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Research Article

SAFETY EVALUATION OF STATIN IN YOGYAKARTA, INDONESIA

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ABSTRACT

Background : The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-Co-A) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum Low-Density Lipoprotein cholesterol (LDL-c) concentrations. They are first-line agents for patients who require drug therapy to reduce serum LDL-c concentrations. Although these drugs have been very successful in managing the cardiovascular health of many patients, there are also potential adverse effects that have been identified. The most common adverse effects reported include muscle pain or weakness that can progress to rhabdomyolysis and mortality. If detected early, statin-related symptoms are reversible after withdrawal of the statin.

Objective : This research was aimed to know the safety of statin used at Public Hospitals in Yogyakarta.

Method : This research was observational study with retrospective data collected. The target population are all of diabetes mellitus, cardiovascular and stroke patients that recorded on the medical record of Public Hospitals in Yogyakarta during 2 months.

Results : There were 28 patients who used simvastatin and 8 patients who used atorvastatin, experienced adverse effects of statins (n=157). Headache was the most adverse effect which was experienced by the patients. However rhabdomyolysis was not found in this reasearh. Interaction between simvastatin and nifedipine resulted more adverse effects such as headache, insomnia and abdominal pain than with other drugs.

Conclusions : Simvastatin, rosuvastatin and atorvastatin were well tolerated use in Yogyakarta, Indonesia. Only 22.9% from 157 patients experienced the adverse effects of statin. Adverse effects because of the interaction between simvastatin and other drugs were experienced by 8.92% patients. The result of this study need to be confirmed with additional study with larger sample sizes and vigilant surveillance to abolish the toxicity of the statin.

Keywords: Statin, Adverse Effects, Indonesia

INTRODUCTION

Many people have high blood cholesterol that may lead to Coronary Heart Disease (CHD). A multifaceted approach consisting of diet, exercise, and pharmacological management is recommended to lower the risk of CHD. Elevated low-density lipoprotein-cholesterol (LDL-C) has been established as a major cause of CHD[1].

In Indonesia, although not yet having the national data of the prevalence of CHD, the serious impact of this illness was seen. The CHD occupied the first place of all the death that was 16% in the survey of the health of the household (SKRT) 1992 and increased to 18.9% in SKRT 1995. Otherwise the Surkesnas 2001 showed the figure of CHD was 26,4% [2]. The increase of low-density-lipoprotein-chlesterol (LDL-C) was the main cause of the coronary heart disease [1]. Moreover, the diabetes melitus was one of the main factors the cause of the risk emergence of the CHD that as a result of by hyperlipidemia [3]. Indonesia occupied the 4th place biggest in the world in the number of diabetes melitus (8.6% from the total population) [4].

The group of cholesterol-lowering drugs known as statins are widely and successfully used in the management of atherosclerotic disease processes that include CHD, myocardial infarction, stroke, and peripheral

vascular disease. Statins inhibit the formation of HMG-Co-A reductase, which is essential in forming mevalonate, a precursor to cholesterol and other compounds. Lowering LDL-C is the goal of statin therapy, and multiple studies indicated that lowering LDL-C decreases the risk for CHD in people without a history of CHD and decreases the risk for cardiovascular events in people with a history of CHD. Six statins are currently available, such as: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin[1].

Although these drugs have been very successful in managing the cardiovascular health of many patients, there are also potential adverse effects that have been identified. Statins are generally used for long-term exposure. Longer durations of therapy would be anticipated in younger patients with less overt vascular disease. Acquisition of safety data are also cumulative, because the safety profile of a pharmaceutical agent becomes more precise with increasing exposure of the molecule to subjects. During initial drug development, animal toxicology is used to recognize those compounds that have already raised possible safety concerns before clinical evaluation. Early short-term clinical efficacy studies, as designed, can only be expected to detect adverse events that occur with relatively high frequency. Indeed, it is acknowledged that regulatory approval for clinical use "does not and cannot guarantee safety" [1].

The most common adverse effects reported include muscle pain or weakness that can progress to rhabdomyolysis and mortality. If detected early, statin-related symptoms are reversible after withdrawal of the statin. Early identification of these potentially serious adverse effects makes the information in this update critical for physical therapists, because they frequently screen patients with musculoskeletal complaints [1].

