Original Article

Mahidol University Journal of Pharmaceutical Sciences 2013; 40 (4), 1-7

Risk factors Related to Rhabdomyolysis in Thai Statin Users: A Case-control Study

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Abstract

Previous studies on statin have revealed that increasing age, renal insufficiency, and concomitant medications were associated with rhabdomyolysis. However, there is a lack of analysis on the magnitude of such association in the Asia-Pacific region. The objectives of this study were to identify risk factors of statin-associated rhabdomyolysis in Thai patients and to evaluate the magnitude of association between the risk factors and rhabdomyolysis. The case-control study was carried out at five tertiary-care hospitals in Thailand and patients' data of 2005-2008 were collected. Data of cases with rhabdomyolysis were extracted from patient's profiles. For each case, the researchers randomly selected ten controls for making a comparison. Data extracted included demographics, type of statins, dosage, duration, and concomitant medications. No matching of controls to cases was performed in this study and the data collectors were not blinded. Of the 220 patients, the three most commonly used were simvastatin (80.0%), atorvastatin (15.0%), and rosuvastatin (5.0%). A univariable analysis indicated that the most powerful risk factor for rhabdomyolysis was renal disease, odds ratio (OR, 24.00; 95% CI, 6.68-85.49). The number of concomitant medications was also associated with significant increased risk of rhabdomyolysis, OR 3.85 (95% CI, 1.40-10.61) and 13.23 (95% CI, 1.54-113.62) for one and two concomitant medications, respectively. In multivariable analysis, the only significant association found was between renal disease and rhabdomyolysis with a Coefficient 3.46 (95% CI, 2.21-4.71). This study reiterates that renal disease plays a key role in precipitating statin-associated rhabdomyolysis. Impaired renal function could lower elimination of statins and concomitant drugs, resulting in drug interactions and rhabdomyolysis.

Keyword: statin, rhabdomyolysis, risk factor, drug interaction, renal disease.

INTRODUCTION

Statins or HMG-CoA reductase inhibitors are a group of lipid-lowering agents that has been widely used in order to improve lipid profiles and decrease cardiovascular events and mortality.[1-3] Despite such advantages, one important adverse effect caused by statins is myopathy. Myopathy is divided into myalgia, myositis, and rhabdomyolysis. Of the different kinds of myopathy, rhabdomyolysis is the most serious. It can lead to myoglobin potassium release from damaged muscle cells, which can result in acute renal failure and cardiac arrhythmia.[4] Destruction of the skeletal muscle can also bring about metabolic acidosis and respiratory failure. The USFDA database cites a mortality rate of 7.8% in patients with rhabdomyolysis. The average incidence of rhabdomyolysis from simvastatin, atorvastatin, or pravastatin is 0.1% to 0.5%.[4] In Thai patients, data collected from 198 cases of statin-associated myopathy between

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1984 and 2009 indicated a mortality rate of 6.36% in those with rhabdomyolysis.[5]

There have been previous studies conducted on western countries on risk factors that precipitate rhabdomyolysis. Advanced age, renal disease, and drug interactions have been reported to be associated with statin-related rhabdomyolysis.[6-20] However, results from such studies in Western populations may not be applicable for risk factor identification in Thai population. This stems from differences in genetics, prescribing patterns, and herbal medicines[5,21-22] used between the Western and Thai populations. As a result, a study assessing factors affecting statin-related rhabdomyolysis in the Thai population is warranted.

OBJECTIVES

The study is aimed to identify risk factors precipitating rhabdomyolysis in Thai statin users and assess the magnitude of the association. Results of the study could provide a warning signal of risk factors and assist policy-makers in developing a protocol to minimize risk of statin-associated rhabdomyolysis.

METHOD

Study design

This was a hospital-based case-control study conducted in five tertiary-care hospitals in Thailand. This study was approved by the Faculty of Dentistry/Faculty of Pharmacy, Mahidol University Institutional Review Board (Project Number: MU-DT/PY-IRB 2012/020.1204).

