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Full Length Research Paper

Cardiovascular drug adverse reactions in hospitalized patients in cardiac care unit

Iman Karimzadeh[1], Soha Namazi[2], Gloria Shalviri[3] and Kheirollah Gholami[1]*

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[3]Iranian Adverse Drug Reaction Monitoring Center, Ministry of Health, Tehran, Iran.

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The aim of the present survey was to evaluate different aspects of cardiovascular drug adverse reactions in a cardiac care unit (CCU). All patients admitted to CCU during a 16 months period were recruited into this study. Detection of adverse drug reactions (ADRs) was based on daily chart review and face to face interview with patients. Causality assessment was performed by the World Health Organization (WHO) probability criteria. Seriousness of ADRs was determined by WHO definition. Schumock and Thornton scale was applied to assess preventability of ADRs. Statistical analysis was performed. Among 740 cardiovascular patients admitted to CCU, 70 ADRs were recorded from 44 patients. Headache (15.71%) was the most frequent ADR. The highest ADR rates were attributed to digoxin (44.29%) and atenolol (12.86%). Fifty five (78.57%) of ADRs were serious. The rate of preventable ADRs was 62.86%. Regarding outcome, one (1.43%) ADR led to death. Multivariate logistic regression showed that length of CCU stay (OR = 1.09, 95%CI = 1.02-1.17) and non-ischemic heart diseases (OR = 3.26, 95% CI = 1.57-6.78) were risk factors for ADR occurrence. Cardiovascular drugs could develop fatal adverse reactions in CCU patients. Primary admission diagnosis and duration of CCU stay were risk factors for ADR development.

Key words: Adverse drug reaction, cardiovascular drugs, cardiac care unit patients.

INTRODUCTION

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality (Ramirez et al., 2009). Current studies reveal that ADRs occur in 6.5% to more than 20% of hospitalized patients. These result in prolonged hospitalization, increased cost and complicated treatment (Classen, 2003). According to results of a study on 8,208,960 medicare patients admitted to the United States (US) hospitals in 1998, 141,398 patients (1.73% experienced at least one ADR. The drug classes most frequently associated with ADRs in that study include cardiotonic glycosides, adrenal corticosteroids, antineo-antineoplastic agents, anticoagulants and analgesics.

*Corresponding author. E-mail: khgholami@sina.tums.ac.ir. Tel:/Fax: +98 (21) 66954709.

Abbreviations: ADRs, Adverse drug reactions; **CCU,** cardiac care unit.

ADRs caused $516,034,829 increase in total charges, $37,611,868 in drug charges and $9,456,698 in laboratory charges (Bond and Raehl, 2006). Cardiovascular drugs were the most common class of drugs (36.3%) involved in ADR- related admissions to medicine and cardiology wards of a university hospital in Sweden (Mjörndal et al., 2002). Similarly, in a cohort study conducted in the Netherlands, antithrombotics cardiovascular drugs, antineoplastics immunosuppressives and central nervous system (CNS) drugs accounted for the majority of ADR-related hospitalizations (van der Hooft et al., 2008). Adverse reactions induced by cardiovascular drugs during hospital stay were the subject of several studies. However, to the best of our knowledge, different aspects of cardiovascular drug adverse reactions in coronary care settings have been considered only in very few studies. The aim of the present study was to evaluate adverse reactions of cardiovascular drug in a cardiac care unit (CCU) at a teaching hospital in Iran.

METHODS

From early March 2006 to early July 2007, all patients admitted to CCU of Namazi hospital, a multispeciality healthcare university setting in Shiraz, were included in this study. The hospital's Ethics Committee approved the study. Cardiovascular medication group is defined as drug classes including diuretics, peripheral and central adrenergic inhibitors, direct vasodilators, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, positive inotropic agents, antiarrhythmics, anticoagulants, fibrinolytics, and antiplatelets.

