Adverse Drug Reactions in a Pulmonary Teaching Hospital: Incidence, Pattern, Seriousness, and Preventability

Shadi Baniasadi[1] and Fanak Fahimi[*,2,3]

[1]*Pharmaceutical Care Department, Virology Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2]*Clinical Pharmacy Department, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[3]*Chronic Respiratory Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Abstract: *Introduction*: Monitoring and reporting of adverse drug reactions (ADRs) in specialized hospitals provide an important measure to identify and quantify the risks associated with the use of specific drugs.

Aims: This study aimed to determine the incidence, pattern, seriousness, and preventability of hospital-acquired ADRs, in medical wards of a pulmonary teaching hospital in Iran.

Methods: The study was conducted based on the ADRs reported by clinicians, nurses, and clinical pharmacists between March 2009 and February 2011 to the ADR reporting unit of the hospital. The incidence, pattern, seriousness, and preventability of the reported ADRs were analyzed.

Results: During the period of 24 months, for 11975 patients, 306 ADR reports were received. The most frequently reported reactions were due to anti-infective agents (34.08%). Rifampin accounted for the highest number of the reported ADRs among anti-infective agents. The gastro-intestinal system was the most frequently affected system (21.90% of all reactions). Seventy two (23.53%) of the ADRs were reported as serious reactions and twenty-five (8.17%) of the ADRs were classified as preventable.

Conclusions: Our study shows that ADRs pattern in our hospital is different from the other studies. Preventive measures have decreased the preventable ADRs and ensured safer drug use. Education and clinical pharmacist interventions have increased the quality and quantity of reported ADRs.

Keywords: Adverse drug reaction, clinical pharmacist, hospital, pharmacovigilance, spontaneous reporting, yellow card.

INTRODUCTION

Detection of ADRs in hospitals could provide a mechanism for monitoring the safety of drug use in high-risk patient populations and stimulate the education of health professionals regarding potential ADR [1]. Studies have shown that between 10-20% of hospital inpatients experience an ADR during their hospitalization [2-5]. The rate of reported ADRs in hospitalized patients differs from study to study. This is probably due to the differences in patients' demographics, the number of beds, medications on formulary, and the ADR definition used [6].

Most of the studies have been conducted in general hospitals where patient populations and drug use patterns differ markedly from those of specialized ones. These differences impact on the frequency and nature of ADRs [7]. Detection of ADRs in a specialized hospital is essential to find more information regarding most commonly used drugs. This data is required to improve drug use patterns and drug management system in a hospital [8].

*Address correspondence to this author at the Chronic Respiratory Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Bahonar Ave, Darabad, Tehran 19569, Iran; Tel: +98- 21- 26109503; Fax: +98-21-26109503; E-mails: fanakfahimi@yahoo.com, fahimi@nritld.ac.ir

After the implementation of ADR reporting system in our hospital [9], we educated health care professionals and involved clinical pharmacy students in ADR reporting. This study aimed to determine the pattern of hospital-acquired ADRs, in medical wards of a pulmonary teaching hospital. Another objective was to evaluate our system in quantity and quality of reported ADRs.

METHODS

The study was conducted on 11 wards (9 medical and 2 surgical) at Masih Daneshvari Hospital over a two year period from March 2009 to February 2011. Masih Daneshvari is tertiary care, multidisciplinary teaching hospital.

Clinicians and nurses were asked to inform pharmacovigilance department when they detect ADRs [9]. They were regularly reminded by an ADR bulletin [10], training lectures and direct contacts. After the initial notification, the following information was documented in an ADR standard form: the patient's demographic details, a brief description of the ADR, previous allergies, co morbidities, the name of the suspected medication(s), the dose, the route of administration, the dates of starting and stopping therapy, reason for suspected drug(s) use,

1574-8863/11 $58.00+.00 © 2011 Bentham Science Publishers

concomitant medication(s), management and outcome of the ADR.

As well as clinical pharmacist residents as part of their lung rotations training received a general idea of ADRs, ADR trigger medications, and the hospital's ADR reporting program. They collected ADR data by prospectively reviewing inpatient charts and patient interview. We also, set up designed boxes on each nursing station with the same color as ADR form (yellow) and some explanation on how, when, and why to report ADRs.

An ADR was defined according to the World Health Organization (WHO) definition as: "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

Each ADR was classified according to the WHO system organ classification [11]. All reported ADRs were evaluated for the causality in accordance with Naranjo's algorithm [12]. The seriousness of reported adverse reactions was 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.* [13]. (Appendix **1**)

ADR forms were then sent to the national ADR monitoring centre at the Ministry of Health for further evaluation.

