Short communication

Patients' report of statins use and side-effects in a sample of hospitalized cardiac patients in the Islamic Republic of Iran

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إبلاغ المرضى عن استخدام الستاتينات وعن تأثيراتها الجانبية في عينة من مرضى القلب في مستشفيات جمهورية إيران الإسلامية
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الخلاصة: هدف الباحثون إلى دراسة معدل انتشار التأثيرات الجانبية لمركبات الستاتين لدى المرضى الإيرانيين الذين أدخلوا في مستشفى تخصصي لأمراض القلب وكانوا يتناولون الستاتين قبل دخولهم إليه. وقد قام الباحثون بجمع المعطيات في المدة بين أيلول/سبتمبر 2007 وآذار/مارس 2008، وشملت الدراسة 200 مريض. وقد قام الباحثون باستكمال استبيان من سجلات المرضى ومن مقابلاتهم معهم. وكان متوسط العمر لديهم 61.5 عاماً (الانحراف المعياري 12.3)، وكان 63% منهم من الذكور. وكان أكثر الستاتينات استخداماً الأتورفاستاتين (99% من المرضى). وقد أبلغ 63.5% من مجمل المشاركين عن معاناتهم من تأثيرات جانبية ناجمة عن الستاتينات. وتمثلت هذه التأثيرات الجانبية المبلغ عنها في تأثيرات تنفسية (4%)، وهضمية (18.5%)، وصداع (16.5%)، وطفح (0.5%)، وتفاعلات أرجية (5%)، وأخيراً في تأثيرات جانبية ذات صلة بالعضلات مثل الألم العضلي (9.5%). وعلى الرغم من أن المنافع السريرية ترجح على الاختطار الضئيل للفشل الكبدي والاعتلال العضلي، فإن على السريريين أن يتنبهوا للتأثيرات الجانبية للستاتينات، ولا سيما بعد المعالجات الطويلة الأمد والمتعددة.

ABSTRACT We aimed to study the prevalence of the side-effects of statins among Iranians patients admitted to a cardiac-specialized hospital and had taken statins prior to hospitalization. Data was collected between September 2007 and March 2008 and 200 patients were enrolled. A questionnaire was completed using the patients' records and by interviewing the patients. The mean age of the participants was 61.5 (SD 12.3) years and 63% were males. The most commonly used statins was atorvastatin (99% of the patients). In all, 63.5% of the participants reported experiencing side-effects due to statins. The reported side-effects were respiratory (4%) and gastrointestinal effect (18.5%), headache (16.5%), rash (0.5%) and allergic reactions (5%); 9.5% reported muscle-related side-effects such as myalgia. Although, the clinical benefits outweigh the small risk of liver failure and myopathy, clinicians should be aware of the side-effects of statins.

Utilisation des statines et signalement d'effets secondaires dans un échantillon de patients atteints de cardiopathies et hospitalisés en République islamique d'Iran

RÉSUMÉ Nous avons l'objectif d'étudier la prévalence des effets **secondaires** causés par les statines chez des patients iraniens admis dans un hôpital spécialisé en cardiologie et sous traitement par statines avant leur hospitalisation. Les données ont été recueillies entre septembre 2007 et mars 2008 auprès de 200 patients recrutés pour l'étude. Un questionnaire a été rempli à l'aide des dossiers médicaux des patients et d'un entretien avec eux. L'âge moyen des participants était de 61,5 ans (E.T. 12,3) et 63 % d'entre eux étaient de sexe masculin. La statine la plus fréquemment prescrite (99 % des patients) était l'atorvastatine. En tout, 63,5 % des participants ont signalé avoir souffert d'effets secondaires causés par les statines. Ces effets étaient les suivants : affections respiratoires (4 %), affections gastro-intestinales (18,5 %), céphalées (16,5 %), rougeurs cutanées (0,5 %), réactions allergiques (5 %), mais aussi affections musculaires (9,5 %) telle que la myalgie. Même si les bénéfices cliniques compensent le risque faible d'apparition d'une insuffisance hépatique ou d'une myopathie, les cliniciens devraient connaître les effets secondaires causés par les statines.