At the beginning of this cross-sectional study, yellow cards used in Iran for reporting ADRs were introduced to healthcare team in CCU including doctors and nurses. They were asked to record ADRs due to cardiovascular agents during CCU stay or ADRs of cardiovascular medications which led to CCU admission. Daily chart review and face to face interview with patients were done for ADR detection. The WHO definition of ADR was used in this study: "Any noxious or unintended response to a drug, which occurs at doses normally used in human for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function" (Edwards and Aronson, 2000). Data on ADR yellow cards including patient information (demographic characteristics, other simultaneous diseases, and possible allergy or past ADR history), information about the suspected medicine (name, dose, frequency, route of administration, and indication), concomitantly drugs used and information about the observed ADRs (onset, duration, outcome, clinical manifestation, and laboratory findings), and possible actions for management of detected ADRs were registered. To confirm the collected data, yellow cards were reviewed by the clinical pharmacist. ADR yellow cards were then sent to Iranian Pharmacovigilance Centre. Reported ADRs were categorized according to WHO adverse reaction terminology (WHO-ART) organ-system classification (Meyboom et al., 1997a). In order to determine the causality relationship between reported ADRs and suspected medications, WHO probability scale was used (Meyboom et al., 1997b). According to WHO criteria, ADRs which result in death, life-threatening situation, persistent or significant disability/incapacity, hospital admission or prolonged existing hospital stay were categorized as serious (Safety monitoring of medicinal products, 2000). Preventability of ADRs was assessed based on Schumock and Thornton questionnaire (Schumock and Thornton, 1992).

Statistical analysis

Categorical variables were expressed as percentage. Continuous variables were reported as mean ± standard deviation (SD). The study subjects were divided into 2 groups: those with ADRs and those without. The association between ADR occurrence and demographic and clinical characteristics including sex, age, length of CCU stay, primary admission diagnosis, concomitant cardiovascular diseases, and total number of drugs taken during CCU stay was examined by both univariate and multivariate logistic regression analysis to calculate odds ratios (OR) and their 95% confidence intervals (CI). P value less than 0.05 was considered to be statistically significant. Statistical analysis was performed by the SPSS 11.5 program (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period (16 months), 740 patients were admitted to the CCU. Demographic characteristics and primary admission diagnosis of patients are shown in Table 1. Of the entire subjects, 54.32% were males. More than two-fifth (46.89%) of patients were 65 years old and over. Coronary artery disease (61.19%) was the most common primary diagnosis at CCU admission. Oral, sublingual or intravenous nitroglycerin (79.05%) was the most frequent cardiovascular medication administered during CCU stay followed by aspirin (78.38%), unfractionated heparin (74.19%), and captopril (65.14%). The mean ± SD number of cardiovascular agents given during CCU stay was 5.19 ± 2.11 (minimum-maximum, 1-12 numbers). Totally, 70 ADRs were recorded in 44 patients including 17 males and 27 females. Their mean ± SD age was 66.11 ± 12.62 years. Of 740 CCU admissions, ADRs were considered to be the cause of admission in 21 (2.84%) patients. Among 44 patients, 27 (61.36%) had only 1 ADR, 8 (18.18%) developed 2, and 9 (20.45%) simultaneously experienced 3 ADRs.

Table 2 shows clinical manifestations, frequency of ADRs, sex ratio, and also drugs suspected of causing them. Headache (15.71%) was the most frequent

Table 1. Demographic characteristics and primary admission diagnosis of total patients admitted to the CCU (n = 740).

Characteristic	Value
Gender	
Male	402
Female	338
Age (years)	
Mean ± SD	61.34 ± 14.15
Minimum-maximum	17-95
CCU stay duration (days)	
Mean ± SD	6.16 ± 4.01
Minimum-maximum	1-38
Primary admission diagnosis	
Coronary heart disease	462
Arrhythmia	157
Heart failure	51
Valvular heart disease	23
Pericardial disease	10
Cardiomyopathy	7
Vascular disease	4
Congenital heart disease	2
Others	
Post angiography	13
Digoxin toxicity	15
Syncopal attack	7
Chest pain	2
Angioplasty	1
Myoxoma	1

CCU: cardiac care unit.

