Simvastatin-Induced Nocturnal Leg Pain Disappears with Pravastatin Substitution

Nataša Stojaković[1], Rajko Igić[1,2]

[1]Department of Pharmacology, Toxicology, and Clinical Pharmacology, Medical School, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[2]Department of Anesthesiology and Pain Management, John Stoger Hospital of Cook County, Chicago, Illinois, USA

SUMMARY

Introduction Statins have similar side effects that do not always occur at the same rate among the various statins. We present a case of simvastatin-induced muscle toxicity that disappeared when pravastatin was substituted for the original drug.

Case Outline A 74-year-old male, a nonsmoker, complained of severe nocturnal leg cramps. The patient also complained that similar painful cramping occurred when he walked rapidly or jogged. Because some components of his lipid panel exceeded the 'desirable' range, and as he had a history of myocardial infarction, his family physician prescribed simvastatin (40 mg/day). The patient had taken this medication for the past eight years. The painful nocturnal episodes started two years ago and affected either one or the other leg. Four months ago we discontinued his simvastatin and prescribed pravastatin (80 mg/day). At a follow-up visit six weeks later, the patient reported that his leg pains at night and the pain experienced after brisk walking had disappeared. Four months after the substitution of pravastatin for simvastatin, the patient reported that his complete lack of symptoms had continued.

Conclusion These painful muscle cramps were probably caused by an inadequate vascular supply to the calf and foot muscles. Perhaps a combination of advanced age and atherosclerotic changes created a predisposition for the simvastatin-induced leg cramps. Pravastatin differs from simvastatin in several ways. It is not metabolized by cytochrome P450 (CYP) 3A4 oxidases, and thus is not influenced by CYP 3A4 inhibitors like simvastatin. Also, simvastatin is associated with single-nucleotide polymorphisms located within the SLCO1B1 gene on the chromosome 12 and established myopathy, while pravastatin lacks this association. These differences may contribute to increased tolerance to pravastatin in this particular case.

Keywords: statins; simvastatin; pravastatin; nocturnal leg cramps

INTRODUCTION

Statins reduce cardiovascular events both in primary and secondary prevention of lipid abnormalities [1]. These drugs (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) may have similar muscular side effects, but these effects do not always occur at the same rate among various statins. The muscular pain and cramping associated with statin use may lead patients to stop taking their drug, but discontinuation may cause a negative rebound effect related to the vascular events. We present a case of severe simvastatin-induced nocturnal leg cramps in an elderly patient who experienced relief and disappearance of the symptoms after the substitution of pravastatin for simvastatin.

CASE REPORT

A 74-year-old male, who never smoked, complained of severe leg pain at night; this occurred once or twice each night at a frequency of three or more times a week. The pain abated within several minutes if he stood or walked around. The patient described these events, which occurred in only one leg at a time, as extremely painful, almost unbearable, cramps of his calves and feet.

These nocturnal episodes started two years ago. At first, they occurred just a few times a month, and the patient thought they were related to his advanced age and glucose intolerance. When he finally sought medical attention, his family physician advised him to use magnesium carbonate, an over-the-counter medicine, to prevent the attacks. Daily usage of magnesium carbonate effervescent tablets (300 mg) did not help, but the patient had taught himself to diminish the severity of the attacks by getting up and standing for a while. The patient also complained that similar painful leg cramping occurred when he walked rapidly or jogged for approximately five to ten minutes. When he stopped, the pain quickly subsided. In contrast to the nocturnal leg cramping, the pain associated with jogging affected both legs at a time.

The patient's history included glucose intolerance, persisting for the past twenty years, and moderate obesity. Two years ago, he had a myocardial infarction (MI). He was admitted to the hospital, but refused coronary arteriography. Two of his four older sisters had type 2 diabetes that appeared when they were in their sixties.

Correspondence to:
Rajko IGIĆ
Department of Anesthesiology and Pain Management
John Stoger Hospital of Cook County
Chicago, Illinois 60612
USA
r.igic@excite.com

Table 1. Lipid panel before simvastatin, and during simvastatin and pravastatin treatments. Fasting levels of lipids are expressed in mmol/L.