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Introduction

Coronary heart diseases (CHD) is in an epidemic state in countries such as the United States of America (USA), Canada, Australia, New Zealand, the United Kingdom, Finland, Denmark and is moving fast towards such a state in others such as the Russian Federation, and former Soviet Union republics [1]. According to the World Health Organization (WHO), cardiovascular diseases kill more people every year than any others. In 2004, 7.2 million people died of coronary heart disease, 5.7 million from stroke or other forms of cerebrovascular disease worldwide [2]. In 2002, 42% of deaths in the Islamic Republic of Iran were caused by cardiovascular diseases, while in 2004, this figure rose to 44% [3,4].

One of the major risk factors for these diseases is dyslipidaemia, and a previous study has shown that in Iranian adults the prevalence of dyslipidaemia is very high and urgent preventive programmes and changes in lifestyle are required [5]. One of the most common medicines used for correcting serum lipid profile are hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins. They are used as primary prevention of cardiovascular diseases in high-risk people and secondary prevention of cardiovascular events, peripheral artery diseases or cerebrovascular diseases and the mortality resulting from them [6]. The medicines in this group include atorvastatin, cerivastatin, mevastatin, lovastatin, pravastatin, fluvastatin, pitavastatin, simvastatin and rosuvastatin.

Despite the fact that statins produce beneficial effects, as with any other medicine, they can also generate side-effects; many are not serious but some, despite being rare, are very serious and even life-threatening. Some of the side-effects of statins include headache, altered liver-function tests and rarely hepatitis, paraesthesia, and gastrointestinal effects such as abdominal pain, flatulence, constipation, diarrhoea, nausea

and vomiting. Rash and hypersensitivity reactions, including angioedema and anaphylaxis, have been reported rarely. Reversible myositis is also a rare but significant side-effect of statins [6]. The possibility of myositis occurring is increased in case of co-prescription of statins with several other medicines such as cyclosporin, daptomycin, fibrates, gemfibrozil or nicotinic acid. Probably the most serious side-effects of statins are liver failure [7–10] and rhabdomyolysis [8–10]; fortunately these are rare. With rhabdomyolysis there is damage to muscles which can progress to loss of muscle cells, kidney failure, and even death [11–13]. It occurs more often when statins are used in combination with other drugs that could cause rhabdomyolysis [8,13,14] or with drugs that cause a reduction in the elimination of statins thus resulting in raised plasma levels of statins [15–18]. Another serious side-effect of statins is transient elevation in serum transaminases; this is mostly self-limiting but there are reports of severe liver failure and even one case of death following atorvastatin use [19].

Because of the seriousness of the adverse effects of statins, especially with long-term use or co-prescription, we aimed to examine the level of side-effects seen as result of statins use in Iranian hospital patients. The results of the present study will be useful for those who prescribe statins and will provide practical information from a familiar setting.

Methods

The present study was a descriptive cross-sectional study and data collection was conducted between September 2007 and March 2008. The data were collected in 2 wards of Shahid Madani hospital, a specialized heart hospital in Tabriz, in the north-west of the Islamic Republic of Iran. The hospital has 4 wards in total with 32 beds for each ward. The hospital serves a population of patients from urban, semi-rural and

rural areas from East Azarbaijan and neighbouring provinces or countries such as Azerbaijan.

Criteria for enrolment in the study were: admittance to the hospital and had received statins for control of dyslipidaemia prior to admission. Patients who received statins for the first time while in hospital or did not wish to participate in the study were excluded. Suitable subjects were identified by their hospital records, approached and those who consented to the study were enrolled in the study. A total of 300 patient records were checked and 200 patients were identified who were eligible for inclusion in the study. There were no refusals to participate.

Some of the information was gathered from patient records and some were asked directly from patients using a questionnaire.

The questionnaire was completed in face-to-face interviews but it was kept anonymous and identifiable by a number-letter code. The questionnaire included mainly questions that could be answered by ticking boxes corresponding to the patients' views. The questions were divided into 4 sections. In the first part, questions related to demographic information about the participant, such as age, educational status, and history of illness and medications. In the second section, questions were about diagnosis and treatment protocols from admission until discharge (there were no transfers or deaths). In the third section, questions were about side-effects of statins including the signs and symptoms of the adverse drug reactions and their management, extracted from British National Formulary [6]. In the last section, all the laboratory tests performed during hospitalization and their results were recorded. No patient received extra medication or additional tests because of the present study.