Table 2. Clinical manifestations, frequency, sex ratio, and cardiovascular drugs suspected of causing adverse reactions (n = 70).

Type of ADR	n (%)	Male/Female	Suspected drug (n)
Headache	11 (15.71)	2/9	Nitroglycerin (7), Atenolol (2), Digoxin (2)
Dizziness	10 (14.29)	2/8	Digoxin (6), Atenolol (3), Propranolol (1)
Nausea and Vomiting	8 (11.43)	1/7	Digoxin (7), Atenolol (1)
Hematuria	6 (8.57)	5/1	Streptokinase (1), Heparin (4), Warfarin (1)
Epigastric pain	4 (5.71)	0/4	Digoxin (3), Atenolol (1)
Vertigo	4 (5.71)	0/4	Digoxin (3), Atenolol (1)
GI bleeding	3 (4.29)	2/1	Streptokinase (2), Heparin (1)
Weakness	3 (4.29)	1/2	Digoxin (3)
Dyspnea	3 (4.29)	2/1	Digoxin (1), Atenolol (1), Propranolol (1)
Ventricular tachycardia	2 (2.86)	2/0	Streptokinase (2)
Ventricular fibrillation	2 (2.86)	2/0	Streptokinase (2)
Palpation	2 (2.86)	0/2	Digoxin (2)
Fatigue	2 (2.86)	0/2	Digoxin (2)
Hypokalemia	1 (1.43)	0/1	Furosemide (1)
Rash	1 (1.43)	1/0	Clopidogrel (1)
AV block	1 (1.43)	0/1	Digoxin (1)
Speech disorder	1 (1.43)	0/1	Lidocaine (1)
Tinnitus	1 (1.43)	1/0	Lidocaine (1)
Peripheral cyanosis	1 (1.43)	0/1	Dopamine (1)
Cough	1 (1.43)	0/1	Captopril (1)
Epistaxis	1 (1.43)	1/0	Heparin (1)
Atrial fibrillation	1 (1.43)	0/1	Digoxin (1)
Bleeding at angiography site	1 (1.43)	1/0	Aspirin (1), Heparin (1), Warfarin (1)

ADR: adverse drug reaction; GI: gastrointestinal; AV: atrioventricular.

Table 3. Organ-systems involved by cardiovascular drug adverse reactions (n = 70).

Organ-system	n (%)
Central and peripheral nervous system disorders	26 (37.14)
Gastrointestinal system disorders	15 (21.43)
Heart rate and rhythm disorders	8 (11.43)
Urinary system disorders	6 (8.57)
Respiratory system disorders	5 (7.14)
Body as a whole - general disorders	5 (7.14)
Vascular (extracardiac) disorders	1 (1.43)
Platelet, bleeding and clotting disorders	1 (1.43)
Endocrine disorders	1 (1.43)
Skin and appendages disorders	1 (1.43)
Hearing and vestibular disorders	1 (1.43)

reported ADRs followed by dizziness (14.29%), nausea and vomiting (11.43%), and hematuria (8.57%). Digoxin (44.29%) and atenolol (12.86%) caused the most and clopidogrel, captopril, furosemide, and aspirin (1.43%) the least ADRs. All reported ADRs attributed to digoxin and atenolol resulted in admission to the CCU. Organ-systems affected by cardiovascular drug adverse reactions are demonstrated in Table 3. The 3 most common involved organ-systems were central and peripheral nervous system (37.14%), gastrointestinal system (21.43%), and heart rate and rhythm (11.43%).

Table 4 provides causality assessment results of detected ADRs. Most ADRs (62.86%) were recognized to be possible. Regarding the outcome of ADRs, 67was as a result of gastrointestinal (GI) bleeding attributed to streptokinase. The reaction occurred in a 67-year old male patient who received 1,500,000 units streptokinase intravenously for ST-elevated myocardial infarction. GI

Table 4. Causality assessment of detected adverse drug reactions (n = 70).

