Iranian Journal of Pharmaceutical Research (2008), 7 (3): 223-228
Received: February 2008
Accepted: May 2008

Original Article

Adverse Drug Reactions in the Post Coronary Care Unit Inpatients of a Teaching Hospital

Fanak Fahimi[a,b], Shadi Baniasadi[a*] and Somayeh Amini[b]

[a] *TB and Lung Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University, M. C., Tehran, Iran.* [b] *Clinical Pharmacy Department, School of Pharmacy, Shahid Beheshti University, M. C., Tehran, Iran.*

Abstract

The monitoring and reporting of adverse drug reactions (ADRs) in hospitals aims to identify and quantify the risks associated with the use of drugs. The present study was performed to characterize the rate and the pattern of ADRs, due to cardiovascular drugs and anticoagulants, in a tertiary care teaching hospital. For this purpose, all the patients treated with cardiovascular drugs and anticoagulants in the post coronary care unit (CCU) from September 2006 until January 2007 were actively monitored for ADRs. Data evalution was conducted for various parameters which included patient demographics, number of prescribed drugs, drug and reaction characteristics, and outcome of the reactions. Assessment was also done for causality, seriousness, and preventability. A total of 64 ADRs during the 4 months study period were evaluated. The overall rate of ADRs calculated from the patient population was 53%. No significant difference was seen in the overall rate of ADRs in males vs. females. The most commonly affected organ was gastro-intestinal system (14.06%). Nitroglycerin tablet (long-acting) and digoxin were the drugs most frequently reported (28.28%). In 20.31% of the reports, the patient had recovered from the reaction at the time of data collection. Upon causality assessment, the majority of the reports were rated as probable (64.06%). Serious and non-serious reactions accounted for 3.13% and 96.87% of the ADRs, respectively. In 9.37% of the reports, reaction was considered to be preventable. Our data revealed that ADRs in the post CCU occur rather frequently during hospitalization. Such studies enable us to obtain information on the rate and pattern of ADRs in the local population. These evaluations need to be followed by dissemination of the information to healthcare professionals to improve the quality of patient care and ensure safer use of drugs.

Keywords: Adverse drug reaction reporting system; Cardiovascular drugs; Hospital; Coronary care unit.

Introduction

An adverse drug reaction (ADR) is defined by the WHO as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of disease, or for the modification of physiological function (1). It has been estimated that as many as 35% of the hospitalized patients experience an ADR during their hospital stay (2). Although many of the ADRs are non-serious and disappear when the drug is discontinued or the dose is

* Corresponding author:
E-mail: Baniasadishadi@yahoo.com

reduced, others are serious and last longer. Therefore, ADRs are amongst the leading causes of morbidity, mortality and rising hospital costs (3). Studies have shown that the drugs which most commonly cause adverse drug events (ADEs) are analgesics, anti-infective agents, cardiovascular drugs, anticoagulants, sedatives and anti-neoplastic drugs (4, 5). In one study, drugs used for the treatment of cardiovascular diseases were implicated in ADRs by about 3% of the 2367 patients seen in an ADR clinic (6). In a meta-analysis, McDowell et al reported that patients from different ethnic groups have different risk factors for important ADRs to cardiovascular drugs (7). Therefore, it may be useful to determine the incidence and pattern of ADRs to cardiovascular drugs in different ethnic groups.

Collecting ADRs in a hospital setting provides data on safety of drug use in special patient populations and data on drugs used exclusively in hospitals. Different systems have been applied to detect ADRs occurring during hospital stays. Active monitoring seems to give the most reliable figures on the incidence and the pattern of ADRs and thereby helps to design improvement strategies for the safety of drug use and patient education (8).

We established an ADR reporting and monitoring center in our hospital to stimulate spontaneous reporting of health care professionals. Since the incidence of ADRs reported by physicians and nurses was found to be low (9), we performed the present study to determine the incidence and characteristics of the ADRs occurring in the post CCU ward of our hospital.

