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International Journal of Collaborative Research on Internal Medicine & Public Health
Vol. 3 No. 12 (December 2011)

International Journal of Collaborative Research on Internal Medicine & Public Health (IJCRIMPH)

ISSN 1840-4529 | Journal Type: Open Access | Volume 3 Number 12

Journal details including published articles and guidelines for authors can be found at:
http://www.iomcworld.com/ijcrimph/

To cite this Article: AbdulRazzaq HA, Abd Aziz N, Sulaiman SAS, Hassan Y, Ismail O. Development Tool for Self-Reporting of Adverse Drug Reactions of Statin. *International Journal of Collaborative Research on Internal Medicine & Public Health*. 2011; 3(12):847-856.

Article URL: http://iomcworld.com/ijcrimph/ijcrimph-v03-n12-01.htm

Correspondence concerning this article should be addressed to Hadeer Akram AbdulRazzaq; Ph.D (candidate), Department of Clinical Pharmacy , School of pharmaceutical Sciences, Universiti Sains Malaysia (USM), 11800 Penang, Malaysia / / Tel. Malaysia: + 60174379282 / Tel. Iraq: + 9647703481427 / Email: hadproof@yahoo.com

Paper publication: 19 December 2011

Development Tool for Self-Reporting of Adverse Drug Reactions of Statin

Hadeer Akram AbdulRazzaq (1) [*], Noorizan Abd Aziz (2), Syed Azhar Syed Sulaiman (3), Yahaya Hassan (4), Omar Ismail (5)

1) Department of Clinical Pharmacy, School of pharmaceutical Sciences, Universiti Sains Malaysia (USM), Malaysia
2) Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Selangor, Malaysia
3) School of pharmaceutical Sciences, Universiti Sains Malaysia (USM), Malaysia
4) Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Selangor, Malaysia
5) Department of Cardiology, Hospital Pulau Pinang, Malaysia

** Corresponding Author*

ABSTRACT

Introduction: Statins cause adverse drug reactions (ADRs) in patients on chronic use of medications. No specific tool available for patients to report these ADRs. Most of previous studies based on the doctors' reports.

Aim: development specific tool for reporting of satins-ADRs for cardiac outpatients, and to determine the incidences and correlations among these ADRs.

Method: the questionnaire based on the commonly reported ADRs of statins, researchers' agreements and the consistent understanding of the questions by cardiac clinic outpatients. Also a comparison conducted between current study and literatures depending on type of reporting

Statistical analysis: SPSS version 18.0 used for the analysis of results collected in this study. For preparation of specific questionnaire, factor analysis used to determine the ADRs correlated to statin depending on the statistical value of terms (must be equal or more than 0.4), as well as, Cronbach's alpha and Spearman-Brown tests used to approve the reliability of the questionnaire (must be more than 0.7).

Results: factor analysis showed six classes of ADRs found (musculoskeletal, neurological, reparatory, urological, gastrointestinal and others) identified with acceptable statistical values ranging from 0.406 to 0.737. The reliability of the questionnaire for both Cronbach's alpha and Equal-length Spearman-Brown coefficient were 0.853 and 0.890 respectively. The incidence of multiple ADRs significantly increased with the increased number of groups. The musculoskeletal and neurological group showed highest significant incidence (91%).

Conclusion: validity and reliability of the questionnaire and its terms within acceptable range to approve for clinical studies, therefore it considered as a suitable tool for cardiac outpatients in reporting the ADRs of statins. Besides, this simple approach to determine ADRs from outpatients on chronic therapy. Patients' self-reporting is more reliable than doctors reporting type.

Keywords: Questionnaire, ADRs, validity, reliability and cardiac outpatients

Introduction

Statins are the drug of choice of dyslipidemia and used as prophylaxis for congestive heart failure, MI, strokes, revascularization procedure and other cardiovascular mortalities [1,2]. High incidence of cardiac patients on statin therapy [3], therefore, high incidence of adverse drug reactions accompanied this medication [4-6]. Adverse drug reactions (ADRs) defined as a noxious and unintended effects that occur during the use of drugs in normal doses for prophylaxis, diagnosis and treatment of disease [7]. ADRs considered being the fourth to sixth cause of death in USA [8]. Recent studies found that high incidence of doctors were unfamiliar to the problems that occur because of statin therapy, and patients were uncomfortable to express their problems to their doctors or could not express them well [9, 10]. Type of reporting for medications based on patients' beliefs lacked in hospital services in many countries [11]. Patients considered the main source of information related to the symptoms of their drug therapy [12]. Cardiac patients are usually more susceptible to ADRs because multiple long-term therapies [13]. Previous studies proved that half of all admitted patients suffering from ADRs were cardiac patients [14]. There is relationship found between serious ADRs and initial symptoms [15]. The objective of this study is to develop specific tool in identifying and reporting of ADRs induced by statin which the common medication prescribed for cardiac patients.