According to the rules of the Ethics Committee of the university, the studies which are not interventional do not require the approval of the Committee

and therefore it was not sought for the present study. However, patients were provided with an information sheet which explained the aim and method of the study and they were assured that their participation was voluntary and they were free to leave the study at any time without affecting their care. Sufficient discussion and time to make an informed decision or consult with relatives or physicians was given to each participant. Written informed consent was obtained from each participant prior to the study.

Data were analysed using the SPSS software, version 14.

Results

Of the 200 participants, 74 (37%) were female and 126 (63%) were male. Mean age [standard deviation (SD)] was 61.5 (SD 12.3) years with a range of 28 to 99 years. Mean age among females was 64.0 (SD 12.5) years with a range of 31 to 99 years, and mean age among males was 59.9 (SD 12.0) years with a range of 28 to 90 years. Most patients were in age range of 56–65 years for females and 46–55 years for males. Characteristics of the patients and data on hospitalization and past medical and medication history are shown in Table 1.

Mean number of medications (other than statins) used routinely by the patients prior to hospitalization was 1.13 (SD 1.3) with a range of 0 (140 patients) to 7 (1 patient). The medications included anticoagulants, benzodiazepine, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, digoxin, calcium channel blockers, vitamins, hypouricemics, analgesics, neuroleptics proton pump inhibitors, fibrate and hypoglycaemic medicines. Mean number of medications used during hospitalization was 3.6 (SD 2.7) with up to 10 medicines being prescribed; these included medications of a similar range as prior to hospitalization with a few changes.

Prior to hospitalization, the used statins were atorvastatin by 198 (99%)

Table 1 Patients characteristics and medical history

Variable	No. (n = 200)	%
Sex		
Male	126	63.0
Female	74	37.0
Age (years)		
≤ 40	8	4.0
41–50	30	15.0
51–60	56	28.0
61–70	58	29.0
71–80	38	19.0
> 80	12	6.0
Reason for hospitalization		
Surgery	44	22.0
Non-surgical	156	78.0
Medical history		
Myocardial infarction	21	10.5
Cerebrovascular incidences	7	3.5
Previous PTCA	11	5.3
Diabetes	36	17.8
Addiction	38	19.0
Smoking	33	16.5
Medication history^a		
Acetylsalicylic acid;	39	19.5
Nitrocontin	27	13.5
Gemfibrozil	19	9.5
Metoral	19	9.5
Digoxin	16	8.0
Amlodipine	14	7.0
Losartan	13	6.0
Captopril	11	5.5
Atenolol	10	5.0
Omeprazole	8	4.0
Warfarin	7	3.5
Propranolol	6	3.0
Glibenclamide	5	2.5

^aOnly the most common medications are included here.

PTCA = percutaneous transluminal coronary angioplasty.

patients and lovastatin by 2 (1%). The same statins continued to be used during hospitalization for each patient. The administered dosage of atorvastatin during hospital stay was 10 mg/day (2, 1%), 20 mg/day (43, 21.7%), 40 mg/day (151, 76.3%) and 80 mg/day (2, 1%); for both subjects who using lovastatin, the dose was 40 mg/day.

In total, 127 (63.5%) patients reported experiencing some kind of side-effects

caused by statins. Table 2 shows the prevalence of the side-effects reported by the patients. Gastrointestinal effects and headache were the most common side-effects reported (18.5% and 16.5% of patients respectively). Myalgia was observed in 0%, 18.6%, 6.0% and 100% after doses of 10, 20, 40 and 80 mg/day of atorvastatin respectively. None of those who received lovastatin reported myalgia. All 19 subjects who reported