Lipid*	Before simvastatin treatment	Six weeks of simvastatin treatment	The last day of simvastatin treatment	Six weeks of pravastatin treatment
Total cholesterol	4.31	2.92	3.41	3.82
Triglyceride	2.65	1.72	1.73	1.49
LD cholesterol (calc.)	2.71	1.37	1.78	2.19
HDL cholesterol	0.64	0.77	0.82	0.95
Non-HDL cholesterol	-	-	2.58	2.87

* According to the National Cholesterol Education Program guideline, desirable values for cholesterol are <5.15 mmol/L, triglyceride <1.7 mmol/L, LDL <2.59 mmol/L, HDL >1.05 mmol/L, and non-HDL <3.36 mmol/L.

When our patient gradually increased his physical activity and changed his diet, his body weight reduced to normal. Ten years ago, his diastolic pressure increased slightly (92-94 mmHg measured over several visits to his doctor), but since that time, his blood pressure has been well regulated by treatment with lisinopril (10 mg/day) and atenolol (25 mg/day). Because his lipid panel was not within 'desirable' limits, and because of his previous MI, his family physician prescribed simvastatin (40 mg/day, to be taken at night). The values of triglyceride and LDL cholesterol soon reached normal levels. The values of HDL cholesterol were lower than desirable but still slightly improved (Table 1). The patient had been taking simvastatin for eight years by the time we saw him.

The patient maintained glycemic control with diet alone, but his glycohemoglobin (HbA1c) increased slightly over a six-year period: 5.5% in 2006, 5.8% in 2009, 6.5% in 2011, and 7.1% in 2012 (normal range: 4.0-6.2%). The results of other blood tests were within normal range, including the concentration of potassium, 4.4 mmol/L (normal range: 3.5-5.5 mmol/L), sodium 141 mEq/L (normal range: 135-148 mEq/L), chloride 107 mEq/L (normal range: 95-108 mEq/L His kidney function was normal. There was a slight increase in creatinine phosphokinase (CPK) (238 U/L) where the normal range extends to 170 U/L).

This patient's mental state, including thought processes, mood, and intellectual function, was in excellent condition. The physical exam was unremarkable, except that arterial pulsations were weaker in both legs. Blood pressure was 140/75 mmHg, and the pulse was 55/min. An ultrasound of the abdominal aorta, kidneys and large arteries showed no evidence of abdominal aortic aneurism, but atherosclerotic plaques and ectasia of the distal aorta and common iliac arteries were noted. No abnormalities were found on electromyography of the legs.

At this time (October 2011), simvastatin was discontinued and pravastatin was prescribed (80 mg/day, taken at night). Other medications (lisinopril 10 mg/day, atenolol 25 mg/day and aspirin 100 mg/day) were continued as before. Six weeks later, at the follow-up visit, the patient reported that his leg pains at night and pain after brisk walking had completely stopped. At this time, the lipid risk panel was similar to that when the patient was on simvastatin, CPK was within normal range, and HDL cholesterol was still lower than optimal (Table 1). Four months after the substitution of pravastatin for simvastatin, the patient reported that he had neither leg pains at night nor pain provoked by brisk walks.

DISCUSSION

Simvastatin, in a dose of 40 mg/day, was initially well tolerated by our patient. It effectively reduced elevated hyperlipidemia for several years before leg pain at night appeared. Because this type of pain is common among elderly people [2], the patient did not think that it was connected to simvastatin treatment. We observed earlier that reducing the dose of simvastatin to 10 mg/day or discontinuing the drug entirely eliminated nocturnal leg cramps [3]. However, because we considered that there could be rebound effects related to the vascular effects, we prescribed pravastatin instead of simvastatin. This substitution resulted in an adequate lipid-lowering effect but did not cause the leg pain.

Simvastatin is a prodrug; it is hydrolyzed to its active form, simvastatin acid, which is a specific inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This enzyme is an important component of the biosynthetic pathway for cholesterol. Because of their effectiveness and well-established safety profiles [4-6], simvastatin and other HMG-CoA reductase inhibitors are the mainstays for management of high cholesterol and associated cardiovascular complications. Statins may have similar side effects, but these effects do not always occur at the same rate among the various statins. Muscle toxicity is the most significant adverse effect related to statins [7,8]. It includes myalgia, myopathy, and rhabdomyolysis. The pharmacokinetic disposition of simvastatin, but not pravastatin, depends upon individual differences in tissue content of cytochrome P450 (CYP) 3A4 oxidases [9], and it may be influenced by CYP 3A4 inhibitors, such as ketoconazole, verapamil, mibefradil, and grapefruit. None of these known inhibitors were factors for our patient.