Method

Construction of the items

Items included in questionnaire form were the common symptoms that patients may have during statin therapy, and these symptoms were collected from different sources such as FDA website [16] and previous studies [5,17-20]. Construction of questionnaire depended on the existence of ADRs and the severity (mild, moderate and severe) to measure the intensity of ADRs [21]. One point was given for mild, two for moderate, and three for severe cases. Unambiguous and easily answerable closed questions involved in this questionnaire. The form was reviewed by two senior lecturers of Faculty of Pharmacy to identify any unacceptable questions and eleven items omitted from the questionnaire. Following this piloting a 39 item questionnaire designed to examine the signs and symptoms during statin therapy. Questionnaire then reviewed by a cardiologist and four items were deleted from the questionnaire.

Language validity

The questionnaire validated by the University Language Translation Centre, and the languages used were Bahasa Malaysia and English.

Pilot study

A pilot study conducted for cardiac outpatients at a general hospital in Northern part of Malaysia Peninsula. The approval of this study was granted from Ethical Committee of the Hospital. Five hundred out of 1900 patients attended and voluntarily participated in this study. Two types of questions used in this questionnaire; nine related to demographic data and duration of statin therapy, and 26 related to symptoms induced by statin.

Data Analysis

SPSS version 18.0 used to analyze the collected data. The reliability analysis of the questionnaire performed using the Cronbach's alpha and split half tests (statistical value must be more than 0.7) to approve for clinical studies. Validation of questionnaire is done by factor analysis (statistical values must be equal or more than 0.4) which is the common

statistic test used to validate the terms of questionnaire. Chi-square also used to determine the association among the ADRs groups induced by statin.

Results

The percentage of males (70%) who enrolled in this study was higher than females (30%). The majority were Chinese (37.6%) followed by Malay (34.4%), Indian (26.6%) and others (1.4%). About 12% were smokers and 9% alcohol consumers. The mean age of the patients was 60±10 years and 30% were over than 60 years. The mean duration of satin use was 3.5-year, as shown in Table 1.

Item selection and validity

Fifteen items deleted from the questionnaire following reviewing by senior academics and the cardiologist. These items were sexual dysfunction, sense of detachment, blood sugar changes, blood pressure changes, localized pain, myalgia, asthenia, bronchitis, sleep disturbances, upper respiratory system, infection, accidental injury, allergic reactions, arthropathy, and arthralgia. Thus, the items selected were demographic data and the common symptoms of statin therapy.

Selecting of items depended on the result of factor analysis. Factor analysis is the common statistic test use to show validity and correlations of questionnaires' terms or domains, in other word to differentiate between observed and correlated than unobserved and uncorrelated terms for the main finding. When terms were not correlated or with small statistical values (less than 0.4), that means there were other factors associated and not related to this finding. For example if the symptom with value less than 0.4 then this symptoms was not related to statin but to other medications or diseases. The produced factors were different in the class and the cumulative contribution rate of these factors was 54.12%. According to Table 2, there were six factors of the questionnaire items were; first; musculoskeletal ADRs included back pain, muscle pain, joint pain and fatigue. Second respiratory ADRs were; cough, flu, swallowing difficulty, phlegm, sneezing and nasal congestion. Third gastrointestinal ADRs were; abdominal cramps, flatulence, indigestion, constipation, diarrhea, nausea and vomiting. Fourth neurological ADRs were; headache, insomnia, dizziness, limbs tingling and pricking during sleep. Fifth urological symptoms were; dark urine and burning sensation during urination. Finally others were; fever, chest pain, visual disturbances, breathing difficulty and skin rash. The Kaiser-Meyer-Olkin (KMO) is 0.826 and the Bartlett's Test is 3591.54.

Reliability of the questionnaire

Reliability of the questionnaire items examined using Cronbach's alpha and Equal-length Spearman-Brown coefficients. The Cronbach's alpha coefficient was 0.853 and Equal-length Spearman-Brown coefficient was 0.890. The Cronbach's alpha for each factor ranged from 0.523 to 0.732. The Equal-length Spearman for all factors ranged from 0.60 to 0.822, as shown in Table 3.