Table 2 Side-effects of statins reported by the patients

Side-effect	No. (n = 200)	%
Gastrointestinal effects	37	18.5
Headache	33	16.5
Increased serum transaminase concentration	25	12.5
Muscle-related	19	9.5
Allergic reactions	10	5.0
Respiratory effects	8	4.0
Rash	1	0.5

muscle-related side-effects were using gemfibrozil prior to hospitalization, which was discontinued during hospital stay. Lactate dehydrogenase (LDH) concentration was not significantly different among patients with or without myopathy (754.4 vs. 638.9 U/L) but it was significantly higher than its normal range (50–150 U/L) [19]. Mean age of patients with or without myalgia was 62.8 (SD 14.5) years and 59.6 (SD 16.8) years respectively, and included 3 female and 16 male patients. Creatine phosphokinase (CPK) concentration was higher than normal in 1 female and 1 male patient (5 times the normal limit).

High-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride and total cholesterol concentrations were: 41.0 (SD 20.3) (20–186) mg/dL, 112.2 (SD 48.3) (33–282) mg/dL, 182.0 (SD 48.4) (97–282) mg/dL, and 129.0 (SD 54.4) (56–434) mg/dL respectively. Despite receiving statins LDL cholesterol, triglycerides and total cholesterol were higher than normal limits in 36, 14 and 58 patients respectively.

The side-effects were not severe enough to discontinue administration of statins, except for the 2 patients who had CPK 5 times the normal limit.

Discussion

The safety profile and high tolerability of statins support their use as the first-line therapy for patients at high risk of coronary heart disease. Although the clinical

benefits outweigh the small risk of liver failure and myopathy, clinicians should be aware of the adverse effects of statins, especially after long-term multiple-drug therapies. The progression of myalgia or myositis to rhabdomyolysis is rare, but if progressive muscle symptoms are ignored then fatalities can occur [20]. Therefore, physicians should be alert to this risk, particularly when statins are co-prescribed with other medicines with the same side-effect profile as statins, such as gemfibrozil. In our study, the patients with signs of myalgia had also received gemfibrozil prior to hospitalization. This is a known cause of increased incidence of myalgia, myositis or rhabdomyolysis [21] and discontinuation of one of the medicines is advisable. Gemfibrozil was the most commonly prescribed interacting drug with statins in other studies such as Song and co-workers study [22]. Special care is required when prescribing these 2 medicines together.

Another important issue in our study was the high concentration of CPK in 2 patients with muscle-related signs which required discontinuation of statins [6]. Although we found out that muscle-related side-effects were more prevalent in higher doses of statins and similar results have been seen in case of rosuvastatin [23], another theory is that muscle-related side-effects of statins are related to inter-individual variability in the degree of skeletal muscle co-enzyme Q(10) [CoQ(10)] depletion, sensitivity of muscle to decreases in CoQ(10), or both [24]. As a prevention method,

gemfibrozil was discontinued in our patients but statins were continued after high level of CPK.

Among our subjects the side-effects were not so severe to cause discontinuation of statins but previous studies by Tikkanen and co-workers and Chiang and co-workers showed that 7.9% and 2.7% of patients had to stop taking statins because of serious side-effects [25,26]. In the Tikkanen study, increase in CPK level was not seen after statins use [25] but in Chiang study increases in CPK were seen in 2.2% of patients [26]. Increased CPK in our study was seen in 2 patients (1%).

There are some limitations to the study; we included only patients hospitalized for acute illnesses, who therefore might have some abnormalities in their laboratory results which could affect our results. Hospitalization would also increase the number of medications used by each patient and therefore the possibility of drug-drug interactions and more side-effects. In future studies we suggest recording the side-effects in a more controlled environment and studying the effects of various risk factors, such as duration of statins consumption, on the appearance side-effects or their severity. Our study showed that the prevalence of statins side-effects in an Iranian population and the need to follow this further. It is necessary to educate patients to report any potentially significant symptoms and it is necessary to perform baseline liver function tests and 6 to 12 weeks after starting statins therapy or any dose escalation [27]. Thereafter, annual monitoring of liver function tests is usually sufficient to recognize any possible liver damage before serious dysfunction occurs. Special attention should be paid to patients with risk factors for myopathy or rhabdomyolysis. Prescribers should pay attention to the signs and symptoms of serious side-effects of all medications including statins.

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