RESULTS

During 2 years, a total of 11975 patients were admitted to the hospital, and 306 ADRs were reported from 272 patients. The ADR was the primary reason of hospitalization in 35 patients. At least one ADR was reported in 1.98% (95% confidence interval [CI]: 0.017-0.023) of patients during hospitalization and 0.30% (95%CI: 0.002-0.004) of admissions were caused by ADRs. In terms of the patient demographics in the reported ADRs, 3.1% (95%CI: 0.026-0.036) were women and 2.2% (95%CI: 0.019-0.025) were men. Incidence of ADRs in pediatric (0–18 years), adult (19–60 years) and geriatric (>60 years) groups was 1.2 (95%CI: 0.007-0.017), 3.1% (95%CI: 0.027-0.035) and 2.2% (95%CI: 0.017-0.027), respectively. The majority of the ADR reports was from the Department of Internal Medicine (32.03%), followed by the Coronary Care Unit (18.63%) as presented in Table **1**. The most frequent reports were due to anti-infective agents (34.08%), followed by central nervous system agents (12.69%) and antineoplastic agents (12.47%). The drug class involved in the ADRs is shown in Table **2**.

Rifampin was the most frequent anti-infective agent associated with the suspected ADRs such as nausea, vomiting, abdominal pain, urticaria, hepatic enzyme increased, pancytopenia, and stevens johnson syndrome (Table **3**). The gastrointestinal system was the most frequently affected system (21.90% of all reactions), followed by the skin and appendages system (18.98%). The classification of the ADRs by system-organ class is demonstrated in Table **4**. The causality assessment of ADRs revealed that 0.66% of the cases were detected as highly probable, 37.58% as probable and 61.76% as possible reactions. Seventy two (23.53%) of the ADRs were classified as serious according to the WHO definition and resulted in prolonged hospital stay, persistent disability or death. Table **5** shows the drugs in reports with a serious reaction.

Twenty-five (8.17%) of the ADRs were classified as preventable according to the scale developed by Schumock *et al.* [13]. Table **6** shows the drugs reported in a preventable reaction.

DISCUSSION

In March 2006, our hospital's pharmacovigilance unit was established to educate health care professionals regarding ADRs, promote the reporting of ADRs and monitor the safety of drug use in the patients [9]. The under-reporting of ADRs was observed in our previous study. It was presumed that physicians and nurses' unawareness of ADR monitoring and reporting mechanism and the extensive workload of physicians and nurses could be two important reasons for under-reporting. We continued our educational program for health care professionals as lectures, morning report discussions, ADRs bulletin [10], and added ADRs review to the daily responsibilities of clinical pharmacist residents. The number of ADRs reported to our unit was increased by 36.61% over the last two years that shows our programs could be useful to increase ADR reporting. Sullivan *et al.* showed that pharmacy student participation in

Table 1. Wards Associated with Reported ADRs

Incidence (95% CI)	Percentage	Number of ADRs	Ward
3.5% (0.028-0.042)	32.03	98	Internal Medicine
8.4% (0.063-0.105)	18.63	57	Cardiac Care Unit
1.8% (0.013-0.023)	13.72	42	Oncology
14.9% (0.103-0.195)	11.11	34	Intensive Care Unit
1.8% (0.012-0.024)	10.13	31	Tuberculosis
0.8% (0.004-0.012)	6.86	21	Surgery
6.1% (0.028-0.094)	3.92	12	Transplant
0.7% (0.003-0.011)	3.59	11	Pediatric

Table 2. Drug Class Implicated in ADRs

Percentage	Number of ADRs	Drug Class
34.08	153	Anti-infective agents
12.69	57	Central nervous system agents
12.47	56	Antineoplastic agents
7.80	35	Cardiovascular drugs
6.90	31	Autonomic drugs
6.24	28	Miscellaneous therapeutic agents
5.34	24	Blood formation and coagulation
4.45	20	Hormones and synthetic substitutes
3.34	15	Electrolytic, caloric, and water balance
2.67	12	Gastrointestinal drugs
1.78	8	Local anesthetics
1.11	5	Antitussives, expectorants, and mucolytic agents Agents
0.44	2	Antihistamine drugs
0.44	2	Vitamins
0.22	1	Eye, ear, nose, and throat preparations

the ADR reporting significantly increases the number of ADRs documented [6]. In other study, quality and quantity of spontaneous reporting ADRs were improved by economic incentives and educational activities [14].