Incidences of ADRs

Significant correlation found of the main ADR groups occurred during use of statin. Musculoskeletal, gastrointestinal and other groups highly significant correlated to neurological group. Thus, neurological ADRs are the common correlated group of symptoms followed by musculoskeletal, gastrointestinal and other, as shown in Table 4. Also, incidence of multiple ADRs proportional correlated with the number of groups. Association between musculoskeletal and neurological groups showed highest incidence

(91%) than other combined dual groups, as shown in Table 5.

Discussion

This study used a specific questionnaire in reporting the ADRs of statins in cardiac outpatients. Previous studies differed in collecting data, most of them were dependent on doctor reporting of ADRs [19, 22, 23]. Only one study based on patients' reports and this study based on the results from others surveys with lower number of symptoms [10]. Several confusing questions deleted from the questionnaire because of the difficulty to self-diagnose, and evaluate these problems (examples hypertension, sexual dysfunction, sensing of detachment, blood sugar changes, blood pressure changes and few others).

Statistical discussion

Using statistical tests in preparation of questionnaire is commonly used in previous studies [24, 25] depending on factor analysis to approve the validation of contents and reliability to make questionnaire eligible for data collection in clinical studies. The factor analysis classified the symptoms into groups according to the nature of these groups. These groups included musculoskeletal, respiratory, urological, neurological and other symptoms. Classification of these groups gave higher specificity of these symptoms. Higher value of KMO proved the high correlation of questionnaire symptoms to statin therapy because satisfactory of KMO value must not be lower than 0.5 to prove the correlation of symptoms to statin. It also proved low effect of the partial causes on these symptoms. Besides that, there was highly significant relationship among the items ($p < 0.001$), which proved that symptoms mostly not coming alone but accompanied with other symptoms. To give an example, neurological ADRs significantly correlated with gastrointestinal ADRs. However, about 91% of patients complained musculoskeletal and neurological ADRs in same time. This finding may improve the knowledge about the ADRs incidence that may not occur alone but followed by other symptoms for same medication or disease.

High reliability of the questionnaire found after using specific statistical tests such as Cronbach's alpha and Spearman-Brown tests. Cronbach's alpha showed higher internal consistency for all the items and for each group alone. Equal-length Spearman-Brown showed higher reliability when the items divided into two parts of questionnaire. The musculoskeletal ADRs were the most reliable group using Cronbach's alpha followed by respiratory, neurological, gastrointestinal, other and urological. Thus musculoskeletal ADRs are the most significant symptoms related to statin as mentioned in literatures. The benefit of this classification is to predict the relation of these groups to demographic data, types and doses of statins, and duration of use.

Comparison in reporting types of ADRs

Self-reporting done by patients in previous studies showed higher incidence of patients with ADRs than reporting done by doctors, because doctors either unaware or not care about ADRs of medications. Golomb *et al* mentioned types of reporting but not for all ADRs. Self-reporting in current study showed higher incidence of ADRs reported by patients if compared to doctors reporting studies, as shown in Table 6. Also, no previous study determined acceptable and flexible tool to report the multiple ADRs of statin. This tool characterized the easy to determine the ADRs caused by statins other than ADRs or symptoms caused by other disease or medications, because symptoms usually

followed each other depending on their groups. For example, muscle pain, abdominal cramps and visual disturbance must follow the fatigue. Thus it is easy to say yes it related to statin in cardiac outpatients.

Conclusion

This study proved that patients' self-reporting questionnaire has high validity and reliability for a large sample. This questionnaire is appropriate tool for reporting of ADRs with simple, low cost approach, and achieves rapid ADR reporting for cardiac outpatients. The information got is useful for doctor to evaluate patients' comfort and the severity of ADRs that follow statin therapy. Even though, this tool does not depend on doctors' diagnosis, it can give an early warning of the ADRs that occur in patients on statin therapy.

Conflict of interest
None to declare

References

1- National cholesterol education program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Final Report*. 2002;106(25):3143–3421.

2- AlRazzaq HAA, Abd Aziz N, Hassan Y, Najjar M. F, Ismail O. Dyslipidemia control and contributing factors in cardiac clinic of Malaysia. *HealthMED*. 2009;3(4): 343-351

3- Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA*. 1998; 279(18):1458-1462.

4- Savoie I, Arminée K. Utilization of lipid-lowering drugs in men and women: a reflection of the research evidence?. *J Clin Epidemiol*. 2002;55(1):95–101.

