Original paper

Frequency Of Potential Adverse Effects Of A Semisynthetic Statin (Simvastatin) Compared To A Synthetic Statin (Atorvastatin) Used To Reduce Cardiovascular Risk For Patients In Basra

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Abstract

Background: The confirmed benefits of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) for cardiovascular and cerebrovascular disease are well recognized in the medical literature.
Objectives: This study aimed at examining the frequency of potential side-effects seen as a result of statins therapy, because of the importance of statins adverse effects.
Therefore, this paper aims to evaluate the frequency of potential adverse effects reported by patients using a semi synthetic statin (Simvastatin) and the synthetic statin (Atorvastatin) in Al-shafaa general Hospital in Basra.
Patients and Methods: A total of 350 patients were included in this cross – sectional study to evaluate the frequency of potential adverse effects reported by patients using a semi synthetic statin (simvastatin) and the synthetic statin (atorvastatin) from November 2014 to March 2015 at the out-patient departments of Al-shafaa general Hospital in Basra.
Results & discussion: 246 patients (70.3%) report about 302 symptoms, overall symptoms reported were similar between the two types of statins and included muscle pain, joint pain, increased serum transaminase enzymes, gastrointestinal effects, respiratory effects and hair falling effects. The only adverse effects significantly reported for simvastatin more than atorvastatin were headache and dizziness. The side-effects were not severe enough to discontinue administration of statins.
Conclusions: There is no significant difference in the frequency of potential side effects reported by patients using a semi synthetic statin (simvastatin) and the synthetic statin (atorvastatin), apart from headache and dizziness reported significantly with simvastatin more than atorvastatin.
Key wards: side effects, statins, synthetic and semisynthetic, simvastatin, atorvastatin.

Introduction

Atherosclerosis disease is the major common cause of morbidity and mortality in developed countries. Reduction of low-density lipoprotein cholesterol (LDL-C) extenuates the progression of atherosclerosis and decreases the risk of cardiovascular events [(1)]. Statins are the most frequently used agents to reduce elevated levels of serum low-density lipoprotein cholesterol (LDL-C) concentration and have the potential to decrease cardiovascular risk factors and effectively reduces cardiovascular morbidity and mortality [(2)]. Statins are known as 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. The statins or their active metabolites are structural analogues of HMG-CoA and competitively inhibit HMG-CoA reductase, causes a decrease in

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the production of cholesterol and other metabolic intermediates in the cholesterol synthetic pathway. There may also be influence on the transcriptional arrangement of HMG-CoA reductase synthesis [3].

Statins were initially isolated from a mold, and the original statin approved for use in humans, lovastatin (previously known as mevinolin), was isolated from Aspergillus terreus. Simvastatin is a semisynthetic methylated analogue of lovastatin; pravastatin is an isolated metabolite of mevastatin; and atorvastatin, fluvastatin, cerivastatin, rosuvastatin, and pitavastatin are completely synthetic [3] as indicated in table 1. Even though statins have a similar mechanism of action, they differ in their potency and ability to reach either a 30% - 50% or over 50% reduction in low-density lipoprotein (LDL) cholesterol values. According to the guidelines, an individual's risk group should be the major initial consideration in the choice between the available statins [4].

While statins are considered safe and are well-tolerated drugs, they may cause a variety of musculoskeletal manifestation, for example asymptomatic creatine kinase elevation, myositis, myalgias and rhabdomyolysis [5- 6]. Muscle symptoms, such as muscle pain, weakness and cramps are the most common and important adverse effect in patients taking statins [7]. The study of 26 trials and 6726 patients revealed that no significant increase in liver function parameters or risk of rhabdomyolysis (raised creatinine phosphokinase concentrations) was observed in chronic kidney disease patients receiving statins in comparison with placebo [8].

In March 2012, the US Food and Drug Administration (FDA) new recommendations for the use of statins were issued. These recommendations included periodical observation of hepatic enzymes, blood glucose increases, adverse event information concerning cognitive impairment, and drug interaction label changes for lovastatin [9]. Laboratory monitoring prior to statin treatment includes a baseline fasting lipoprotein analysis, creatine kinase (CK) and hepatic transaminases.

Table 1. Source, dose and pharmacokinetic properties of statins

Statin drug	Origin	Solubility	Daily dose (mg)	Half-life (h)	Excretion (%)	
					Hepatic	Renal
Lovastatin	Fungi	Lipophilic	20 -80	2 -3	69	30
Simvastatin	Semisynthetic	Lipophilic	10 -80	2 -3	79	13
Pravastatin	Fungi	Hydrophilic	20 -80	1 -2	46	60
Fluvastatin	Synthetic	Intermediate	40 -80	0.5 -2	> 68	> 6
Atorvastatin	Synthetic	Lipophilic	10 -80	13 -16	-	>2
Rosuvastatin	Synthetic	Hydrophilic	10 -40	19	63	10

Objectives

This study aimed at examining the frequency of potential side-effects seen as a result of statins therapy, because of the importance of statins adverse effects.

In Iraq the mostly used statins are the semisynthetic statin (Simvastatin) and the synthetic statin (Atorvastatin), for that reason our study concentrated on these two drugs. Therefore, this paper aims to evaluate the frequency of potential adverse effects reported by patients using a semi synthetic statin (Simvastatin) and the synthetic statin (Atorvastatin), using a questionnaire asked to the patients and the laboratory results during the treatment with statins. A study was conducted at Al-shafaa Jeneral Hospital in Basra, south of Iraq, from November 2014 to March 2015. The patients were over 20 year's old taking Simvastatin or Atorvastatin for about one month or more.