Identification of case and control group

Patients identified as cases were included based on their diagnosis of rhabdomyolysis during 2005 to 2008 and confirmed by the definition of rhabdomyolysis issued by ACC/AHA/NHLBI.[9] Rhabdomyolysis was defined as muscle symptoms with marked creatinine kinase elevation (typically greater than 10 times the upper limit of normal range and with creatinine elevation, usually with brown urine and urinary myoglobin). Selection of the control group was based on simple random sampling method among patients receiving statins during the same period, but without any reports of rhabdomyolysis. The ratio of case to control was 1:10. The index date was the date that a patient with rhabdomyolysis received any statin for the first time between 2005 and 2008. Controls were included if they received statins at the index date, took statins for at least one month, and did not develop rhabdomyolysis at the index date. No matching of controls to cases was performed in this study. Data extracted included demographics, type of statins, dosage, duration, and concomitant medications.

Assessment of Risk Factors

Risk factors were assessed in both groups at the time that the cases developed rhabdomyolysis. The period of assessment extended from the index date to the date that the cases developed rhabdomyolysis. The risk factors assessed were gender, age, renal disease, hepatic disease, diabetes mellitus, hypothyroidism, infections, trauma, surgery, electrolyte abnormalities, heavy alcohol intake, dehydration, drug abuse, rigorous exercise, gout, type of statins, overall drug interactions, concomitant use of fibrates, cyclosporine, macrolides, colchicine, amiodarone, non-dihydropyridine calcium channel blockers (non-DHP CCBs), azole antifungals, warfarin, digoxin, niacin, and protease inhibitors.

Statistical analysis

Patient's demographic data were presented as mean ± S.D. or percentage. The risk factors of rhabdomyolysis were analysed with logistic regression and calculation of odds ratio (OR) with 95% confidence intervals (CIs). The statistical software employed was STATA® program

Version 10.1. A significance level of $\alpha = 0.05$ was set for the analyses. Age and gender were controlled in the establishment of logistic regression models.

RESULTS

Demographic data

There were 20 cases with rhabdomyolysis and 200 controls included in this study (Table 1). The average age of rhabdomyolysis cases (67.10 + 10.77 years) was significantly higher than that of the control group (60.84 + 11.58 years, $p < 0.05$). Nine out of 20 patients with rhabdomyolysis were women. The three most commonly used statins were simvastatin (80.0%), atorvastatin (15.0%), and rosuvastatin (5.0%). The average simvastatin dose of the rhabdomyolysis group (32.81 ± 20.00 mg/day) was twice of the control group (16.09 ± 10.55 mg/day, $p < 0.05$). The three most common comorbidities in patients with rhabdomyolysis included renal disease (50.0%), diabetes mellitus (50.0%), and gout (35.0%), with significantly higher percentages of renal disease and gout in the rhabdomyolysis group ($p < 0.05$). The number of drug interactions was also significantly higher in the rhabdomyolysis group (60.0%) than in the control group (22.5%, $p < 0.05$). Colchicine (30.0%) and gemfibrozil (20.0%) were the two most common concomitant medications in the rhabdomyolysis group. The percentages of patients taking the two medications were also significantly higher in the rhabdomyolysis group ($p < 0.05$).

Univariate and Multivariate analyses

Risk factors of statin-associated rhabdomyolysis (Table 2) were renal disease (OR = 24.00, $p < 0.05$), azole antifungals (OR = 10.47, $p < 0.05$), colchicine (OR = 6.16, $p < 0.05$), overall drug interactions (OR = 5.17, $p < 0.05$), gout (OR = 4.59, $p < 0.05$), and gemfibrozil (OR = 3.92, $p < 0.05$). We found that an increasing number of concomitant medications were positively associated with incidences of rhabdomyolysis. Having one concomitant medication was associated with a 3.85-fold increase in rhabdomyolysis (95% CI, 1.40-10.61), and two concomitant medications was 13.23-fold increase (95% CI, 1.54-113.62). Results for drugs that caused a significant change in rhabdomyolysis based on univariable analysis, namely azole antifungals, colchicine, and gemfibrozil; were further analysed using multivariate analysis. Azole antifungals were not significantly associated with an increased incidence of rhabdomyolysis, while colchicine (OR = 4.92; 95% CI, 1.53-15.82) and gemfibrozil (OR = 4.14; 95% CI, 1.14-14.99) were. However, such effects of drug interactions and each concomitant medication on rhabdomyolysis were offset by the effect of renal disease. Adding renal disease to the logistic regression equation made the other factors no longer predictors of rhabdomyolysis (Table 3). In other words, renal disease was the most important risk factor significantly associated with rhabdomyolysis in Thai statin-treated patients (beta coefficient 3.46 95% CI, 2.21-4.71)

