Prevalence of Potential Statin-Drug Interactions in Dyslipidemic Patients at Srinagarind Hospital

Jantira Roddech[1], Panadchanun Phiwbang[2], Panjittra Kitirach[2], Patcharin Nisanggad[2], Pansu Sriangkan[1], Chaiyasith Wongvipaporn[3], Verawan Uchaipichat[2*]

[1]Pharmacy Unit, Srinagarind Hospital, [2]Division of Pharmacy Practice, Faculty of Pharmaceutical Sciences, [3]Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen Thailand 40002

[*]Corresponding author, E-mail: veruch@kku.ac.th

Background and Objective: Statin-drug interaction is one of the major factors associated with musculoskeletal adverse effect and may lead to statin intolerance and discontinuation. This study aim to investigate the prevalence and clinically significant level of potential statin-drug interactions in prescriptions for dyslipidemia patients at the Srinagarind Hospital, Khon Kaen University.

Methods: Data of outpatients who received statins, including simvastatin (SVS) (n=400) and atorvastatin (ATV) (n=500) during January to December 2012 were retrieved and randomly selected from hospital electronic database and patient medical records. The potential interacting drug lists and the clinically significant level were defined according to Drug Interaction Fact 2011 reference.

Results: Overall, the potential statin-drug interactions were found in 145 patients (16.1%). Of 3379 prescriptions screened, we found 496 prescriptions (14.7%; SVS 15.3%, ATV 14.0%) with 539 pairs of potential statin-drug interactions. Of these, most frequent drug interaction was diltiazem (21.9%), colchicine (21.5%), and gemfibrozil (13.4%). The potential statin-drug interaction found in the level of probable was 33.4% (SVS 38.4%, ATV 28.1%), suspected was 37.5% (SVS 28.3%, ATV 47.1%) and possible was 29.1% (SVS 33.3%, ATV 24.4%). We found potential statin-drug interaction with clinically significant level 1 of 36.0%, level 2 of 34.5% and level 4 of 29.1%.

Conclusion: Potential statin-drug interactions were found in drug prescriptions of dyslipidemic outpatients at Srinagarind Hospital. The levels of documentation were mostly in suspected and probable levels, and in high potential for clinical significance. Data suggested that an increase in awareness of prescription of statin over drug interactions and monitoring for the adverse effects may improve the therapeutic outcome.

Keywords: Statin-drug interaction, drug interaction, simvastatin, atorvastatin.

ศรีนครินทร์เวชสาร 2559; 31 (suppl): 92-96. ♦ Srinagarind Med J 2016; 31 (suppl): 92-96.

Proceeding

Introduction

Statins are the important treatment for dyslipidemia as there is strong evidence supporting their use for primary and secondary prevention of cardiovascular diseases.[1] Generally, statin use is well tolerated, however musculoskeletal adverse effects may occur in some patients. Drug-drug interaction is one of the major factors associated with statin induced myopathy and may lead to statin intolerance and discontinuation.[2-5] Although the computerized screening program has been developed and implemented to increase awareness of potential drug interactions, the statin-drug interactions or the co-prescription of statins with potential interacting drugs have been reported in several studies.[6-9] The prevalence of potential statin-drug interactions were reported in the

*Corresponding author, E-mail: Verawan Uchaipichat, Division of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen Thailand 40002. E-mail: veruch@kku.ac.th

range of 6-13%.[6-9] The Srinagarind Hospital is the tertiary care setting where several statins in particular simvastatin and atorvastatin were widely prescribed, however studies investigating the prevalence of potential statin-drug interactions in this setting are still limited.

This study aims to investigate the prevalence and clinically significant level of potential statin-drug interactions in dyslipidemic outpatients who received statins at Srinagarind Hospital, Khon Kaen University

.