Table 3. Anti-Infective Agents Implicated in ADRs

Percentage	Number of ADRs	Anti-Infective Agents
18.67	28	Rifampin
16.67	25	Isoniazid
12.67	19	Pyrazinamide
10.00	15	Ceftriaxone
10.00	15	Vancomycine
6.00	9	Clindamycin
4.00	6	Co-trimoxazole
4.00	6	Clarithromycine
2.67	4	Ethambutol
2.67	4	Azithromycin
2.67	4	Ofloxacin
1.33	2	Ciprofloxacin
0.67	1	Erythromycin
0.67	1	Metronidazole
0.67	1	Amikacin
0.67	1	Bleomycin
0.67	1	Chloramphenicol
0.67	1	Co-amoxiclav
0.67	1	Linzolid
0.67	1	Nitrofurantoin
0.67	1	Penicillin
0.67	1	Cefalexin
0.67	1	Meropenem
0.67	1	Piperacillin
0.67	1	Valgancyclovir

Table 4. Organ Systems Associated with ADRs

Percentage	Number of ADRs	System Associated with ADRs
21.90	90	Gastro-intestinal system
18.98	78	Skin and appendages
11.92	49	Central & peripheral nervous system
6.33	26	Platelet, bleeding & clotting
6.08	25	Liver and biliary system
6.08	25	Vascular (extracardiac)
6.08	25	Metabolic and nutritional
4.38	18	Respiratory system
3.16	13	Body as a whole-general
3.16	13	Psychiatric
1.95	8	Vision
1.46	6	Cardiovascular
1.46	6	Urinary system
1.46	6	Red blood cell
1.46	6	White cell and RES
1.22	5	Musculo- skeletal system
0.97	4	Application site
0.73	3	Heart rate and rhythm
0.73	3	Resistance mechanism
0.24	1	Hearing and vestibular
0.24	1	Reproductive

Incidences of ARDs have a high variability among different studies. Lazaro *et al*. in a meta-analysis reported the overall incidence of 6.7% for serious ADRs in US hospitals

Table 5. Drugs Reported in Serious ADRs by Frequency of Times Reported and Type of Reaction

Drugs	Times Reported	Type of Reaction
Rifampin	11	Hepatic enzyme increased
	1	Pancytopenia
	1	Stevens Johnson Syndrome
	1	Urticaria, Pruritus
Isoniazid	7	Hepatic enzyme increased
Heparin	4	Thrombocytopenia
	1	Haematuria, Gastric ulcer hemorrhagic, Ecchymosis
Ceftriaxone	3	Allergic reaction
	1	Stevens Johnson Syndrome
Cyclosporin	2	Leucopenia, Hepatic enzyme increased
	1	Nephropathy toxic, Hepatic enzyme increased
	1	Vomiting, Nausea
Vancomycin	1	Pruritus, Urticaria
	1	Renal failure
	1	Thrombocytopenia
Carboplatin	1	Pancytopenia
	1	Haemoglobin decreased, Thrombocytopenia
	1	Leucopenia, Anaemia
Anti-thymocyte globulin	3	Thrombocytopenia
Mycophenolate mofetil	3	Leucopenia, Neutropenia
Ranitidine	1	Dyspnoea, Pruritus
	1	Thrombocytopenia
Gemcitabine	2	Dyspnoea, Vertigo
Insulin Regular	2	Hypoglycaemia
Amiodarone	1	Thrombocytopenia, Anaemia
Betaxolol	1	Dyspnoea, Bronchospasm
Carbamazepine	1	Dyspnoea, Dermatitis
Clindamycin	1	Diarrhoea
Clopidogrel	1	Petechiae, Ecchymosis
Co-amoxiclave	1	Urticaria, Hypotension
Co-trimoxazole	1	Anaemia
Digoxin	1	Thrombocytopenia
Cyclophosphamide	1	Pulmonary oedema, Oedema peripheral
Enoxaparin	1	Thrombocytopenia
Hyoscine	1	Dyspnoea
Insulin NPH	1	Hypoglycaemia
Morphine sulfate	1	Convulsion
Propranolol	1	Bronchospasm, Dyspnoea, Consciousness decreased
Chloramphenicol	1	Vision blurred, Neuropathy pripheral
Allopurinol	1	Stevens Johnson Syndrome
Pyrazinamid	1	BUN increased
Sodium valproate	1	Thrombocytopenia
Docetaxel	1	Angioedema, Urticaria
Warfarin	1	Pulmonary haemorrhage

[15] which is higher than our result. This variability could be explained by the different methods of detection of ADRs, as well as by the different wards where the patients are studied. It has been shown that the frequency of adverse drug events detected by spontaneous reporting is significantly lower than that assessed by patient monitoring. Besides higher frequencies of adverse drug events have been reported in studies performed on internal medicine wards or geriatric wards than in studies performed on general medicine wards [16].

