

ORIGINAL REPORT

Adverse drug reactions in patients in an Iranian department of internal medicine[†]

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SUMMARY

Purpose Adverse drug reactions (ADRs) are a major cause of hospital admission and inpatient morbidity. The department of internal medicine is not an exception to this issue. This study was performed to determine the nature and frequency of ADRs in an internal medicine ward in Iran.

Methods This survey was a prospective observational study based on admissions of 400 patients to the internal medicine ward over a 15-week period. Patients were intensively followed in order to assess any ADR as a cause of admission or occurring during hospitalization. Any suspicious ADR was confirmed by a pharmacist/pharmacologist.

Results There were 47 patients of 400 patients (11.75%) that experienced at least one ADR. ADR leading to the admission was seen in seven cases (1.75%) and in 40 (10%) it occurred during hospitalization. ADRs were identified as preventable reactions in 50% of cases and as predictable in 94.3%. The severity of 18.6% of the ADRs was identified as mild, 62.9% as moderate, 14.3% as severe and 4.3% as lethal. Gastrointestinal system disorders (44.3%) represented the most frequent ADRs. The therapeutic groups that most commonly associated with suspected ADRs were antineoplastic, immunosuppressive and medicines used in palliative care (54.8%).

Conclusions ADRs are common among hospitalized patients in department of internal medicine and can be severe and even lethal. Since most ADRs occurred during hospitalization in studied patients and half of them were preventable, prevention strategies should be considered in hospitals. Also, our findings confirmed the role of hospital pharmacists in the reducing ADRs. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — adverse drug reaction; internal medicine; adult

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INTRODUCTION

The WHO's definition of an adverse drug reaction (ADR), which has been in use for about 30 years, is 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function'.¹ The most ADRs occur in anyone, known as *Augmented* reactions or type A and include side effects and drug interaction. Others

occur in susceptible patients, known as *Bizarre* reactions or type B and include intolerance, allergies or pseudo allergic reaction.^{1,2} However ADRs are believed to constitute an important health care problem,^{3–5} because they result in a considerable part of medical expenses^{6,7} and contribute to a high mortality and morbidity.^{8,9} Lazarou *et al.* estimated that ADRs could constitute the fourth to the sixth leading cause of death in the United States.¹⁰ However, studies have shown that almost half of the ADRs could be avoidable with greater prescription care.^{5,9} Thus, the safety of drug therapy is an important subject of medicine.¹¹ The literature related to the frequency of ADRs resulting in hospital admission and ADRs in already admitted patients reports variable

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ranges. For example, frequency of ADRs in children is less than adults in the reported literature^{11,12} or in geriatric department, there is a higher incidence of drug related problems.^{9,13} ADRs were shown in up to 20% of patients during hospitalization⁸ and ADR related admissions was 3–11% of hospital admissions in internal medicine.^{3,4,7,8} Fattinger *et al.* conducted an analysis on 4331 hospitalizations in two Swiss departments of internal medicine and found that clinically relevant ADRs occurred in 11% of all hospitalizations.³ Incidence of fatal ADRs in the divisions of internal medicine of three teaching hospitals in Switzerland was 0.054%.¹⁴ The overall incidence of ADRs with all severities in both patients admitted to the hospital due to an ADR (ADRad), and those experience an ADR while in the hospital (ADRin), was 15.1% of hospital patients.^{10,11} Several characteristics have been suggested as risk factors for the development of ADRs including advanced age, female gender, multiple drug therapy, current disease, history of previous ADR, duration of hospital stay, route of drug administration and duration of therapy.²

Since there are few published works from Iran exploring the nature and possible cause of ADRs in the internal medicine department, we therefore took the initiative to study prospectively all patients admitted to a department of internal medicine in a general hospital in Iran, in order to determine the nature and frequency of ADRs as a cause for admission, or when occurring after admission. We also identified the drugs involved in the ADRs and determined the predisposing risk factors.

METHODS

This prospective observational study was conducted in the internal medicine department of the general university hospital of Mostafa Khomeini in Tehran, Iran. This hospital is one of the main referral hospitals in Tehran, Iran. The internal medicine ward has 35 beds, admitting patients from a wide range of internal medicine diseases, including patients with malignancy.

