction was 62 (clearly <5%). She was admitted in our hospital with the diagnosis of rhabdomyolysis for further care. The patient's laboratory test values at presentation were: creatine kinase (CPK) – 9658 U/L (reference value 40-170), CK-MB fraction – 62 ng/mL (reference value ≤25), troponin-T test (semi-quantitative) – negative, creatine – 0.63 mg/dL (reference value 0.3–1.1), SGOT – 217 U/dL (reference value ≤40), SGPT – 117 Ud/L (reference value ≤42), LDH – 1330 Ud/L (reference value 240-480), arterial blood pH – 7.52 (reference value 7.37-7.42), D-dimers – 176 ng/mL (reference value ≤500), plasma glucose – 138 mg/dL, glycosylated haemoglobin (HbA1c) – 6.8%.

About the therapeutic management of such a condition, the first level of approach included supportive management and prevention or treatment of possible complications. The second level included the identification and subsequent withdrawal of the potential causative agent and the possible coexisting precipitating factors.

No randomised trials for treatment of rhabdomyolysis have been conducted. The primary aim in a patient diagnosed with rhabdomyolysis is the prevention or treatment of renal and cardiac complications. The fundamental management principle is intravascular volume expansion by using saline and sometimes mannitol to maintain urine output at more than 200-300 ml/hour, with careful monitoring of sodium and calcium serum concentrations. In terms of reducing the risk of tubular obstruction by myoglobin casts and subsequent renal failure, alkalinising the urine can be achieved by using sodium bicarbonate. However, the risk of renal damage cannot be eliminated, since myoglobin is also intrinsically nephrotoxic and can precipitate acute tubular necrosis through other mechanisms. These include iron dependent inhibition of oxidative phosphorylation and iron

independent inhibition of glyconeogenesis. In case of renal failure despite these measures, continuous haemofiltration or haemodialysis will be required. Interestingly, our patient had no signs of renal damage through her hospitalisation and no specific measures had to be taken to support renal function. She was immediately started on high-volume intravenous saline administration.

As for the identification of the potential causative factor(s), our effort was focused on excluding as many of the reported causes of rhabdomyolisis as possible. From the patient's history, she denied having any recent illness or alcohol, antibiotic or over-the-counter medication use. Her thyroid function was normal, as indicated by the laboratory test values: thyroxine (T_4) total – 7.9 µg/dL (reference value 5–12), triiodothyronine (T_3) total – 112 ng/dL (reference value 90-190), thyroid-stimulating hormone (TSH) – 4.8 µU/mL (reference value 0.6-5.8). The CK-MB fraction was <5% in repeated measures and the troponin-T test was negative. Besides, the standard 12-lead electrocardiogram, repeatedly performed throughout the patient's hospitalization, revealed sinus rhythm with no signs indicative of myocardial ischemia or necrosis according to current guidelines [6], thus excluding myocardial origin of the dramatic CPK elevation. The echocardiogram, which was performed for both the clarification of the aetiology of lower extremity oedema exacerbation and the detection of possible cardiac involvement of muscular damage, revealed findings compatible with the pre-existing hypertensive cardiopathy, i.e. left ventricular hypertrophy, with a normal ejection fraction (E.F. – 58%).

As a result, the history of simvastatin use was incriminated for our case of rhabdomyolysis. Besides, the rarity of rhabdomyolysis in persons not receiving lipid-lowering drugs renders reasonable to attribute all cases of rhabdomyolysis observed in persons receiving statins and/or fibrates to those drugs [7].

The patient's laboratory test values and symptoms progressively improved throughout her hospital stay. Both myalgia and lower extremities oedema resolved and the CPK levels fell within normal range in 6 days. The patient was discharged 7 days after admission, with a serum CPK concentration of 147 U/L. Transaminase and CPK concentrations fell rapidly, suggesting they were of muscular rather than hepatic origin. Before discharge the literature was fully reviewed for assessing the best choice of statin, since dyslipidaemia could not be left untreated. Our choice, which will be fully explained later in discussion, was fluvastatin. Six months later our patient had exhibited no adverse effects, and her laboratory test values revealed no signs of muscular or hepatic dysfunction (CPK – 122 U/L, CKMB – 13 ng/mL, SGOT – 24 Ud/L, SGPT – 38 Ud/L). As for her lipid status, levels of high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) continued to be within desirable limits meeting current guidelines, following alteration of the lipid-lowering agent (HDL-c – 56 mg/dL, LDL-c – 104 mg/dL, cholesterol – 194 mg/dL, triglycerides – 171 mg/dL) [5].

Discussion

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) represent the most successful drug category for the treatment of hypercholesterolaemia and dyslipidaemia. The value of statin therapy is well established in an overwhelming abundance of data generated in organized systems of care with scheduled follow-up, monitoring, and reporting. Statins inhibit the enzyme HMG-CoA reductase, which is critically involved in cholesterol biosynthesis in the liver. This results in a dose-dependent reduction of circulating LDL cholesterol (LDL-c) levels and intermediate-density lipoprotein (available statins vary in potency), reduction of triglycerides in proportion to LDL-c lowering as well as a small but variable increase in HDL-c. Available clinical trial data point to the significant LDL-c lowering produced by statins as the major reason for their efficacy in improving total mortality and reducing coronary heart disease (CHD) events, which is associated with retarding or even reversing the progress of atherosclerosis in all major arterial trees (coronary, cerebral and peripheral) [8-10]. At the same time, statins may also exhibit several so-called pleiotropic effects that may account for some of their beneficial actions beyond lipid lowering [11]. There is a continuing interest in the pleiotropic effects of statins [12], including effects on the endothelial dysfunction, the inflammatory response, the stability of the atherosclerotic plaque, the nitric oxide availability, and even the platelet function and thrombus formation. If these pleiotropic effects are to be proven in clinical trials, statins may be used also for the treatment of congenital pulmonary and cardiac diseases [13].