Table 1. Demographic data of patients in case and control groups

	Number of Patients (%)		Significance Test
	Rhabdomyolysis (N = 20)	Control (N = 200)	P-values
Age (Year)	67.10 ± 10.77	60.84 ± 11.58	0.02*
Age (Group)			0.66
< 39 years old	0	9	
40 – 49 years old	1	25	
50 – 59 years old	4	45	
> 60 years old	15	121	
Gender			0.21
Male	11 (55.00)		
Female	9 (45.00)		
Statin Type			1.00
Simvastatin	16 (80.00)	160 (80.00)	
Atorvastatin	3 (15.00)	28 (14.00)	
Pravastatin	-	2 (1.00)	
Rosuvastatin	1 (5.00)	10 (5.00)	
Average Doses (mg/day)			
Simvastatin	32.81 ± 20.00	16.09 ± 10.55	0.00*
Atorvastatin	13.33 ± 5.77	20.36 ± 10.71	0.25
Pravastatin	-	20	-
Rosuvastatin	10	9.50 ± 1.58	0.75
Comorbidities/Underlying Diseases			
Renal disease	10 (50.00)	8 (4.00)	0.00*
Diabetes mellitus	10 (50.00)	63 (31.50)	0.09
Gout	7 (35.00)	21 (10.50)	0.01*
Electrolyte abnormalities	2 (10.00)	-	0.01*
Dehydration	1 (5.00)	-	0.09
Heavy exercise	1 (5.00)	-	0.09
Hypothyroidism	-	5 (2.50)	1.00
Surgery	-	3 (1.50)	1.00
Hepatic disease	-	2 (1.00)	0.83
Drug abuse	-	1 (0.50)	1.00
Drug Interactions			
Overall drug interactions	12 (60.00)	45 (22.50)	0.00*
Colchicine	6 (30.00)	13 (6.50)	0.00*
Gemfibrozil	4 (20.00)	12 (6.00)	0.04*
Non-DHP CCBs	1 (5.00)	3 (1.50)	0.32
Digoxin	1 (5.00)	3 (1.50)	0.32
Azole antifungals	1 (5.00)	1 (0.50)	0.17
Cyclosporine	1 (5.00)	-	0.09
Other fibrates	-	6 (3.00)	1.00
Protease inhibitors	-	5 (2.50)	1.00
Warfarin		4 (2.00)	1.00

Abbreviations: Non-DHP CCB = non-dihydropyridine calcium channel blockers

* $P < 0.05$

Table 2. Adjusted ORs and 95% CIs of univariable analysis

Risk Factors	Adjusted ORs	95% CIs	P-values
Comorbidities/Underlying Diseases			
Renal disease	24.00	6.68-85.49	0.000*
Gout	4.59	1.38-13.98	0.002*
Diabetes mellitus	2.17	0.77-6.13	0.094
Hypothyroidism	0.00	0.00-7.87	0.474
Hepatic disease	0.00	0.00-19.94	0.653
Drug Interactions			
Overall drug interactions	5.17	1.80-15.40	0.000*
Azole antifungals	10.47	0.13-825.97	0.043*
Colchicine	6.16	1.64-20.67	0.000*
Gemfibrozil	3.92	0.82-14.88	0.022*
Non-DHP CCBs	3.46	0.06-45.13	0.264
Digoxin	3.46	0.06-45.13	0.264