This study was performed from 5 April to 21 July, 2004. All patients admitted to internal medicine ward over the period of the study were considered for inclusion. The exclusion criteria were as follows: hospitalization period less than 24 hours, drugs taken less or more than the dose required therapeutic failure (errors in administration and non-compliance). Each patient was included in study once and patients who did not consume any drugs were omitted. According to our mentioned exclusion criteria, among the 435 patients screened, 400 were eligible for the study. The diagnostic profile of 400 patients admitted to this ward during the study is shown in Table 1.

Table 1. Diagnostic categories at admission in 400 consecutive patients hospitalized over 15-week period

Diagnostic categories	Frequency (% diagnosis at admission)
Cardiovascular disorders	84 (21%)
Infective disorders	43 (10.75%)
Rheumatologic disorders	17 (4.25%)
Nephrology disorders	27 (6.75%)
Neurology disorders	64 (16%)
Gastrointestinal disorders	54 (13.5%)
Hematological disorders and cancer	57 (14.25%)
Pulmonary disorders	30 (7.5%)
Endocrine disorders	24 (6%)

The study protocol was approved by ethics board of the Tehran University of Medical Sciences and from all eligible patients an informed consent was obtained. Two specific questionnaires for data recording were used. The first questionnaire included a complete interview directed to any patient admitted to the internal medicine ward. The patients included were monitored by the same investigator during their entire stay in the internal medicine ward to ascertain a final diagnosis of an ADR. All the patients admitted during the study period were followed up daily until discharge in order to ascertain the final diagnosis and to estimate the frequency of ADRs occurring during hospitalization. If the investigator suspected an ADR, a clinical pharmacologist/pharmacist and an additional clinician determined whether the reported reaction could be an ADR.

The second questionnaire was specific to patients who developed an ADR during their stay in the ward containing all the information necessary for analysis of ADR. Information related to the ADR was then gathered directly from the patients, the medical records including current symptoms, used drugs, medical investigation results and the tests in this questionnaire. The questionnaire included all suspected drugs developing an ADR (according to the WHO classification),¹⁵ route of administration, severity of complication, history of allergy and drug reaction(s) in patients and their family, clinical manifestations/reactions (usually more than one per report) of ADR (according to the classification of Adverse Reaction Terminology (ART) of the WHO ADR Monitoring Register in Uppsala (WHO-ART) into systemic organ classes)¹⁶ and management of drug reaction. We found out whether the effect could be due to a medicine. If the patient was taking several medicines, the problem was to distinguish which, if any, was causative. This problem was complex, because some of the patient's complaints might be due to other diseases or to one or more of the drugs. We used WHO Probability Scale for evaluation of this causality relationship between the

Table 2. Assignment of causality of adverse drug reaction

<i>Certain (Definitive)</i> —Consistent temporal association, including clinical course following withdrawal of drug and, where appropriate rechallenge
<i>Probable</i> —Consistent temporal association but not confirmed by rechallenge
<i>Possible</i> —Likely association but could be explained by another disease or drug
<i>Unlikely</i> —Temporal relationship to drug administration not consistent with causality
<i>Conditional</i> —Lack of data necessary for proper assessment but more data being examined
<i>Unassessable</i> —Lack of data necessary for proper assessment

ADR and the suspected drug therapy case-by-case (Table 2).^{1,2} List of questions used to assess the preventability of an ADR, adapted from Schumock and Thornton. Answering 'yes' to one, or more of the questions suggested that an ADR might have been preventable.¹⁷

A reactions profile was made by calculating the number of reports of each system-organ class of reaction as a percentage of all the reports. Severity was classified into four categories according to this scheme: fatal, severe (directly life-threatening and/or >1 month in duration, associated with organ system dysfunction, reduced life expectancy), moderate (some but not all of the mild criteria and none of the severe criteria) and mild (uncomplicated primary disease, no treatment required, and drug discontinuation not necessary).^{2,18} Also predictability of reactions were determined according to the definition; predictable reactions including pharmacologic side effect, secondary pharmacologic side effect, drug toxicity, and drug-drug interactions and unpredictable ones including pseudoallergic, idiosyncratic and intolerance.²

Statistical analysis of the results was performed. The data were analyzed using the Statistical Package for the Social Science (SPSS) for windows version 11.5 (SPSS Inc., Chicago, IL, USA). *t* test and χ^2 were used to detect the differences between groups. A significant level of 0.05 was selected for all tests. The 95% confidence intervals (95%CI) for frequencies reported were determined using CIs for a proportion.