Experimental

Study design and setting

This prospective study was conducted from September 2006 until January 2007 in the post CCU of Masih Daneshvari Hospital, a multispeciality tertiary healthcare hospital located in Tehran, Iran. ADRs were collected by the active method. A pharmacist actively looked for any suspected ADRs to cardiovascular drugs and/or anticoagulants.

Patients

All patients admitted to the post CCU were screened for eligibility to enter the study. Only those receiving treatment with cardiovascular drugs and/or anticoagulants were included (whether such treatment had been started prior to admission or during hospitalization). Exclusion criteria were dementia or confusion, severe illness and refusal of the patient to participate. The Hospital's Ethics Committee approved the study and all participants gave their informed consent.

Data collection

All the necessary and relevant data were collected from in-patient case notes, treatment charts, laboratory data reports and patient interview. If a suspected ADR was detected, data on that particular suspected drug and reaction was collected and documented in a 'Yellow card'. All report forms were discussed with a clinical pharmacist (FF) in order to validate the data collected.

Definitions

Adverse reaction to a drug was defined in accordance to the World Health Organization's definition for an ADR (1). Cardiovascular drugs were defined as those used for the treatment of hypertension, ischemic heart disease, congestive heart failure and/or arrhythmias. The anticoagulants used were heparin, warfarin or enoxaparin.

Data evaluation and analysis

Data on the reported ADRs were evaluated to understand the pattern of the ADRs with respect to patient demographics, number of prescribed drugs, nature of the reactions, characteristics of the drugs involved, and outcome of the reactions. Parametric variables between males and females were compared by Student's t-test.

Each ADR was classified according to the WHO system organ classification (10). Causality, seriousness and preventability for the reaction were also assessed.

In order to evaluate the causal relationship between drug and reaction, causality assessment was performed using the Naranjo's ADR probability scale (11). The ADRs were classified

Appendix 1. Criteria for determining preventability of an ADR

Answering 'yes' to one or more of the following implies that an ADR is preventable.
1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?
4. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
5. Was a drug interaction involved in the ADR?
6. Was poor compliance involved in the ADR?
7. Was a toxic serum drug concentration (or laboratory monitoring test) documented

as certain, probable, possible and unlikely to be drug induced, depending upon the level of association.

The seriousness of reported adverse reactions were assessed based on the WHO definition, which included any adverse event that resulted in death, life threatening situation, hospitalization, prolonged hospital stay, disability or birth defect. Assessment of preventability was determined using the scale developed by Schumock et al. .(12) (Appendix 1).

Results

During the 4-months study period, 56 patients were admitted to the post CCU. Thirty four patients met the inclusion for the study.

A total of 64 ADRs were detected. Data related to patients with at least one ADR were analyzed. These occurred in 18 patients (9 females and 9 males). Their mean±SD age was 56.81±11.89 years. The average number of drugs taken at the time of the report was 8.63 (4.25 for cardiovascular drugs). There was no significant difference between men and women, regarding these parameters. The causality of these ADRs was defined as either "probable" or "possible", none as "certain", and "unlikely". The classification of the ADRs by system-organ class is described in Table 1.

The number and percentage of ADRs reported for each drug is shown in Table 2. Cardiovascular drugs and anticoagulants were responsible for 86.87% and 13.13 % of ADRs respectively. Most of the suspected drugs were orally administered drugs (n=68). Of those, 45 (66.18%) were started in the hospital and 23 (33.82%) started before the hospital admission.

The results of the analysis performed on the 64 ADRs detected are given in Table 3. Causality was defined as "probable" for 41 (64.1%) reports and as "possible" for 23 (35.9%) reports. In 9.37% of the reports, the

Table 1. Systems associated with ADRs.