Causality	n (%)
Certain	6 (8.57)
Probable	14 (20)
Possible	44 (62.86)
Unlikely	6 (8.57)

bleeding developed 1 day after streptokinase initiation. Despite GI washing through nasogastric tube, he died 2 days later. Among 70 ADRs, 44 (62.86%) was identified as preventable. Details of ADRs considered to be preventable are listed in Table 5. Among seven preventability criteria of Schumock and Thornton's questionnaire, drug-drug interactions and lack of regular therapeutic drug monitoring accounted for most of preventable ADRs.

According to WHO criteria, 55 (78.57%) ADRs were considered to be serious. The most frequent serious ADRs were attributed to digoxin (56.36%), atenolol (16.36%), and streptokinase (10.91%).

The management of ADRs involved discontinuation of causative medications in combination with additional therapeutic measurements (68.57%), withdrawal or reduction the dosage of drugs causing ADRs without any further treatment (18.57%), and additional therapeutic measurements without cessation of the offending medications (10%). Two (2.86%) ADRs need no management. According to results of univariate logistic regression analysis, age ($p = 0.022$), gender ($p = 0.017$), length of CCU stay ($p = 0.001$), primary admission diagnosis ($p < 0.001$), and concomitant cardiovascular diseases ($p < 0.001$) were identified as possible risk factors of cardiovascular drug adverse reactions. However, multivariate logistic regression analysis revealed that only length of CCU stay (OR = 1.09, 95% CI = 1.02-1.17, $p = 0.008$) and non-ischemic heart diseases as primary admission diagnosis (OR = 3.26, 95% CI = 1.57-6.78, $p = 0.002$) were independent risk factors for experiencing an ADR (Table 6).

DISCUSSION

The frequency of ADRs in the present study was 44/740 (5.95%). This rate is much lower than the previous study performed in outpatients with cardiovascular diseases. In that study, 105 out of 518 (20.3%) outpatients developed at least 1 cardiovascular drug adverse reactions (Gholami et al., 2008). In a study conducted by Mohebbi and co-workers on 677 patients admitted to CCU over an 8-months period, the rate of ADRs was 24.2% (Mohebbi et al., 2010). In another study in Danish department of cardiology, the rate of ADRs attributed to cardiovascular agents was 15.3% (Davidsen et al., 1988).

In the current study, 2.84% of CCU admissions were ascribed to ADRs. The rate of ADR-related admissions reported in other studies on Iranian population was quite different. According to a study conducted on 370 Iranian patients in general wards, ADRs has been identified as the cause of 8% of total hospitalizations (Gholami and Shalviri, 1999). In another survey at infectious disease department of a hospital in Iran, 2.2% of all admissions were due to anti-infective ADRs (Gholami et al., 2005). In two further studies in Iranian population, the rate of ADRs causing hospitalization in infectious disease and internal medicine wards were 5.4% (Javadi et al., 2007). and 1.75% (Pourseyed et al., 2009), respectively. In line with result of our present study, of 2,559 admissions to an in tensive cardiac care unit (ICCU) in Israel, 64 (2.5%) were due to major cardiac iatrogenic events. Major cardiac iatrogenic events were defined as life- threatening or serious problems caused by diagnostic procedure or therapy (Hammerman and Kapeliovich, 2000).

Digoxin, atenolol, and streptokinase were the most offending cardiovascular drugs in the current study. In the survey in outpatients, calcium channel blockers especially diltiazem had the highest rate of ADRs (Gholami et al., 2008). The highest number of ADRs in Mohebbi et al. (2010) study was caused by nitroglycerin. In Danish trial, almost 60% of all ADR- related admissions as well as 80% of all detected ADRs were attributed to thiazide diuretics, beta blockers, and calcium channel antagonists (Davidsen et al., 1988) . Among 64 admissions to ICCU which were due to major cardiac iatrogenic events, 58 (91%) patients suffered from arrhythmias caused by beta blockers, calcium channel blockers, amiodarone or combination of these drugs (Hammerman and Kapeliovich, 2000). In contrast to our results, digitoxicity was only proven in 1 patient as the cause of ICCU admissions. The authors explained their latter finding by a decrease in the number of patients treated with digitalis as well as regular monitoring of digoxin blood levels in the study population (Hammerman and Kapeliovich, 2000). According to results of Zaidenstein and co- workers study in an internal medicine ward in Israel, beta blockers and warfarin together were responsible for 40% of detected ADRs (Zaidenstein et al., 2002).