Methods

A retrospective, descriptive study design was used in the study. The study protocol has been approved by the Khon Kaen University Ethics Committee in Human Research, (Reference No. HE561291)

Subjects: Outpatients who received simvastatin (SVS) or atorvastatin (ATV) during January to December 2012 at Srinagarind Hospital, Khon Kaen University. Sample size was calculated based on prevalence of potential statin-drug interaction reported previously.[7]

Data collection: Dosage regimen of prescribed statins and other concomitant drugs were retrieved from hospital electronic database whereas demographic data were retrieved from patient medical records.

Evaluation of potential drug interaction: The medication lists were screened for potentially harmful drug-drug interactions with statins which were defined as documentation level of possible or higher indicated in Drug Interaction Fact 2011 (Table 1)[10]. Based on the same reference, potential drug interactions were further classified for clinically significant level (Table 2)[10].

Results

Of 7591 patients, data were randomly collected from 400 and 500 patients who received SVS and ATV, respectively. Patient characteristics are summarized in Table 3. The patient average age was 61 $\pm$ 13.4 years old. Approximately 54% of patients were female. The most prevalent co-morbidities were hypertension, diabetes mellitus, coronary heart diseases and kidney diseases.

Overall, the potential statin-drug interactions were found in 145 patients out of 900 patients (16.1%). Prevalence of potential interactions with SVS and ATV were 16.8% and 15.6%, respectively. On the other hand, base of the number of prescriptions screened, we found 496 out of 3,379 prescriptions (14.7%) contained potential statin-drug interactions (SVS 15.3%, ATV 14.0%). Of 496 prescriptions, we found 539 pairs of potential statin-drug interactions (SVS 276 pairs, ATV 263 pairs).

Considering the 539 pairs of potential statin-drug interaction, the potential interacting drugs that mostly co-prescribed with SVS and ATV were diltiazem (SVS 26%, ATV 19%), colchicine (SVS 27%, ATV 17%), and gemfibrozil (SVS 14%, ATV 14%) (Figure 1). As classified by documentation level, we found that 106 pairs (38.4%), 78 pairs (28.3%) and 92 pairs (33.3%) of potential drug interactions with SVS were in probable, suspected and possible levels, respectively. For ATV, the respective documentation level for potential drug interaction were found in 74 pairs (28.1%), 124 pairs (47.2%), and 65 pairs (24.7%).

The list of potential interacting drugs in probable, suspected and possible levels were shown in table 4. For probable level, diltiazem was the most common drug that co-prescribed with simvastatin (65.1%) and atorvastatin (66.2%), whereas, in suspected level, gemfibrozil was the most common drug that co-prescribed with simvastatin (46.2%) and atorvastatin (29.0%). Colchicine potentially interact with statins in possible level and it was mostly co-prescribed with simvastatin (78.3%) and atorvastatin (68.0%).

Potential statin-drug interactions were found with clinically significant level 1 36.0% (SVS 39.8%, ATV 32.3%), level 2 34.5% (SVS 26.6%, ATV 43.0%) and level 4 29.1% (SVS 33.6%, ATV 24.7%) (Figure 2). The list of potential interacting drugs in each clinically significant level were shown in figure 2. For a clinically significant level 1, the potential interacting drugs that mostly co-prescribed with simvastatin and atorvastatin were gemfibrozil (33%), amiodarone (14%) and cyclosporine (13%), and gemfibrozil (42%) fenofibrate (31%) and amiodarone (13%), respectively. According to clinically significant level 2, diltiazem was the most common potential interacting drugs that co-prescribed with both simvastatin (94%) and atorvastatin (43%).

Table 1 Documentation level of potential drug-drug interactions[10]

Documentation level
The confidence that an interaction can occur. This evaluation is based on supporting biomedical literature.
Established proven to occur in well-controlled studies
Probable very likely, but not proven clinically
Suspected may occur; some good data, but needs more study
Possible could occur, but data are very limited
Unlikely doubtful, no good evidence of a clinical effect

Table 2 Clinically significant rating of potential drug-drug interactions[10]

Significance rating: Summary of Severity and Documentation		
Significance rating	**Severity**	**Documentation**
1	Major*	Suspected or higher
2	Moderate**	Suspected or higher
3	Minor***	Suspected or higher
4	Major*/Moderate**	Possible
5	Minor***	Possible
	Any	Unlikely