RESULTS

General characteristics of the whole population

During the study period, of 400 admissions eligible for our study. 50.8% of the patients were male. Less than 15% of the patients were under the age of 40 and about

78% of patients were between 40 and 79 years old. Mean age was 60.41 (SD = 16.97 years; range 13–91 years). The age and anthropometric characteristics at admission to hospital were similar in both sexes. The overall population characteristics are given in Table 3. Acute ischemic heart disease (16%), malignancy (15.5%) and cerebral vascular attack (9.9%) were the most common reasons for hospital admission, while, 1.75% was thought to be due to an ADR. The observational period comprises 3276 patient-days. The median duration of hospital stay was 7 days (interquartile range 5–10 days). Aspirin (belonging to analgesics/anti inflammatory agents) was the most frequently used medicine. Drugs were mostly taken as tablets and were mainly administered orally. The mean number of prescribed drugs taken at hospital admission was 6.12 (SD = 3.41 numbers; range 1–15 numbers). Duration of hospital stay was correlated with age ($p < 0.001$) and number of drug intake (duration = $4.47 \pm 0.61 \times$ number of drugs, $r = 0.46$, $p < 0.001$); the older the subjects were the longer they stayed at hospital and the longer the length of hospitalizations, the more drugs they took. In addition, the number of drug intake was correlated with age ($p < 0.001$) (by increasing the age the number of drugs taken increased) and history of ADRs were correlated with patients age (ADRs increased by aging) ($p = 0.02$).

Twenty five per cent (100 cases) of 400 hospitalized patients had history of ADR and the commonest drug used was aspirin the most common reaction was abdominal pain respectively.

Adverse drug reactions

Forty seven of the 400 patients (11.75%) had significant adverse drug reactions: in 7 (1.75%) the ADR caused admission to the hospital, and in 40 (10%)

Table 3. Characteristics of the overall study population

	Total	Men	Women
Number	400	203	197
Mean age in years (range)	60.41 (13–91)	62.08 (17–90)	58.68 (13–91)
Mean duration of stay in days (range)	8.19 (2–30)	7.97 (2–30)	8.42 (2–30)
Mean number of drug classes (range)	6.12 (1–15)	5.72 (1–15)	6.52 (1–15)

Table 4. Characteristics of patients admitted for ADR (ADRad), with ADR in hospital (ADRin) and without ADR (no ADR)

	No ADR	ADRad	ADRin	All ADRs
Number	353	7	40	47
Men/women	183/170	2/5	18/22	20/27
Mean age in years (range)	61.22 (13–91)	63.14 (44–79)	53.40 (28–87)	54.29 (28–80)
Mean number of drug classes (range)	6.10 (1–15)	7.29 (3–15)	6.00 (1–14)	6.19 (1–15)

it occurred during hospitalization. The mean age of patients with ADR was 54.29 ± 2.08 (SEM) years. The analysis of the sample showed that the distribution by sex was similar to that of the overall population. We had 70 reactions in 47 patients; the number of ADRs per case report was calculated approximately 1.5 (range 1–4). Because some patients had several reactions simultaneously or successively, the total number of reactions is greater than the total number of patients having the reactions. A total of 42.6% of reports involved males and 57.4% females. Demographic information of the patients is summarized in Table 4. ADR was not reported during hospitalization of patients admitted with ADR. All the patients admitted because of ADRs (seven cases) and 36 out of 40 (90%) of those whose ADR occurred during hospitalization had type A reactions (91.48% totally), that is related to the drugs' pharmacological properties. None of the ADRs were new, that is unlabelled (not in the summary of product characteristics) at the time of the reaction. Figure 1 summarizes the suspected ADRs detected during period of study according to the organ-system affected.