The highest rate of ADRs reported in this study were headache (15.71%), dizziness (14.29%), and nausea and vomiting (11.43%). Central nervous (37.14%) and gastrointestinal (21.43%) systems were considered to be

Table 5. Details of preventable adverse drug reactions (n = 44).

Age (years)	Sex	Type of ADR	Suspected drug (s)	Preventability criteria
67	Male	Hematuria	Heparin	Drug-drug interaction
80	Female	Hematuria	Heparin	Drug-drug interaction
50	Male	Hematuria	Heparin	Drug-drug interaction
83	Male	Hematuria	Warfarin	Drug-drug interaction
55	Male	Hematuria	Streptokinase	Drug-drug interaction
79	Male	Hematuria, GI bleeding, epistaxis	Heparin	Drug-drug interaction
67	Male	GI bleeding	Streptokinase	Drug-drug interaction
53	Male	Bleeding at angiography site	Aspirin, Heparin, Warfarin	Drug-drug interaction
80	Female	AV block	Digoxin	Drug-drug interaction, TDM not performed
65	Female	Atrial fibrillation	Digoxin	Drug-drug interaction, TDM not performed
77	Female	Vertigo	Digoxin	Drug-drug interaction, TDM not performed
70	Female	Nausea and vomiting, dizziness, weakness	Digoxin	Drug-drug interaction, TDM not performed, Poor compliance
70	Female	Dizziness, headache, dyspnea	Atenolol	Drug-drug interaction
74	Male	Nausea and vomiting, weakness	Digoxin	Drug-drug interaction, TDM not performed
65	Female	Nausea and vomiting	Digoxin	Drug-drug interaction, TDM not performed
72	Female	Headache, vertigo, epigastric pain	Digoxin	Drug-drug interaction, TDM not performed, Poor compliance
69	Female	Nausea and vomiting, dizziness, epigastric pain	Digoxin	Drug-drug interaction, TDM not performed
66	Female	Headache, dizziness, fatigue	Digoxin	Drug-drug interaction, TDM not performed
84	Male	Dizziness, dyspnea	Propranolol	Drug-drug interaction
74	Female	Nausea and vomiting, headache, vertigo	Atenolol	Previous reaction to the drug
54	Female	Nausea and vomiting, palpation, epigastric pain	Digoxin	Drug-drug interaction, TDM not performed
73	Female	Nausea and vomiting, vertigo, fatigue	Digoxin	Drug-drug interaction, TDM not performed
70	Male	Dizziness, dyspnea	Digoxin	Drug-drug interaction, TDM not performed

ADR: adverse drug reaction; GI: gastrointestinal; AV: atrioventricular; TDM: therapeutic drug monitoring.

the most frequent affected organ-systems. These results are in exact agreement with the previous survey (Gholami et al., 2008). Similar results were observed in Mohebbi et al. (2010) study.

Lazarou et al. (1998) reported a 6.7% overall incidence of serious ADRs and mortality of 0.32%. The incidence of serious ADRs in our survey was 4.05% which is comparable to Zaidenstein et al. (2002) finding (4%). In contrast, incidence of serious ADRs in Iranian outpatients with cardiovascular disease (0.58%) was much lower than those reported in the present study (Gholami et al., 2008). Mohebbi et al. (2010) reported a higher incidence of serious ADRs in their study (5.47%). Mean ± SD age of patients with serious ADRs was more than the opposite group (69.53 ± 9 vs. 57.43 ± 15.18 years). However, given the limited number of nonserious ADRs, comparison between age as well as other demographic charactristics and number of cardiovascular drug given in patients with and without serious ADRs was not statistically feasible.

Similar to seriousness, the rate of preventable ADRs in this study (62.86%) is much higher than the value we observed previously (1.9%) (Gholami et al., 2008).