The revised National Cholesterol Education Panel Adult Treatment Panel (NCEP ATP III) guidelines [5] expanded the population of patients targeted for cholesterol-lowering therapy. Furthermore, current guidelines, besides unequivocally advocating statin therapy for high-risk individuals, also encourage lower low-density lipoprotein cholesterol (LDL-c) goals, which would not only broaden the pool of individuals eligible for statin therapy, but might also increases the likelihood that statins will be used at higher doses.

A clinical advisory on the use and safety of statins pointed out that these are generally well-tolerated drugs. Elevated liver transaminases (defined as ≥3 times the upper limit of normal in most studies) occur in 0.5% to 2.0% of clinical trial subjects and are dose dependent, while myopathy and muscle-

related symptoms and/or creatine kinase (CK) elevations are also concerns for clinicians [14]. Increases in liver function tests or new myopathy and myalgia are bothersome, but not serious or fatal side effects, whereas rhabdomyolysis, although rare, is always considered serious and is potentially fatal.

Clinically recorded myotoxicity occurs in about 0.1% of cases. Fatal rhabdomyolysis due to statins is rare and occurs in less than one per million prescriptions. According to the results of a recently published review, the incidence of rhabdomyolysis for statins (excluding cerivastatin, which was withdrawn in 2001) [7] in two large scale cohort studies was 3.4 (1.6 to 6.5) per 100,000 person-years, with case fatality 10%. This estimation was supported by data from 20 randomized controlled trials. The estimated mortality is 0.3 per 100,000 person-years. Incidence was about 10 folds greater when gemfibrozil was used in combination with statins. Apart from rhabdomyolysis, the incidence of myopathy in patients treated with statins, estimated from cohort studies supported by randomized trials, was 11 per 100,000 person-years. If the implementation of evidence-based clinical practice is the goal, a physician should bear in mind that the incidence of rhabdomyolisis significantly differs according to the specific statin. It was about 4 folds higher (4.2 per 100,000 person-years) in persons treated with lovastatin, simvastatin or atorvastatin, which are eliminated by cytochrome P450 (CYP) 3A4, than pravastatin or fluvastatin (1 per 100,000 person-years), which are not metabolised by CYP3A4. Although the exact mechanism of statin-induced myopathy is not fully understood, individual genetic susceptibilities and cytochrome P450 interactions are considered to play a pivotal role. The risk of muscle adverse events related to use of the statins increases significantly with the addition of interacting drugs to a patient's therapeutic regiment. This notion lies in accordance with data concerning reports of statin-related rhabdomyolysis cases, given that >50% of cases were associated with a potential drug interaction with either fibrates or a well known CYP3A4 inhibitor [3]. Drug interactions with statins are mostly attributed to pharmacokinetics rather than pharmacodynamic interactions, since these drugs are highly selective inhibitors of HMG-CoA reductase. Pharmacogenomic factors, characterised by CYP polymorphism, also seem to be involved in inter-individual variations to efficacy and tolerability of statins [15]. However, this safety advantage cannot be interpreted as a sign of overall superiority and therefore preferable use of the 2 above mentioned "safer" statins, considering that statins also vary in pharmacological terms. On the other hand, in daily clinical practice the safety profile of statins is not well established as it has characteristically been demonstrated by the induction of rhabdomyolysis in a patient switching from one statin to another [16].

All the above evidence had been taken into consideration, but our final decision was mainly shaped by the only meta-analysis on statin-related adverse events so far [17]. This meta-analysis concluded that serious myopathy-related events (CPK higher than 10 folds of upper limit of normal) or rhabdomyolysis are infrequent, requiring 3400 people for a statin related myopathy (number needed to harm=3400) and 7428 people for a statin-related rhabdomyolysis (number needed to harm=7428) in order to be observed. A further conclusion concerning the safety profile of each statin confirmed the notion that some statins are more likely to result in adverse events, as follows: atorvastatin>pravastatin=simvastatin=lovastatin >fluvastatin. The fact that atorvastatin was associated with more adverse effects than other statins can partially be explained by the lipophilicity of atorvastatin molecule. Thus our final therapeutical choice was fluvastatin.

Conclusions

In light of the well established treatment benefits of statin use and in an attempt to approach the issue of statin safety in an evidence-based manner, physicians should keep in mind that, according to the meta-analysis, treating 1000 individuals with any statin will prevent 37 cardiovascular events such as myocardial infarction, revascularization, stroke, cardiovascular death, or all-cause mortality and generate 5 reports of statin-induced, mostly non serious, adverse events, including myalgia, myopathy, CPK and liver function tests elevations, alone or in combination [17]. This meta-analysis suggests that although the risk of any adverse events is increased with statin therapy compared with placebo, benefits are greater and clearly outweigh the small risk of minor adverse events that are easily reversible.

The constellation of benefits with little side effect penalty has resulted in the comparison of statins with antibiotics in the global battle against cardiovascular disease [18]. Although statin-associated myotoxicity affects compliance, quality of life of patient and discontinuation rate, yet the low incidence of myotoxicity including rhabdomyolysis and less severity of commonly occurring myopathy and myalgia do not raise doubts about the clinical efficacy and tolerability of statins. In terms of prevention, the statin clinical advisory pointed out that to reduce the risk of statin evoked myopathy, physicians should obtain and critically appraise liver function and CPK values before prescribing statins [19].

Finally we would like to point out that our case interpretation and final therapeutic decision was based on a critical review of the literature that it

was conducted due to our case of rhabdomyolysis. This indicates the high significance of an evidence-based medicine approach that leads to rational therapies and continuous medical education during daily clinical practice.

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