5- Amin C. HMG-CoA reductase inhibitors/statins, Public Health Institute/ Medpin, April, 2007: l42707.

6- ShepherdJ, Hunninghake D, Harris S, Hutchinson H, Pears J. A review of the safety profile of rosuvastatin in an international phase II/III clinical trial program. Paper presented at the XIV international symposium on drugs affecting lipid metabolism New York, US September 2001; 9-12.

7- Bruce H. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health Syst Pharm*. 1995; 52(4):417-9.

8- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA*. 1998; 279(15):1200-1205.

9- Golomb BA., Kane T, Dimsdale JE. Severe irritability associated with statin cholesterol-lowering agents. *QJMed*. 2004;97(4): 229-235.

10- Golomb BA, McGraw JJ, Evans MA, Dimsdale JE. Physician response to patient reports of adverse drug effects. *Drug Safety*. 2007; 30(8): 669-675.

11- Griffin GC, Parkinson RW, Woolley BH. Report every adverse drug reaction! We're all in this together. *J Postgrad Med*. 1997;101(4):13-6

12- Van Grootheest K, de Graaf L, de Jong-van den Berg LT. Future efforts should consider collecting patient - consumer adverse drug reaction reporting: a new step in targeted information using population-based, or pharmaco-vigilance? *Drug Safety*. 2003;26(4): 211-7.

13- Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA*. 1995;274(1):29-34.

14- Levy M, Kewitz H, Altwein W, Hillebrand J, Eliakim M. Hospital admissions due to adverse drug reactions: a comparative study from Jerusalam and Berlin. *Eur J Clin Pharmacol*. 1980;17(1):25-31.

15- Committee on safety of medicines. Cerivastatin (lipobay) withdrawn. Current Problem in Pharmacovigillance. Medicines Control Agency. August, 2001;27:9.

16- U.S food and drug administration: rosuvastatin calcium (marketed as crestor) Information patient information sheet.: http://www.fda.gov/cder/drug /infopage /rosuvastatin /default.html. Published 2005. Accessed 10th March 2010

17- AHFS. HMG-CoA Reductase Inhibitors (Statins) – safety overview. Drug information service, University of Utah, 2007.

18- Fallon S and Enig M.G. Dangers of statin drugs: what you haven't been told about popular cholesterol-lowering medicines. http://www.westonaprice.org /moderndiseases/statin.html. Published 2004. Accessed 17th July 2010

19- Clearfield MB, Amerena J, Bassand JP, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia – prospective study to evaluate the use of low doses of the statins atorvastatin and rosuvastatin (PULSAR). Licensee Biomed Central Ltd. *Trial*. 2006;7:35

20- Golomb BA, Elaine Y, Denenberg J, and Criqui M. Statin-associated adverse events. *Circulation* 2003;107:e7001-e7039,P95.

21- Newman CB, Palmer G, Silbershatz H, Szarek M. Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. *Am J Cardiol*. 2003;92(6):670–676.

22- Ma¨Rz W, Wollschla¨Ger H, Klein G, Neiß A, Wehling M. Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the TARGET TANGIBLE trial). *Am J Cardiol*. 1999;84(1):7-13.

23- Davidson MH. Safety considerations when prescribing statins. *APOLLO Newsletter*. 2005;3:1-6.

24- Rattray J, Jones M. Essential elements of questionnaire design and development. *Journal of Clinical Nursing*. 2007;16:234-243.

25- Rattray J, Johnston M, Wildsmith J. The intensive care experience: development of the intensive care experience (ICE) questionnaire. *Journal of Advanced Nursing*. 2004;47(1):64-73.

Table 1: Characteristics and demographic of cardiac outpatients

Characteristics		Number (%)
Gender	**Female**	149(30)
	Male	351(70)
Race	**Malay**	172(34.4)
	Chinese	188(37.6)
	Indian	133(26.6)
	Other	7(1.4)
Smoking	**Yes**	59(12)
	No	441(88)
Alcohol consumption	**Yes**	47(9)
	No	453(91)
Age Mean (60±10)yr.	**28-50 yr**	94(19)
	51-65 yr	258(51)
	66-92 yr	148(30)
Duration of statins therapy Mean (3.5±3.0) yr.	**≤ 3 mo.**	16(3.2)
	>3mo.-1yr	133(26.7)
	>1yr-5yr	262(52.5)
	>5yr-20yr	89(17.6)