The value of our study is to identify the pattern of ADRs in a specialized hospital. The rate and pattern of ADRs vary

Table 6. Drugs Reported in Preventable ADRs by Frequency of Times Reported and Type of Reaction

Drugs	Times Reported	Type of Reaction
Insulin	3	Hypoglycaemia
Ceftriaxone	2	Pruritus
	1	Nausea
Theophylline	2	Tremor
Warfarin	1	Bruise
	1	Pulmonary haemorrhage
Ceftriaxone	1	Stevens Johnson Syndrome
Co-amoxiclave	1	Hypotension, Urticaria
Co-trimoxazole	1	Nausea, Abdominal pain
Heparin	1	Gastric ulcer hemorrhagic, Haematuria, Ecchymosis
Rituximab	1	Chest pressure sensation of
Omeprazole	1	Abdominal pain
Oxazepam	1	Memory impairment, Vertigo
Propranolol	1	Dyspnoea, Bronchospasm, Consciousness decreased
Pyrazinamid	1	BUN increased
Salmetrol inhaler	1	Heart throbbing
Salmeterol/Fluticasone	1	Moniliasis oral
Vancomycin	1	Pruritus, Urticaria
ATG	1	Thrombocytopenia
Betaxolol	1	Bronchospasm, Dyspnoea
Carboplatin	1	Tingling skin, Neuropathy Pripheral

among different hospitals because of differences in the local population characteristics and hospital major specialties [17]. In our study, the most frequent ADRs were related to antibiotics that are high consumption and great expenditure drugs in our hospital. While in other studies, different drug classes such as antineoplastic, cardiovascular, anticoagulant, nonsteroidal anti-inflammatory, hypoglycemic, and anti-infective agents have been most frequently associated with ADRs [8, 18-22].

Review of ADRs reported with high usage items in a hospital is useful in the promotion of rational drug use [8] and planning of new studies to discover the problems. Our previous study has shown ceftriaxone as the most frequent anti-infective agent associated with the suspected ADRs [9]. But educating health care professionals about appropriate usage of ceftriaxone (indication, dosage, preparation, administration and patient care) changed drug utilization pattern and consequently ADR pattern. In present study, rifampin has been replaced as the most frequent anti-infective agent associated with the suspected ADRs. It could be rational because our hospital is a tuberculosis referral center and rifampin has a high usage. On the other hand, the rate of hepatotoxicity induced by anti-TB drugs is high in our hospital [23]. Several factors have been implicated in the development of hepatotoxicity because of anti-TB treatment. Drug formulation, undernutrition and plasma levels of anti-TB drugs [24] should be investigated as important factors in our patients.

Gastro-intestinal system was the organ system which was most commonly affected by ADRs. Skin and appendages systems have usually been reported as the most affected organ system by ADRs [9, 25, 26]. This reveals our educations have been successful to change the reporters' attentions to the patient's symptoms instead of the merely visible ADRs. Pathological and laboratory data which are objective markers of ADRs should be considered by more education [9]. In addition, the pattern of ADRs may be influenced by the profile of drug prescriptions and the wide use of anti-TB drugs may also partially explain why gastro-intestinal system was the organ system most commonly affected.

In this study, 8.17% of ADRs were preventable. Higher rate of preventable ADRs in other studies (the wide range of 30-70%) [27, 28] and 14.13% reduction in preventable ADRs in our hospital (22.30% preventable ADRs in previous study) suggest that our education programs and preventive strategies have been effective.

Serious ADRs have been increased from 16.70% (in previous study) to 23.53% (in this study). Perhaps our strategy has been successful to detect serious ADRs more efficiently. The assessment of whether an ADR has increased the length of stay or caused persistent disability or

death can be difficult because individual patient factors such as the nature and severity of the underlying disease, and social factors may also contribute to the length of stay [17]. We considered these factors and involved the clinical team for the assessments. We also sent a notice for health care professionals and warned mandatory reporting of serious ADRs according to the Ministry of Health regulations. Increased hepatic enzyme induced by rifampin was the most frequently reported serious ADR, as discussed above should be considered for more evaluations.

During the study, reported ADRs from our center to the national ADR monitoring centre at the Ministry of Health leaded to the batch recalls of two pharmaceutical products. While ADRs reporting remains one of the most common methods of post-marketing drug safety surveillance, promoting ADR reporting improves post-marketing control on pharmaceutical products.