OR = Odds ratio, CI = Confidence Intervals, Non-DHP CCB = non-dihydropyridine calcium channel blockers * $P < 0.05$

Table 3. Coefficients, adjusted ORs, and 95% CIs of multivariable analysis

Risk Factors	Coefficients	95% CIs	P-values
Renal disease	3.46	2.21-4.71	0.000*
Azole antifungals	2.31	0.61-5.24	0.121
Gemfibrozil	1.20	0.38-2.78	0.136
Colchicine	0.55	0.96-2.07	0.474
Overall drug interactions	0.45	0.75-1.66	0.468
Gout	0.40	0.96-1.76	0.562

OR = Odds ratio, CI = Confidence Intervals, * $P < 0.05$

DISCUSSIONS

Our research is aimed to study the pattern of occurrence of rhabdomyolysis among Thai statin-treated patients. Previous studies have found that increased levels of statins in the body are associated with increased incidence of rhabdomyolysis.[6-7, 11-18] The increase in levels can result from drug interaction.[11] Drug interaction may occur through mechanisms of CYP enzymes, influx/efflux pumps, or UGT enzymes. Medications decreasing clearance of statins can cause higher statin concentrations, leading to rhabdomyolysis. Such medications include macrolides, azole antifungals, cyclosporine A, fibrates, non-DHP calcium channel blockers, colchicine, tacrolimus, niacin, warfarin, digoxin, and protease inhibitors.[12-13,16-18] Patients with cardiovascular risk taking statins usually have comorbidity that requires concomitant medications such as renal disease, diabetes mellitus, or hypertension. Comorbidities and polypharmacy may heighten risk of drug interaction and eventually bring about rhabdomyolysis.

Renal disease can be a cause of drug interaction. The interaction can occur in patients with renal insufficiency, even though they are treated with a low-dose statin. The present study found a significant association between drug interaction and renal disease. It is recommended that the dosage of statins needs to be reduced in patients with chronic kidney diseases. For those with a level of glomerular filtration rate of < 30 mL/min/1.73 m^2, the dose ranges of atorvastatin at 10-80 mg/day,

fluvastatin at 10-40 mg/day, lovastatin at 10-40 mg/day, pravastatin at 20-40 mg/day, and simvastatin at 10-40 mg/day are advised.[23-24]

Our study can assist healthcare professionals in avoiding rhabdomyolysis from statin use in Thai patients with renal impairment by demonstrating characteristics of the patients and recommending dosage adjustment of statins. Pharmacists can play a key role in the healthcare team in terms of dispensing of statins and drug selection for statins and possible interacting drugs in patients with renal impairment, medication reconciliation, and advice given to patients and care-givers especially when the patients cannot administer medications on their own.

For limitations of study, the design was a retrospective study based on the data previously collected by healthcare professionals. Therefore, some kinds of bias might exist and in order to minimize such bias, the researchers confirmed cases by the definition of rhabdomyolysis of ACC/AHA/NHLBI. Additionally, results of our study need to be reinforced by a series of research on rhabdomyolysis. There should also be further studies aiming to verify causal relationship among drug interaction, renal disease, and rhabdomyolysis among Thai patients.

CONCLUSION

The present study demonstrates characteristics of rhabdomyolysis from statin use in Thailand. The study indicated that renal disease was the most important risk factor of statin-associated rhabdomyolysis. For recommendations, healthcare professionals need to closely monitor levels of serum creatine phosphokinase and serum creatinine (which reflects renal function) in patients with impaired renal function who receive statins. Healthcare professionals should educate patients to report signs and symptoms of rhabdomyolysis during their course of treatment as well.

ACKNOWLEDGEMENTS

We would like to thank Ramathibodi Hospital, Rajavithi Hospital, Phramongkutklao Hospital, Nopparat Rajathanee Hospital, and King Chulalongkorn Memorial Hospital for the permission to collect and analyze the data.

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