Table 2: Factor analysis for 26 questions of questionnaire

The items of questionnaire	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Back pain	.576					
Muscle pain	.723					
Joint pain	.692					
Cough		.642				
Flu		.737				
Sneezing and nasal congestion		.584				
Phlegm		.642				
Swallowing difficulty		.707				
Breathing difficulty		.710				
Abdominal cramps			.620			
Flatulence			.663			
Indigestion			.740			
Constipation			.610			
Diarrhea			.464			
Nausea and vomiting			.511			
Headache				.723		
Insomnia				.622		
Dizziness				.507		
Limbs tingling and pricking				.406		
Fatigue				.507		
Dark urine					.705	
Burning sensation during urination					.509	
Fever						.499
Chest pain						.935
Visual disturbance						.903
Skin rash						.665

Table 3: Reliability test of the questionnaire

Factor	Cronbach's alpha	Equal-Length Spearman-Brown
Musculoskeletal	.732	.752
Respiratory	.672	.691
Gastrointestinal	.627	.600
Neurological	.648	.667
Urological	.523	.655
Others	.591	.822

Table 4: Correlation among the ADR's groups of statin in 500 cardiac outpatients

	Pearson correlation (*p* value)					
	Musculosk-eletal	Respiratory	Gastro-intestinal	Neuro-logical	Uro-logical	Others
Musculoskeletal		0.329 (<0.001)	0.344 <0.001)	0.463 (<0.001)	0.254 (<0.001)	0.450 (<0.001)
Respiratory	0.329 (<0.001)		0.411 (<0.001)	0.440 (<0.001)	0.279 <0.001)	0.454 (<0.001)
Gastrointestinal	0.344 (<0.001)	0.411 (<0.001)		0.509 (<0.001)	0.366 (<0.001)	0.435 (<0.001)
Neurological	0.463 (<0.001)	0.440 (<0.001)	0.509 (<0.001)		0.362 (<0.001)	0.508 (<0.001)
Urological	0.254 (<0.001)	0.279 (<0.001)	0.366 (<0.001)	0.362 (<0.001)		0.374 (<0.001)
Others	0.450 (<0.001)	0.454 (<0.001)	0.435 (<0.001)	0.508 (<0.001)	0.374 (<0.001)	

Correlation is significant at $p < 0.01$(2 tailed)

Table 5: Incidences of multiple ADRs in 500 cardiac outpatients

Groups	No (%)	P value
Musculoskeletal + Neurological	454 (91%)	<0.001
Musculoskeletal + Neurological + Gastrointestinal	473 (94.8%)	<0.001
Musculoskeletal + Neurological + Gastrointestinal + other	474 (95%)	<0.001
Musculoskeletal + Neurological + Gastrointestinal + other + Respiratory	483 (96.8%)	<0.001
All groups	483 (96.8%)	0.012

Table 6: Comparison between self reporting and physician' reporting for the ADRs of statin

Author's name	Year	Type of reporting	Type of ADRs	Type of statin	Number of patients
Golomb et al [9]	2004	Case series reporting	Muscle symptoms, fatigue and anxiety	Atorvastatin, Simvastatin, Lovastatin Pravastatin	6
Golomb et al [10]	2007	Self-reporting	Muscle (86%) Visual (98%) Neuropathy (96%)	Statins	650
		Physician reporting	Muscle (14%) Visual (2%) Neuropathy (4%)		
Clearfield et al [19]	2006	Physician reporting	Myalgia (2.6%-4.8%) Urinary tract infection (2.6%- 3.3%) Headache (1.4%-1.6%) Nausea (0.8%-1.8%) Bone pain (0.6%-1.6%) Muscle cramp (0.6%-1%) Peripheral edema (0.6%- 1%)	Atorvastatin, Rosuvastatin	1041
Ma¨rz et al [22]	1999	Physician reporting	Myalgia (0.4%-0.9%) Nausea (0.5%-0.8%) Abdominal pain (0.4%-0.8%) Vertigo (0.4%-0.8%) Asthenia (0.3%-0.8%) Rash (0.3%-0.6%)	Atorvastatin Simvastatin	4097
Davidson et al [23]	2005	Physician reporting	Upper respiratory tract infection (14%-15%) Headache (7%-9%) Nausea (4%-6%)	Simvastatin	2645
Current study	2011	Self-reporting	Musculoskeletal ADRs (17.50%) Respiratory ADRs (20.30%) Gastrointestinal ADRs (20%) Neurological ADRs (23.80%) Urological ADRs (3.6%) Other ADRs (14.80%)	All types of statin	500