Considering that more than 76 million prescriptions for statins in 2000, there was increased concern about the safety of statins. One statin, cerivastatin, was voluntarily withdrawn from the market by the manufacturer in 2001, following its implication in severe adverse muscle reactions and death. In 2002, the American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute (ACC/AHA/ NHLBI) issued a clinical advisory about the use of statins[1,5] .

One of the risk factor that might increase the adverse effects of statin used is drug interaction. The cytochrome P450 (CYP) isoform CYP3A4 serves as the major pathway for metabolism of lovastatin, simvastatin, atorvastatin, and cerivastatin . Inhibition of the activity of CYP3A4 can increase serum levels of these statins, which raises the potential for adverse effects. Pravastatin does not undergo metabolism through the CYP450 system but is metabolized by sulfation and conjugation. Fluvastatin is metabolized mainly by CYP2C9 and to a lesser extent by CYP3A4 and CYP2D6. Rosuvastatin is metabolized mainly by CYP2C9 and CYP2C19. Although it was initially suspected that gemfibrozil increased statin levels by inhibiting CYP450 enzymes, it is now thought that its inhibition of glucuronidation of statins may be a likely culprit. Gemfibrozil undergoes extensive glucuronidation by the UDP-

glucuronosyltransferase (UGT) isoforms UGT1A1 and UGT1A3, which also mediate glucuronidation of statins. Glucuronidation is now recognized as a major pathway for elimination of the active hydroxy acid metabolites of statins. Fenofibrate does not appear to interfere with the UGT1A1 and UGT1A3 enzymes that mediate statin glucuronidation (fenofibrate is glucuronidated by UGT1A9 and UGT2B7). Perhaps statin fenofibrate combinations may have less risk for interactions than therapy with statins and gemfibrozil [6].

The purpose of this article is to describe the adverse effects of statins so that physical therapists will be better prepared to recognize possible statin-adverse effects

MEHODS

Patients

We investigated the medical record of all patients with diabetes melitus, CHD and stroke that was given the statins' group in Yogyakarta hospitals during 2 months. Eligible patients were men and women between 18 and 80 years of age.

Study design

The research was observational study and the data was collected retrospectively. We investigate the patients'complaints in the medical record during the use of statins'group for 2 months.

Data analysis

Data was analysed descriptively by counting the percentage of patients who experienced the adverse effects of statins.

RESULT AND DISCUSSION

The safety of a pharmaceutical agent is a relative term. Safety concerns for agents used long-term in the treatment of relatively well individuals as preventive therapies would differ from those for agents used for the treatment of life-threatening illnesses for shorter durations.

One hundred and fifty seven patients were included in this study. Demographics data of the patients were listed in Table 1.

Table 1: Patients' demographics data

Patients' data		
Age	Mean ± SD	
Male	56.43 ± 12.44	
Female	57.73 ± 10.73	
	Total number	Percentage (%)
Sex		
Male	93	59.24
Female	64	60.76
Diagnosa		
Diabetes mellitus	42	26.75
CHD	76	48.41
Stroke	27	17.20
Others	12	7.64
Statin used		
Simvastatin	120	76.43
Atorvastatin	34	21.66
Rosuvastatin	3	1.91

We recruited 157 patients with diabetes mellitus, cardiovascular, stroke and other patients (93 males and 64 females). The most number of patients were used simvastatin (76.43%), however rosuvastatin were rare to used in Indonesia (1.91%), this was caused by uncovered price of rosuvastatin in Indonesia.

The adverse effects that were caused by the use statins' group in hospitalized patient with diabetes melitus, CHD and stroke could be seen in the figure 1.