System associated with ADRs	Number of ADRs	Percentage
Gastro-intestinal system disorders	9	14.06
Respiratory system disorders	9	14.06
Cardiovascular disorders	8	12.50
Platelet, bleeding and clotting disorders	6	9.38
Skin and appendages disorders	6	9.38
Metabolic and nutritional disorders	5	7.81
Psychiatric disorders	5	7.81
Body as a whole-general disorders	4	6.25
Heart rate and rhythm disorders	4	6.25
Central and peripheral nervous system disorders	3	4.69
Urinary system disorders	3	4.69
Musculo-skeletal system disorders	1	1.56
Vascular (extra-cardiac) disorders	1	1.56
Total	64	100

Table 2. Suspected drugs implicated in ADRs.

Suspected drugs	Number of ADRs	Percentage
Cardiovascular drugs		
Digoxin	14	14.14
Nitroglycerin tablet (long-acting)	14	14.14
Captopril	12	12.12
Furosemide	11	11.11
Losartan	7	7.07
Metoprolol	5	5.05
Spironolactone	4	4.04
Diltiazem	4	4.04
Isosorbide	4	4.04
Hydrochlorothiazide	4	4.04
Atenolol	3	3.03
Amlodipine	1	1.01
Enalapril	1	1.01
Nitroglycerin sublingual capsule	1	1.01
Propranolol	1	1.01
Anticoagulants		
Enoxaparin	8	8.08
Warfarin	3	3.03
Heparin	2	2.02
Total[a]	99	100

[a]Total is different from the total number of ADRs reports, since in many cases more than one drug was suspected.

reaction was considered to be preventable. Two ADRs (3.13%) were classified as serious, both of them causing life threatening situations. In the first case, metoprolol induced bronchospasm in a patient suffering from asthma. In another case arrhythmia was induced following digoxin and diltiazem co-administration. In 20.31% of the reports, the patient had recovered from the reaction at the time of the ADR report.

Discussion

ADRs can significantly increase a patients' mortality, disability and overall healthcare costs (13). The most commonly applied methods to detect ADRs in hospitals involve stimulated spontaneous reporting of health care professionals, comprehensive collection by trained specialists and computer-assisted approaches using routine data from hospital information systems. The different methods of ADR detection used can result in different rates and types of ADRs (8).

The incidence of ADRs identified in the post CCU of our hospital was 53%, which is higher than the other reports. Tran et al. and Zaidenstein et al. reported the incidence of ADRs and ADEs caused by cardiovascular drugs as being 3% and 4% respectively (6, 14).

This can be attributed to our criterion for inclusion in the study, the setting of the study, the method of ADR detection and the criteria for ADR evaluation. Our criterion for the study included those receiving treatment with cardiovascular drugs. The average age of patients receiving cardiovascular drugs is relatively high. However, age as a risk factor for ADRs is a controversial issue (15-17). Moore et al. found an inverse relationship between age and adverse events for ADRs occurring during hospital stay (18). The study setting was the post CCU of the hospital where

Table 3. Classification of the ADRs (n=64).

Characteristic	*Number of ADRS (%)*
Reports per gender	
Male	9 (50%)
Female	9 (50%)
Causality	
Probable	41 (64.06%)
Possible	23 (35.94%)
Severity	
Serious ADR (life threatening situations)	2 (3.13%)
Non-serious ADR	62 (96.87%)
Relationship to spontaneous reports	
Reported spontaneously	0 (0%)
Reported actively	64 (100%)
Preventability	
Preventable	6 (9.37%)
Non-preventable	58 (90.63%)
Outcome	
Recovered	13 (20.31%)
Not yet recovered	51 (79.69%)

the severity and complexity of the disease, use of multiple drugs and drug interactions could be well-known risk factors for developing ADRs (19). Our method for ADR detection was intensive, since all the necessary and relevant data were collected from in-patient case notes, treatment charts, laboratory data reports and patient interview. The studies which have compared prospective active surveillance with voluntary reporting found that the incidence of reports using the surveillance method is much higher (20). In relation to ADR assessment, Zaidenstein et al. (14) included only "certain" and "probable" serious events, while we also included "possible" ADRs.