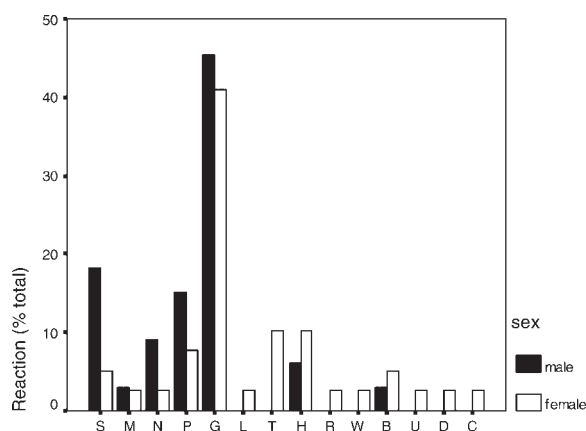


Figure 1. Profiles of the proportion of the total number of suspected adverse drug reactions for each of the major organ-systems distributed by sex. S, skin and appendages disorders; M, musculo-skeletal system disorders; N, central and peripheral nervous system disorders; P, psychiatric disorders; G, gastro-intestinal system disorders; L, liver and biliary system disorders; T, metabolic and nutritional disorders; H, heart rate and rhythm disorders; R, red blood cell disorders; W, white cell and RES disorders; B, platelet, bleeding and clotting disorders; U, urinary system disorders; D, body as a whole—general disorders; C, resistance mechanism disorders

As shown in this figure, gastrointestinal system disorders (44.3%) represented the most frequent ADRs, followed by psychiatric disorders, skin and appendage disorders (11.4% each) and heart rate and rhythm disorders (8.6%).

The most common clinical manifestations of ADR were nausea and vomiting (32.2%), abdominal pain (8.6%) and tachycardia (5.4%). Regarding probability of the 70 ADRs, according to WHO causality terms, 27.1% of ADRs were considered definitive, 24.3% probable and 48.6% possible. The severity of 18.6% of the reactions was identified as mild, 62.9% as moderate, 14.3% as severe and 4.3% as lethal. Table 5 shows details of severe and fatal ADRs. Among 70 reactions, 35 cases (50%) were identified as preventable and 66 (94.3%) were predictable. ADRs increased by increasing age ($p = 0.008$) while no correlation was found between gender, length of stay and number of drugs taken on the one hand and the occurrence of ADRs on the other hand. The mean number of pharmaceutical formulations consumed during the study period for suspected ADR was 6.19 ± 0.45 per patients, while the number of consumed by patients who did not suffer from ADR was 6.10 ± 0.18 .

Among 201 pharmacological formulations suspected, 37 drugs alone or in combination caused ADR as shown in Figure 2. The therapeutic groups most commonly associated with suspected ADRs were antineoplastics, immunosuppressive and medicines used in palliative care (54.8%), psychotherapeutic medicines (8.2%), analgesics, NSAIDs (non-steroidal anti-inflammatory medicines) and DMARDs (disease modifying agents used in rheumatoid disorders) (5.5%), anti-infective medicines (5.5%), hormones, other endocrine medicines and contraceptives (5.5%) and anti-allergic and medicines used in anaphylaxis (5.5%). The most common ADR-related pharmaceutical formulation was fluorouracil (5FU), observed in 15 cases, followed by cisplatin (related to 14 cases of suspected ADR) and epirubicin (7 cases).

DISCUSSION

ADRs represent an important proportion of the disease burden in the general population. The prevalence and

Table 5. Details of adverse drug reactions classified as severe and fatal

Age (years)	Sex	Indication	Suspected drugs	ADR effects	Causality	Severity
52	Male	Headache	Tramadole Hydrochloride	Hypotension	Certain	Severe
79	Male	Lung cancer	5-fluorouracil	Leukopenia gastroenteritis	Certain	Severe
32	Female	Intravenous pyelography	Omnipaque	Anaphylaxis	Certain	Severe
70	Female	Arthritis rheumatoid	Methotrexate	Pancytopenia; infective diarrhea; septic shock; Disseminated intravascular coagulopathy	Certain	Fatal
80	Female	Diabetes mellitus	Glibenclamide	Hypoglycemia	Certain	Severe
55	Female	Hyperlipidemia	Gemfibrozil; Simvastatin	Myopathy	Possible	Severe
75	Female	Diabetes mellitus	Glibenclamide	Hypoglycemia	Certain	Severe
44	Female	Tuberculosis	Rifampin; Isoniazid	Hepatitis; thrombocytopenia	Possible	Severe
67	Female	Diabetes mellitus	Human insulin NPH	Hypoglycemia	Certain	Severe
69	Male	Lung cancer	5-fluorouracil	Myocardial infarction; ventricular fibrillation; cardiac arrest	Probable	Fatal

importance of this phenomenon obviously varies in the different health care systems.^{5,19}