*Major, life-threatening or permanent damage; **Moderate, deterioration of patient's status; ***Minor, bothersome or little effect

Table 3 Demographic data

Patient characteristics	Total (n=900)	Simvastatin (n=400)	Atorvastatin (n=500)
Age [mean ± SD]	61 ± 13.4	58 ± 15.8	63.7 ± 11.5
Female [no. (%)]	489 (54.3)	207 (51.8)	282 (56.4)
No. of diseases [mean ± SD]	3.7 ± 1.70	3.8 ± 1.57	3.6 ± 1.70
No. of prescriptions screened per patient [(mean ± SD)]	3.8 ± 2.56	4.3 ± 3.30	3.3 ± 1.79
Underlying diseases [no. (%)]			
Hypertension	560 (62.2)	251 (63.0)	309 (41.0)
Diabetes mellitus	375 (41.7)	171 (42.8)	204 (41.0)
Coronary heart disease	228 (25.3)	146 (37.0)	82 (16.0)
Kidney disease	148 (16.4)	73 (18.0)	75 (15.0)
Musculoskeletal diseases	148 (16.4)	55 (13.8)	93 (18.6)
Infections	121 (13.4)	49 (12.3)	71 (14.2)
Neurological disorders	98 (10.9)	52 (13.0)	14 (2.8)
Liver diseases	81 (9.0)	37 (9.0)	44 (8.8)
Cancer	40 (4.4)	20 (5.0)	20 (4.0)
Psychiatric disorders	20 (2.2)	11 (3.0)	9 (8.2)

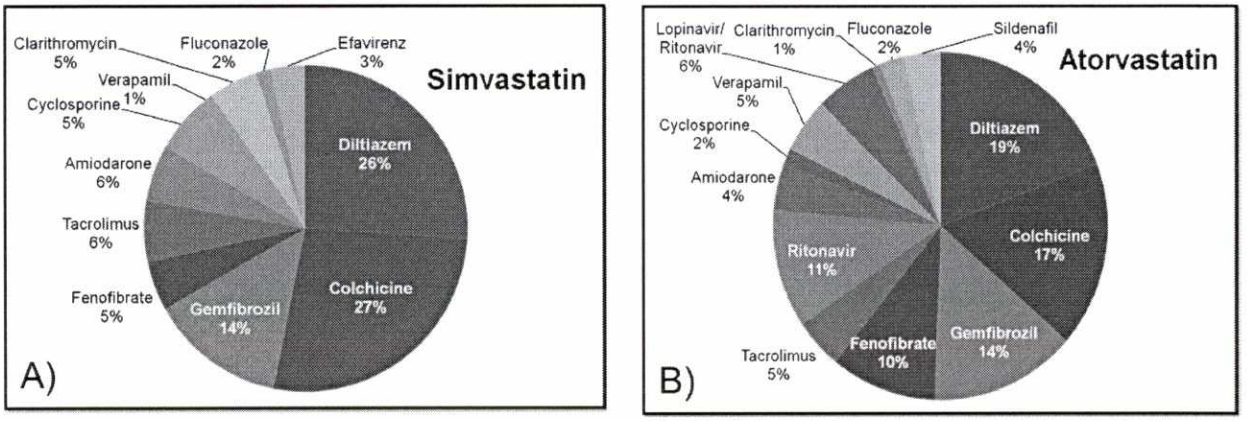

Figure 1 The list of potential interacting drugs co-prescribed with simvastatin (n=276; Panel A) and atorvastatin (n=263; Panel B)