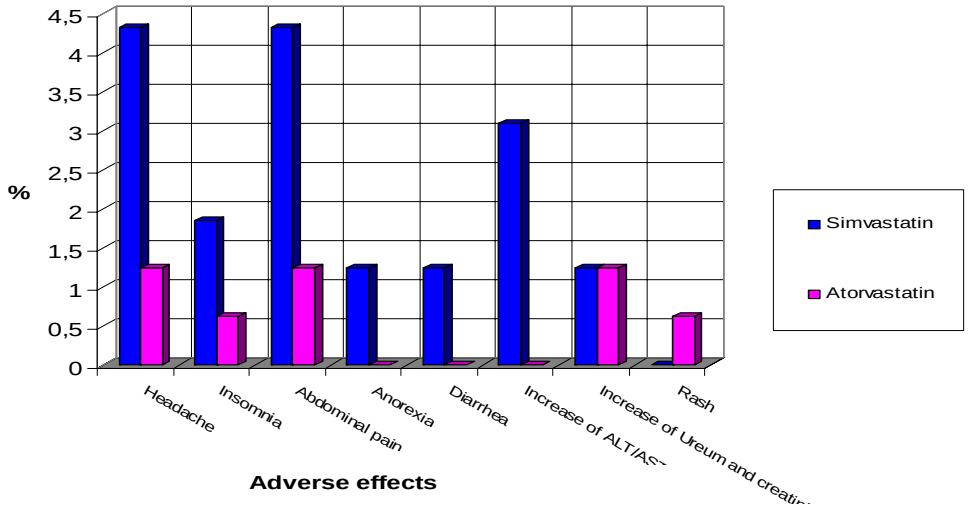

Fig. 1. Adverse effects of simvastatin and atorvastatin

In this study, the number of patients who experienced the adverse effect because of the use simvastatin were 28 patients and 8 patients used atorvastatin. The patients who experienced the headache were 9 patients (5.73%). The headache adverse effects was happened after the use simvastatin for 1-2 days. Based on the characteristics of its chemical physics, simvastatin had the penetration capacity to the central nervous system so as to be able to disrupt the central nervous system and may cause the headache. Moreover, other factors that caused this adverse effect from the use simvastatin is the existence of the patients who suffered hypertension that was shown with the increase in blood pressure and other illness like diabetes mellitus and hyperglicemia. Several illnesses could cause the headache. So this adverse effect could be caused by two matters, in case, the use of simvastatin and the existence of the risk factor of the illness that was suffered by the patient.

Insomnia was experienced by 4 patients (2.54%). Based on the characteristics of its chemical physics, simvastatin was hydrophobic, so it could penetrate blood brain barrier and reached the central nervous system. Simvastatin could influence the activity of the brain, including the activity of the brain that was connected with the sleep regulation so as to be able to cause the adverse effect to be difficult to sleep. Moreover, this adverse effect then possibly was caused because of the condition for the patient who suffered the diabetes mellitus, hyperglicemia, and CHD that was marked by the breathless existence, chest pain, and other factors that caused the function situation of his body to descend and trigger the disturbance emergence of thoughts to the

patient so as to cause the adverse effect to be difficult to sleep.

The other adverse effect that happened because of simvastatin was abdominal pain. This adverse effect was experienced by patients with the percentage 5.54%. The adverse effect was happened after the use simvastatin for several days.

All of the statins are rarely associated with elevations in liver transaminase levels (>3X ULN), occurring in approximately 3.09% of patients. The clinical significance of asymptomatic liver enzyme elevations from statins has been questioned, however. The risk increases with increasing doses. In the previous study comparing atorvastatin 80mg to simvastatin 80mg daily, there was a significantly higher incidence of transaminase elevation in the atorvastatin group compared to simvastatin. The reduction in LDL-c was greater with atorvastatin 80 mg compared with simvastatin 80 mg (53.6% vs 48.1%; $p<0.001$) in the same study[7].

Rhabdomyolisis was not found in this study. The symptoms progress toward rhabdomyolysis as long as patients continue to take the drug. Rhabdomyolysis is a syndrome that results from severe skeletal muscle injury and lysis, causing the widespread release of myoglobin with dark brown urine secondary to myoglobinuria. An analysis of data from the Adverse Event Reporting System (AERS) of the FDA showed that as of June 2001, fatal rhabdomyolysis had been reported at rates of <1 death per 1 million prescriptions for all statins, except cerivastatin, which had an incidence of >3 deaths per 1 million prescriptions[8].

However, there were 4 patients experienced the increase of ureum and creatinin. The occurrence of renal toxicity relatively early after initiation of therapy (within the first 12 weeks on average), suggests that vigilant surveillance for adverse effects during initiation of therapy may help ameliorate the risk of toxicity, especially in rosuvastatin [9].

The interaction of simvastatin and other drugs could be seen on figure 2. In this research, there were some medicine that were interacted with simvastatin through the mechanism of the enzyme inhibition CYP3A4. The parameter that was seen was the patient's complaint was recorded in medical record after the patient used simvastatin with other medicine and caused the adverse effect.