Subjects and Methods

This cross – sectional study was conducted at the out-patient departments of Al-Shafaa general Hospital in Basra, south of Iraq, from November 2014 to March 2015. The patients over 20 years old, taking simvastatin or atorvastatin for about one month or more were selected. Patients with cognitive problems were excluded from this study. A questionnaire was asked to the patients to recognize potential adverse symptoms that they suspected to be linked to statins use. The questionnaire were included information such as: age, sex, and the adverse effects description, duration and the action of the patient to that effect e.g. stopping the drug intake or reducing the dose.

Ethics approval was obtained from Basra Health office, Ethics Committee for Human Research and from Al-shafaa Jeneral Hospital in Basra.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (version 5.0, GraphPad Software, Inc., San Diego, CA). Pearson Chi square test and one –way ANOVA were used. Results with $P < 0.05$ were considered significantly different.

Results

A total of 350 patients were participated in this study, of which 136 (39%) were females and 214 (61%) were males. Mean age [standard deviation (SD)] was 52.8 (SD 10.9) years with a range of 30 to 75 years. Females mean age was 53.2 (SD 10.5) years and males mean age was 52.6 (SD 11.2) years. Most patients were in age range of 51–60 years for both females and males. Characteristics of the patients and the reported at least one adverse effect of simvastatin and atorvastatin are shown in Table 2. A total of 302 symptoms were reported by 246 patients (70.3%). The proportion of patients who identified at least one adverse symptom was similar between the two types of statins (simvastatin 71.2% and atorvastatin 69.7%). Table 3 shows the prevalence of these side-effects reported by the patients. Overall the symptoms reported were similar between the two types of statins and included muscle pain, joint pain, increased serum transaminase enzymes, gastrointestinal effects, respiratory effects and hair falling effects. The only adverse effects significantly reported for simvastatin more than atorvastatin were headache and dizziness. The side-effects were not severe enough to discontinue administration of statins.

Discussion

Statins are used in the first-line therapy for patients at risk of coronary heart disease because of their safety and high tolerability. Benefits outweigh the small risk of myopathy and liver failure.

Table 2. Sex and age of patients using statins and the reported adverse effects

Characteristics	**Simvastatin**	**Atorvastatin**	**Total**	***P* value**
No. of patients (%)	132 (37.7)	218 (62.3)	350	
Sex				
Male (%)	72 (33.6)	142 (66.4)	214 (61)	0.0488*
Female (%)	60 (44)	76 (56)	136 (39)	
Age				
≤ 40 (%)	21 (35.6)	38 (64.4)	59 (16.9)	0.0450**
41-50 (%)	28 (33.7)	55 (66.3)	83 (23.7)	
51 -60 (%)	42 (39.6)	64 (60.4)	106 (30)	
> 60 (%)	41 (40)	61 (60)	102 (29)	
Reporting statin adverse effects (%)				
None				
At least one effect	38 (28.8)	66 (30.3)	104 (29.7)	0.7679*
	94 (71.2)	152 (69.7)	246 (70.3)	

* Pearson Chi square test, **One –way ANOVA All not significant (significance $P < 0.05$)

Table 3. The most common statins adverse effects reported by patients

Adverse effect	Simvastatin (n = 132)	Atorvastatin (n = 218)	Total (n = 350)	*P* value
Muscle related effect				
Muscle pain (%)	26 (19.7)	37 (17)	63 (18)	0.5202
Joints pain (%)	13 (9.8)	35 (16)	48 (13.7)	0.1018
Increased serum transaminase (%)	17 (12.9)	24 (11)	41 (11.7)	0.5981
GIT effect				
Constipation (%)	22 (16.7)	35 (16)	57 (16.3)	0.8806
Flatulence (%)	20 (15)	40 (18.3)	60 (17)	0.4418
Respiratory effect (%)	5 (3.8)	7 (3.2)	12 (3.4)	0.7738
Headache/ dizziness	16 (12)	1(0.46)	16 (4.6%)	**< 0.0001***
Hair falling	0	5 (2.3%)	5 (1.4%)	0.0797

Analysed by Pearson Chi square test
*Bold indicates statistical significance (*P* <0.05)

The development of myalgia or myositis to rhabdomyolysis is rare, but if progressed muscle symptoms are unnoticed then fatalities can occur [10].

In our study the reported side-effects were not too severe to cause discontinuation of statins but previous studies showed that 7.9% and 2.7% of patients had to stop taking statins because of serious side-effects [11- 12]. For that reason, physicians should be aware about this risk, especially when statins are prescribed with other medicines that have the same side-effect profile like statins, for example gemfibrozil.

The frequently used statins in Iraq are the semisynthetic statin (Simvastatin) and the synthetic statin (Atorvastatin), so this study concentrated on these two drugs to show the frequency of statins side effects in Basra population and the need to follow this further. It is required to educate patients to report any potentially significant symptoms and it is needed to do liver function tests 6 to 12 weeks after starting statins therapy [13]. Especially important are patients with risk factors for myopathy or rhabdomyolysis.

The only adverse effects significantly reported for simvastatin more than atorvastatin were headache and dizziness, this is an important point needs further study.

Prescribers should give an attention to the signs and symptoms of severe side-effects of all medications including statins.

Conclusions

There is no significant difference in the frequency of potential side effects reported by patients using a semi synthetic statin (simvastatin) and the synthetic statin (atorvastatin), apart from headache and dizziness reported significantly with simvastatin more than atorvastatin.

Recommendations

In future studies we recommend recording the side-effects in a more controlled setting and studying the effects of a range of risk factors, such as duration of statins consumption and concomitant drugs used on the appearance of the side-effects or their severity.

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