Table 4 The list of potential interacting drugs based on the documentation level

	Simvastatin (n=276)	Atorvastatin (n=263)
Probable [no.(%)]		
Diltiazem	69 (65.1)	49 (66.2)
Cyclosporine	14 (13.2)	4 (5.4)
Clarithromycin	13 (12.3)	2 (2.7)
Verapamil	4 (3.8)	13 (17.6)
Fluconazole	4 (3.8)	6 (8.1)
Itraconazole	2 (1.9)	-
Suspected [no.(%)]		
Gemfibrozil	36 (46.2)	36 (29.0)
Amiodarone	15 (19.2)	11 (8.9)
Fenofibrate	13 (16.7)	26 (21.0)
Efavirenz	9 (11.5)	-
Nevirapine	5 (6.4)	-
Ritonavir	-	28 (22.6)
Lopinavir/ritonavir	-	15 (12.1)
Indinavir	-	8 (0.6)
Possible [no.(%)]		
Colchicine	72 (78.3)	44 (68.0)
Tacrolimus	16 (17.4)	12 (18.5)
Ezetimibe	3 (3.3)	-
Cilostazol	1 (1.1)	-
Sildenafil	-	9 (13.8)

Conclusion and Discussion

The prevalence of statin-drug interactions found in the prescriptions of outpatients who received simvastatin or atorvastatin during January to December 2012 at Srinagarind Hospital, Khon Kaen University was approximately 15%. The prevalence we found was consistent with those reported from other studies which were in the range of 6-13%.[7-9,11,12] However, some inconsistent results were found in terms of the list of potential interacting drugs. In this study, the potential interacting drugs mostly co-prescribed with simvastatin and atorvastatin were diltiazem, colchicine and gemfibrozil, while other studies reported that verapamil, diltiazem and macrolide antibiotics were the potential interacting drugs commonly co-prescribed with statins.[7-9,11,12] The inconsistent results may be explained from the difference between the studies such as the criteria to identify potential statin-drug interactions, research setting and patient characteristics.

The list of top three potential interacting drugs co-prescribed with simvastatin or atorvastatin in our setting was diltiazem, gemfibrozil and colchicine. Of these, gemfibrozil is in the highest clinically significant level (level 1), while diltiazem and colchicine were in the level 2 and 4, respectively. Potential drug interaction of gemfibrozil and statin could be explained from both pharmacokinetic and pharmacodynamic drug interactions. Gemfibrozil itself can cause myotoxicity. In addition, gemfibrozil can also increase plasma level of all statins by inhibiting OATP1B1 transporter-mediated hepatic uptake[13,14] and UGT-mediated lactonization[15], and may increase the risk of musculoskeletal adverse effects[16,17]. According to USFDA 2011 warning[18], gemfibrozil is also in the contraindication list of co-prescription drugs with simvastatin. Although musculoskeletal adverse events were not investigated in this study, rhabdomyolysis during concomitant use of simvastatin and gemfibrozil have been previously reported [5, 19, 20]. It should be noted that previous report from the Thailand database

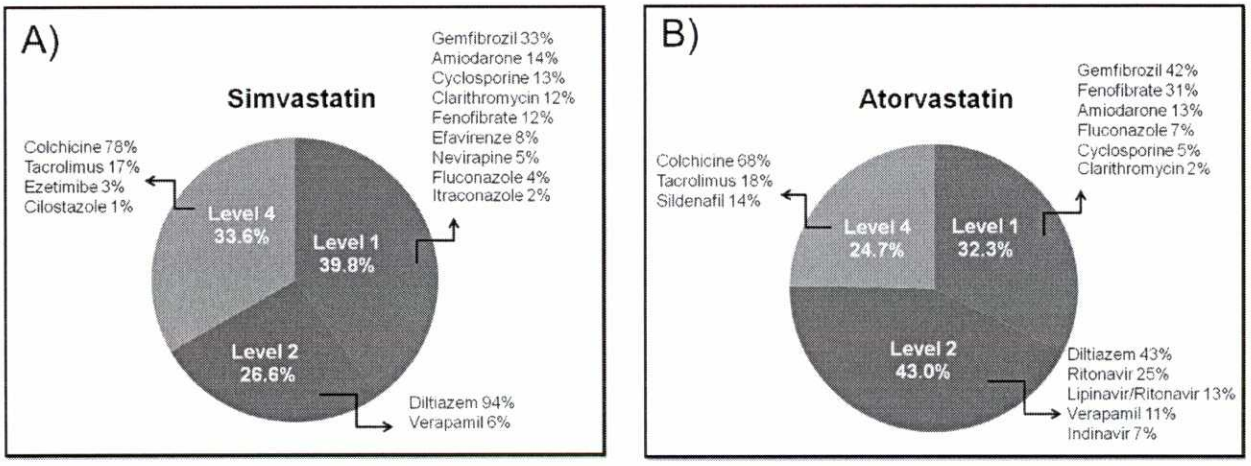

Figure 2 The list of potential interacting drugs based on the clinically significant level