The present study assessed ADRs observed in an internal medicine department at a teaching hospital in Iran. It was predictable that the most patients comprised the elderly (mean age: 60.4 ± 0.84) because of the study setting which was in accordance with the study performed by Wasserfallen *et al.* in a university hospital in Switzerland (mean age: 61.4 with range 16–93).⁵ The most common causes of admission in this study included ischemic heart diseases and malignancies which are explainable by the mean age of the studied group and it is comparable to the study by Chan *et al.* study.²⁰ In the present study, there was the predominance of patients

aged 60 years and older. Furthermore, the duration of hospital stay was longer in older patients and they also took more drugs significantly. However, no correlation was found between length of stay and number of drugs taken on the one hand and the occurrence of ADRs on the other hand in our study. In the study by Lepori *et al.* age stratification revealed that with increasing of age, the risk for ADRs increased as well and that the patients who were sicker, were consuming more drugs and had longer hospital stays.²¹ Also follow-up length, number of drugs used before hospitalization and number of drugs prescribed during hospitalization were all independent risk factors for the development of an ADR in internal medicine units at a university hospital in Brazil.²² The mean number of drugs administered per day (6.12) and the duration of cohort stay (8.19) was similar to that recorded by Fattinger *et al.*³

It is of no surprise that aspirin is the most commonly used drug, since the most common causes of patients admission was ischemic heart diseases and aspirin is generally recommended because of its efficacy in prevention of platelet aggregation.

The prevalence of at least one ADR in our study was 11.75%, which is comparable to values reported in the literature. A review of Pirmohamed *et al.* reported ADR frequencies between 10 and 20% in different groups of inpatients.²³ Moore *et al.* reported that in 21 of 329 hospitalized patients (6.6%) end up with significant ADRs during the hospital stay in an internal medicine department at a general hospital in France.⁷ However the rate of ADR in our study is lower than the study performed by Lagnaoui *et al.* on 444 patients in which 26.1% of all hospitalized patients in a department of internal medicine experienced at least one ADR (156 ADRs in 116 patients).⁸

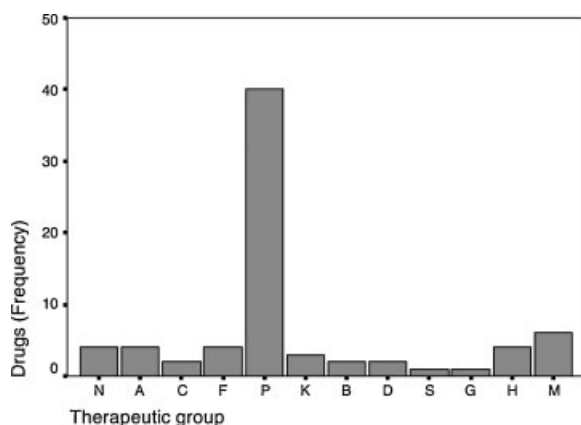


Figure 2. Profiles of the proportion of the total number of suspected adverse drug reactions for each therapeutic group. N, analgesics, nsaims and dmards; A, anti-allergic and medicines used in anaphylaxis; C, antic-onvulsants; F, anti-infective medicines; P, antineoplastic, immunosuppressive and medicines in palliative; K, antiparkinsonism medicines; B, medicines affecting blood; D, cardiovascular medicines; S, diagnostic agents; G, gastro-intestinal medicines; H, hormones and other endocrine medicines; M, psychotherapeutic medicines