According to a systematic review conducted on eight studies published between 1991 and 2006, the median overall incidence of in-hospital adverse events was 9.2% and almost 50% of

Table 6. Demographic and clinical characteristics of patients with and without adverse drug reactions (n = 740).

n (%)	Patients with ADRs	Patients without ADRs	OR (95% CI)	*p*
	44 (5.95)	696 (94.05)		
Gender				
Male, n (%)	17 (38.64)	385 (55.32)	0.07	0.07
Female, n (%)	27 (61.36)	311 (44.68)		
Age (years)				
Mean ± SD	66.11 ± 12.62	61.04 ± 14.19	0.19	0.19
Minimum-maximum	27-84	17-95		
CCU stay duration (days)				
Mean ± SD	8.34 ± 7.25	6.02 ± 3.68	0.008	0.008
Minimum-maximum	2-38	1-23		
Primary admission diagnosis				
Ischemic heart diseases, n (%)	15 (34.09)	457 (65.66)	0.002	0.002
Non-ischemic heart diseases, n (%)	24 (54.55)	157 (22.56)		
Concomitant cardiovascular diseases†	32 (72.73)	418 (60.06)	0.22	0.22
Total number of drugs taken during CCU stay				
Mean ± SD	9.37 ± 2.89	8.92 ± 3.5	0.75	0.75
Minimum-maximum	4-16	1-28		

ADRs: adverse drug reactions; OR: odds ratio; CI: confidence interval; CCU: cardiac care unit. † Other than primary admission diagnosis.

these events were considered to be preventable (de Vries et al., 2008). The results of another literature review revealed that preventable adverse drug event rate in hospitalized patients was 35.2% (minimum -maximum, 18.7-73.2%) and cardiovascular drugs were responsible for 17.9% (minimum-maximum, 4.3-28.1%) of preventable adverse drug events (Kanjanarat et al., 2003). In a system analysis of ADRs by Leape and colleagues, they estimated that drug-drug interactions represent 3-5% of all preventable ADRs in hospitals (Leape et al., 1995). Drug-drug interactions and inadequate therapeutic drug monitoring were the major causes of preventable ADRs in the present study. Preventive strategies such as development of ADR surveillance centre in hospitals, instructing health team professionals especially doctors and nurses regarding detecting and reporting ADRs, participation of clinical pharmacists in drug prescription, dispensing, administration, and patient follow-up, using computer-based prescription systems and regular level monitoring of drugs with narrow therapeutic index could considerably reduce the rate of ADR occurrence in medical settings.

Different factors such as genetic predisposition, co-prescribed drugs, and disease state can alter patient's susceptibility to ADRs (Ferner, 2003). In Zaidenstein and co-workers study, patients with adverse drug events induced by cardiovascular agents stayed about 2 days more in hospital compared to those without adverse drug events (p = 0.018) (Zaidenstein et al., 2002). Duration of hospitalization was significantly longer in patients who experienced an ADR in an infectious diseases ward in Iran (14.6 vs. 10.2 days,

$p < 0.001$) (Kourorian et al., 2009). In the current study, patients with non-ischemic heart diseases as primary admission diagnosis and those who had a longer CCU stay were at risk of experiencing an ADR.

The difference between results of our survey and other studies about cardiovascular drug adverse reactions could be attributed to ethnic differences, different possible risk factors for ADR development (e.g. demographic characteristics, type and number of co-administered drugs, duration of therapy, length of stay in hospital, and comorbidities), and variable sources of detecting and reporting ADRs. In this regard for example, a pharmacist looked for ADRs in Mohebbi et al. (2010) study whereas in the current survey, doctors and nurses detected and reported ADRs.

Conclusion

Our data demonstrate that cardiovascular drugs could develop serious and even fatal adverse reactions in CCU patients. Primary admission diagnosis and duration of CCU stay were risk factors for ADR development. Since most of detected ADRs in this study were preventable, strategies such as ADR surveillance centre development in hospitals and healthcare team training could substantially reduce ADR occurrence in medical settings.

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