indicated that gemfibrozil and colchicine has been identified as the most common interacting drug associated with statin-induced myopathy[5]. Generally, fenofibrate is safer and recommended to use as a substitute for gemfibrozil as it contains only pharmacodynamic drug interaction without interfering statin pharmacokinetic properties.[1]

In conclusion, potential statin interactions were found in drug prescriptions for dyslipidemia patients at Srinagarind Hospital. About 16% of the prescriptions may have potential drug interaction. For the concerned prescriptions, more than half of statin-drug interactions were in documentation level of suspected and probable, and in high potential for clinical significance. This may increase the risk of statin induced myopathy. Data suggested that an increase in awareness of prescription of statins over drug interactions and monitoring for the adverse effects may improve the therapeutic outcome.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129 (25 suppl 2): S1-45.
2. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006; 114: 2788-97.
3. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006; 97: 52C-60C.
4. Armitage J. The safety of statins in clinical practice. Lancet 2007; 370(9601): 1781-90.
5. Boonmuang P, Nathisuwan S, Chaiyakunapruk N, Suwankesawong W, Pokhagul P, Teerawattanapong N, et al. Characterization of Statin-Associated Myopathy Case Reports in Thailand Using the Health Product Vigilance Center Database. Drug Saf 2013; 36:779-87.
6. Piacentini N, Trifiro G, Tari M, Moretti S, Arcoraci V. Statin-macrolide interaction risk: a population-based study throughout a general practice database. Eur J Clin Pharmacol 2005; 61: 615-20.
7. Ratz Bravo AE, Tchambaz L, Krahenbuhl-Melcher A, Hess L, Schlienger RG, Krahenbuhl S. Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. Drug Saf 2005; 28: 263-75.
8. Tirkkonen T, Ryynanen A, Vahlberg T, Irjala K, Klaukka T, Huupponen R, et al. Frequency and clinical relevance of drug interactions with lovastatin and simvastatin: an observational database study. Drug Saf 2008; 31: 231-40.
9. Bakhai A, Rigney U, Hollis S, Emmas C. Co-administration of statins with cytochrome P450 3A4 inhibitors in a UK primary care population. Pharmacoepidemiol Drug Saf 2012; 21: 485-93.
10. Tatro DS. Drug interaction facts. Missouri: Wolters Kluwer Health; 2011.
11. Ming EE, Davidson MH, Gandhi SK, Marotti M, Miles CG, Ke X, et al. Concomitant use of statins and CYP3A4 inhibitors in administrative claims and electronic medical records databases. J Clin Lipidol 2008; 2: 453-63.
12. Devold HM, Molden E, Skurtveit S, Furu K. Co-medication of statins and CYP3A4 inhibitors before and after introduction of new reimbursement policy. Br J Clin Pharmacol 2009; 67: 234-41.
13. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. Pharmacol Ther 2006 ; 112: 71-105.
14. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 2006; 80: 565-81.
15. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. Drug Metab Dispos 2002; 30: 1280-7.
16. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions. Expert Opin Drug Saf 2012; 11(6): 933-46.
17. Corsini A. Statin-related muscle complaints: an underestimated risk. Cardiovasc Drugs Ther 2005 ; 19: 379-81.
18. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. 2011 [updated 15 December 2011; cited 21 April 2014]; Available from: http://www.fda.gov/drugs/drugsafety/ucm256581.htm.
19. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004; 292: 2585-90.
20. Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. Am J Cardiol 2010; 106: 1594-601.