In our study, 1.75% of the admissions were caused by ADRs, while this rate was relatively different in other studies. In a national prospective study in 62 medical departments of 33 hospitals in Sweden, 3.2% of the admissions were caused by ADRs,⁴ and in Australia an incidence of between 2.4 and 3.6% was found.²⁴ In a current study at an internal medicine ward in Sweden, this rate was reported 11%.²⁵ The rate of ADR causing hospitalization in department of internal medicine was reported 3.03,⁷ 7.2⁸ and 6.6%²⁶ in French studies. The interview of the 56 geriatric patients in Belgium indicated that 20% of them were admitted to the hospital because of an ADR.¹³

In almost studies on ADR, approximately 90% of reactions were type A; 91% in the study by Mjörndal *et al.*⁴ 89% in the study by Euler M *et al.*²⁵ and 92.5% in the study by Tribino G *et al.*²⁷ In the other studies, it was revealed that the majority of ADRs were type A reactions.^{21,22}

Regarding severity of reactions, the most ADRs were moderate. Mild, severe and lethal ADRs have fewer frequencies, respectively, like previous studies carried out in Iran.^{18,28} This finding is also consistent with the results of the study by Tribingo *et al.* performed at a level 3 hospital internal medicine ward in Colombia, where moderate reactions were 81.3%.²⁷ They also found 74.3% of ADRs were probable while the most ADRs were possible (62.5%) in a Brazilian study in internal medicine units at a university hospital.²² This finding is in accordance with ours; 48.6% of reactions were possible in our study. However the causal probability of ADRs was evaluated with the Naranjo algorithm in two studies mentioned above while we employed WHO probability scale for this evaluation. The relationship between the medication and the reaction was possible in most cases (74.7%) in the study by Mjörndal *et al.* in Sweden. They also used WHO criteria for their judgements.⁴

Consequently, the similarities and differences between data of our study and other studies could be due to: (1) different patient population, (2) different classes of drugs used in different studies, (3) different definitions used for ADRs, (4) diverse methods of detecting ADRs, (5) the number of drugs used and (6) lack of participation and/or involvement of the medical staff in collecting and reporting ADRs.^{28,29} The most frequently reported reactions by organ-systems in our study (gastrointestinal reactions) coincided with some other studies.^{5,21–23,30,31} The relative large number of psychiatric disorders due to drug, suggested the susceptibility of the central nervous system in older age group (psychiatric disturbances was higher in older patients), and reflected a widespread use of drugs

especially benzodiazepines and antidepressant agents in this group of patients who suffered from cancers as chronic and life-threatening diseases. These results were similar to that obtained by Moore *et al.* in France.⁷ The noticeable use of antineoplastic drugs (67.1% of drugs associated with ADRs) was because of the large number of cancerous patients admitted in this ward. This result agreed with those obtained by other authors.^{3,5,14}

Regarding preventability, 50% ADRs were preventable in our study. This result is comparable with previous study in a department of infectious diseases in Iran which was 58.8%.²⁸ Preventability of ADR was the subject of 14 publications that revealed about 30% of all ADRs to be preventable and so avoidable. Policy-makers were suggested to invest more into ADR monitoring and preventive measures.¹⁹

Our result about percentage of predictable ADRs was similar to that obtained in an Iranian department of infectious diseases in 1996.²⁸

Certain limitations must be considered in interpreting our findings. First, duration of our study may be viewed as short period, and if the study had been performed over a longer period this would have led to greater accuracy of the estimates. On the other hand, this survey was conducted during fixed periods of the year (spring and summer) and seasonal variations in the rate of ADR-related admissions due to decrease outbreaks in certain periods of the year were overlooked. An important limitation of this study relates to generalizability of the results. These findings, which are based on hospitalized population, cannot be extrapolated to subjects living in the community.

CONCLUSION

According to our results, ADRs are common among hospitalized patients in department of internal medicine where drug-related diseases are often discussed and they can be severe and even lethal. Since most ADRs occurred during hospitalization and half of them were preventable, prevention strategies should be considered in hospitals. We conclude that a key factor that should promote recognition and reduction of ADRs is the presence of a well-established ADR reporting network. A good ADR team should include clinicians and clinical pharmacologists/pharmacists as seen in our study. This team can play very important role in identifying and managing ADRs.

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