The drugs which most commonly caused ADRs in our study were nitroglycerin tablet (long-acting) and digoxin. Together, these two drugs were responsible for 28.28% of the ADRs induced by cardiovascular drugs and anticoagulants. These results could be expected, since unstable angina and congestive heart failure were the most common cardiovascular conditions among the patients included in our study.

Conclusion

The incidence of ADRs caused by cardiovascular drugs can be expected to increase due to the proliferation of drugs for cardiovascular conditions and the gradual rise in life expectancies. Such studies enable us to obtain information on the incidence and pattern of ADRs induced by cardiovascular drugs in the local population. Similar data evaluation needs to be followed by dissemination of the information to the healthcare professionals, which could help to improve the quality of patient care by ensuring safer use of drugs.

References

(1) World Health Organization. Technical Report Series 498. World Health Organization, Geneva (1972)

(2) Murphy BM and Frigo LC. Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. *Hosp. Pharm.* (1993) 28: 1199-1204, 1240

(3) Ramesh M, Pandit J and Parthasarathi G. Adverse drug reactions in a South Indian hospital-their severity and cost involved. *Pharmacoepidemiol Drug Saf.* (2003) 12: 687-92

(4) Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R,Vander Vliet M, Nemeskal R and Leape LL. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* (1995) 274: 29-34

(5) Classen C, Pestotnik SL, Evans RS and Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA* (1991) 266: 2847-51

(6) Tran C, Knowles SR, Liu BA and Shear NH. Gender differences in adverse drug reactions. *J.Clin. Pharmacol.* (1998) 38: 1003-9

(7) McDowell SE, Coleman JJ and Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ* (2006) 332: 1177-81

(8) Thurmann PA. Methods and systems to detect adverse drug reactions in hospitals. *Drug Saf.* (2001) 24: 961-8

(9) Baniasadi S, Fahimi F and Shalviri G. Developing an adverse drug reaction reporting system at a teaching hospital. *Basic Clin. Pharmacol. Toxicol.*(2008) 102: 408-11

(10) Uppsala Monitoring Centre. Adverse Reaction Terminology. Uppsala, World Health Organization Collaborating Centre for International Drug Monitoring (2003)

(11) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I,

Roberts EA, Janecek E, Domecq C and Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.* (1981) 30: 239-45

(12) Schumock GT and Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp. Pharm.* (1992) 27: 538

(13) Classen C, Pestotnik SL, Evans RS, Lloyd JF and Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* (1997) 277: 301-6

(14) Zaidenstein R, Eyal S, Efrati S, Akivison L, Michowitz MK, Nagornov V and Golik A. Adverse drug events in hospitalized patients treated with cardiovascular drugs and anticoagulants. *Pharmacoepidemiol. Drug Saf.* (2002) 11: 235-8

(15) Hoigne R, Lawson DH and Weber E. Risk factors for adverse drug reactions- epidemiological approaches. *Eur. J. Clin. Pharmacol.* (1990) 39: 321-5

(16) Gurwitz JH and Avorn J. The ambiguous relation between aging and adverse drug reactions. *Ann. Intern. Med.* (1991) 114: 956-66

(17) Carbonin P, Pahor M, Bernabei R and Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalised medical patients? *J. Am. Geriatric Soc.* (1991) 39: 1093-9

(18) Moore N, Lecointre D, Nobelt C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br. J. Clin Pharmacol.* 1998; 45:301-8

(19) Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, Hebert L, Newhouse JP, Weiler PC and Hiatt H. The nature of adverse events in hospitalized patients-Results of Harvard medical practice study II. *N. Engl. J. Med.* (1991) 324: 377-84

(20) Al-Tajir GK and Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. *Ann. Pharmacother.* (2005) 39: 1169-74

This article is available online at http://www.ijpr-online.com