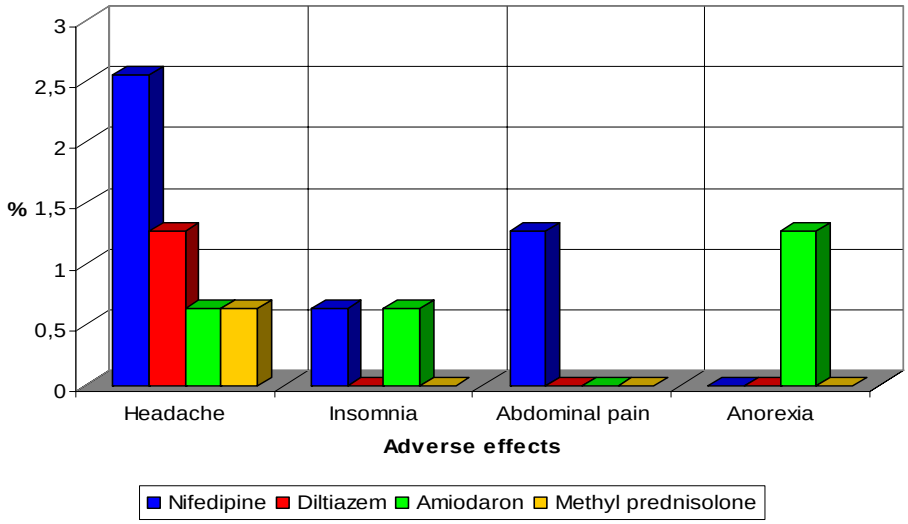

Fig. 2 : Adverse effects which were caused by interaction between simvastatin and other drugs.

Some drugs interacted with simvastatin both through the mechanism of the induction and the enzyme inhibition CYP3A4. These drugs were nifedipine, amiodarone, diltiazem, and methyl prednisolon. The four drugs inhibited CYP3A4 sub-enzyme. With this mechanism, the level of simvastatin in plasma will increase so as to have the potential to cause the adverse effect [8].

Nifedipine was a calcium channel blocker that often was used in hypertension medical treatment. Nifedipine experienced extensive metabolism pre-systemic with orally bioavailability of 45%. Nifedipine also showed high plasma clearens that was caused by the hepatic extraction. The metabolism of nifedipine took the form of first stage oxidation formed pyridin analogous metabolite that joined with the acid metabolite formation which was excreted in the urine. Nifedipine interacted with simvastatin through the CYP P450 pathway [8]. The competition happen between simvastatin and nifedipine to bind in the active site of CYP3A4. The occurrence of the competition between simvastatin and nifedipine could cause the number simvastatin fewer than that without the existence of nifedipine. Moreover, the use simvastatin could cause the rise the level of simvastatin in plasma. This could cause the increase in the risk of the headache.

This adverse effect may also caused by the risk factor of hypertension and cardiovascular disease that was experienced by the patient. It was shown from the blood pressure data (160/100). Diltiazem was a calcium channel blocker that often used in hypertension medical treatment and angina pectoris. The mechanism of interaction was the same with nifedipine. Amiodarone was used for the patient with arrhythmia. The interaction mechanism of amiodarone and simvastatin was the same with nifedipine. Many patients with hypercholesterolemia also have high blood pressure and may be receiving antihypertensive therapy with calcium channel antagonists. Of particular note is the interaction of statins with mibefradil, which was withdrawn from the global market because of a range of serious drug–drug interactions. Several cases of statin-associated rhabdomyolysis were reported in patients receiving mibefradil [8].

We suggest to consider the result of this study in the clinical practice in Indonesia. The healthcare professional must increase the monitoring of statin used in community and hospital by informing the adverse effects of statins to the patients. If patients do not get information about statins' adverse effect, they will not realize whether the symptoms are related with the statins used or not. However result of this study is still need to be confirmed with larger sample sizes, longer period of study and based on vigilant surveillance.

CONCLUSION

Simvastatin, rosuvastatin and atorvastatin were well tolerated use in Yogyakarta, Indonesia. Only 22.9% from 157 patients experienced the adverse effects of statin. However, 8.92% patients experienced the adverse effects of statins' interaction with other drugs, especially with antihypertension. The result of this study need to be confirmed with additional study with larger sample sizes and vigilant surveillance to abolish the toxicity of the statin.

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