An association between single-nucleotide polymorphisms located within SLCO1B1 gene on the chromosome 12 and established myopathy was recently reported for patients treated with simvastatin [10]. Similar findings have been reported for type 2 diabetic patients treated with simvastatin. However, no such association has been recorded with pravastatin.

The strong, but short lasting, leg cramps that affected our patient were not associated with significant increase of serum CPK level. These painful muscle cramps were probably caused by an inadequate vascular supply to the calf and foot muscles. We do not know the mechanism of these changes caused by simvastatin. Perhaps a combination of advanced age, glucose intolerance, and atherosclerotic changes create a predisposition for the simvastatin-induced nocturnal leg cramps. Mentioned differences between the two statins may contribute to better tolerance of pravastatin.

doi: 10.2298/SARH1306387S

REFERENCES

1. Gotto AM, Moon JE. Recent clinical studies of the effects of lipid-modifying therapies. Am J Cardiol. 2012; 110(1 Suppl):15A-26A.
2. Young G. Leg cramps. Clin Evid (Online). 2009. pii: 1113.
3. Ljubojević G, Tomić N, Stojaković N. Statin-induced leg pain at night. Scr Med. 2011; 42:109.
4. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Survival Study (4S). Lancet. 1994; 344:1383-9.
5. Saks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996; 335:1001-9.
6. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. Drug Saf. 2000; 22:441-57.
7. Kažić T. Statini – neželjena dejstva i interakcije. Scr Med. 2011; 42:84-91.
8. Blairer O, Lishner M, Elis A. Managing statin-induced muscle toxicity in a lipid clinic. J Clin Pharm Ther. 2011; 6:336-41.
9. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet. 2000; 38:41-57.
10. Puccetti L, Scarpini F, Cappellone R, Auteri A. Genetic influence in statin intolerance. Clin Pharmacol Ther. 2011; 90:365.

Ноћни грчеви у ногама изазвани симвастатином нестају после супституције правастатином

Наташа Стојаковић[1], Рајко Игић[1,2]

[1]Катедра за фармакологију, токсикологију и клиничку фармакологију, Медицински факултет, Универзитет у Бањалуци, Бањалука, Република Српска, Босна и Херцеговина;
[2]Одељење за анестезиологију и контролу бола, Болница Џон Стоџер Округа Кук, Чикаго, САД

КРАТАК САДРЖАЈ

Увод Статини имају сличан профил нежељених дејстава, али постоје разлике у степену учесталости између појединих статина. У чланку је приказан случај код којег је мишићна токсичност изазвана симвастатином нестала када је уместо њега у терапију уведен правастатин.

Приказ болесника Мушкарац стар 74 године, непушач, повремено је имао јаке ноћне болне грчеве у ногама. Жалио се и на болне грчеве у ногама при брзом ходању или трчању. Пошто је липидни статус био изван оптималног, а и због инфаркта миокарда ранијих година, лекар је преписао симвастатин (40 *mg* дневно). Болесник је узимао тај лек осам година. Епизоде ноћних болова су почеле пре две године, а захватали су једну или другу ногу. Пре четири месеца терапија симвастатином је замењена правастатином (80 *mg* дневно). Шест недеља касније ноћних и болова који су се јављали при брзом ходању није више било. Четири месеца након замене симвастатина правастатином болесник и даље није осећао никакве тегобе.

Закључак Болни грчеви ногу вероватно су изазвани неодговарајућим снабдевањем крвљу мишића потколенице и стопала. Могуће је да је комбинација старијег животног доба и атеросклеротских промена била предиспозиција за појаву грчева ногу изазваних симвастатином. Правастатин се разликује од симвастатина јер га не метаболизују цитохром *P450* (*CYP*) *3A4* оксидазе, као што је случај са симвастатином. Поред тога, миопатија изазвана симвастатином, али не и правастатином, повезана је с полиморфизмом једног нуклеотида који је локализован у гену *SLCO1B1* дванаестог хромозома. Те разлике између два лека могле би допринети бољем подношењу правастатина код болесника приказаног у овом чланку.

Кључне речи: статини; симвастатин; правастатин; ноћни грчеви у ногама

Примљен • Received: 09/03/2012 **Прихваћен • Accepted:** 26/04/2012