In conclusion, the pattern of ADRs in our hospital which is a specialized hospital with specific drug usage pattern is different from the studies conducted in other hospital settings. Dissemination of our experiences e.g. addition of ADRs review to the daily responsibilities of clinical pharmacist residents helps to improve the quality of patient care by ensuring safer use of drugs. We are planning to design a multicenter study to understand the ADRs pattern in our population.

CONFLICT OF INTEREST

There is no conflict of interest to be declared.

ACKNOWLEDGEMENTS

We would like to thank all healthcare professionals at the Masih Daneshvari Hospital and specially Nahid Shahsavari, Dr. Maryam Karimi, Dr. Maryam habibi and Farzaneh Ahmadi for their helpful assistance on data entry and analysis.

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?

REFERENCES

[1] ASHP guidelines on adverse drug reaction monitoring and reporting. American Society of Hospital Pharmacy. Am J Health Syst Pharm 1995; 52(4): 417-9.

[2] Seidl LG, Thornton GF, Cluff LE. Epidemiological studies of adverse drug reactions. Am J Public Health 1965; 55: 1170-5.

[3] Smith JW, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactions. V- Clinical factors influencing susceptibility. Ann Intern Medicine 1966; 65(4): 629-40.

[4] Hurwitz N, Wade OL. Intensive hospital monitoring of adverse reactions to drugs. BMJ 1969; 1(5643): 531-6.

[5] Ogilvie RI, Ruedy J. Adverse drug reactions during hospitalisation. Can Med Assoc J 1967; 97(24): 1450-7.

[6] Sullivan KM, Spooner LM. Adverse-drug-reaction reporting by pharmacy students in a teaching hospital. Am J Health Syst Pharm 2008; 65(12): 1177-9.

[7] Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998; 45(3): 301-8.

[8] Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res 2006; 54(3): 226-33.

[9] Baniasadi S, Fahimi F, Shalviri G. Developing an adverse drug reaction reporting system at a teaching hospital. Basic Clin Pharmacol Toxicol 2008; 102(4): 408-11.

[10] Baniasadi S, Fahimi F. Namdar R. Development of an adverse drug reaction bulletin in a teaching hospital. Formulary 2009; 44(11): 333-35.

[11] Uppsala Monitoring Centre. Adverse Reaction Terminology. World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, 2003.

[12] Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30(2): 239-45.

[13] Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992; 27(6): 538.

[14] Pedrós C, Vallano A, Cereza G, *et al*. An intervention to improve spontaneous adverse drug reaction reporting by hospital physicians: a time series analysis in Spain. Drug Saf 2009; 32(1): 77-83.

[15] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998 ;279(15): 1200-5.

[16] Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007; 30(5):379-407.

[17] Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009; 4(2): 4439.

[18] Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. Int J Qual Health Care 2003; 15 Suppl. 1: i49-59.

[19] Pirmohamed M, James S, Meakin S, *et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329(7456): 15-9.

[20] Camargo AL, Cardoso Ferreira MB, Heineck I. Adverse drug reactions: a cohort study in internal medicine units at a University hospital. Eur J Clin Pharmacol 2006; 62(2): 143-9.

[21] Schneeweiss S, Göttler M, Hasford J, *et al*. First results from an intensified monitoring system to estimate drug-related hospital admissions. Br J Clin Pharmacol 2001; 52(2):196-200.

[22] Suh DC, Woodall BS, Shin SK, *et al*. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother 2000; 34(12): 1373-9.

[23] Baniasadi S, Eftekhari P, Tabarsi P, *et al*. Protective effect of N-acetylcysteine on antituberculosis drug-induced hepatotoxicity. Eur J Gastroenterol Hepatol 2010; 22(10): 1235-8.

[24] Fahimi F, Kobarfard F, Tabarsi P, Hemmati S, Salamzadeh J, Baniasadi S. Isoniazid blood levels in patients with pulmonary tuberculosis at a tuberculosis referral center. Chemotherapy 2011; 57(1): 7-11.

[25] Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. Am J Health Syst Pharm 2003; 60(17): 1750-9.

[26] Murphy BM, Frigo LC. Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. Hosp Pharm 1993; 28(12): 1199-204, 1240.

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

[28] Ducharme MM, Boothby LA. Analysis of adverse drug reactions for preventability. Int J Clin Pract 2007; 61(1): 157-61.

Received: July 19, 2011 Revised: October 7, 2011 Accepted: October 10, 2011