

Prevalence of Potential Drug Interactions in an Iranian General Hospital

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The hazards of prescribing many drugs, including side-effects, drug-drug interactions and difficulties of compliance have long been recognized as particular problems when prescribing. This study estimates the rate and factors associated with potential drug-drug interactions in prescriptions from wards of An Iranian General Hospital. Data were retrieved from the pharmacy of a general hospital (200 beds) during one year period 2010. Potential drug-drug interaction were identified using a computerized drug-drug interaction database system (Prescription Analyzer 2000, Sara Rayane Co., Iran). Patients of both genders and 15 years-old or more were included in this study. Prescriptions with two or more drugs prescribed were selected during one year period 2010. Gender number of drugs and therapeutic drug classes on prescriptions were explored as associated factors to drug-drug interaction. The overall prevalence of potential drug-drug interaction was 20.3%. The risks of severe potential drug interactions were relatively high and the rate of potential drug-drug interaction was significantly higher in women (60.6%) and the patients aged over 60 years old (57.1%). The frequency of the potentially severe drug-drug interaction was 10.8% with digoxin-furosemide as the most common interacting pair (5.91%). A positive correlation was found between drug-drug interaction, patient's age, number of drugs and drugs acting on cardiovascular system. So cardiology women inpatients, age more then 60 years old, and patients prescribed digoxin and angiotensin-converting enzyme inhibitors should be closely monitored for adverse outcomes from drug-drug interaction.

Key words: General hospital, Iran, potential drug-drug interactions, moderate, severe

Adverse drug events affect millions of patients each year and are responsible for up to 5% of hospital admissions^[1,2]. They also pose an enormous financial burden, with an estimated cost of more than \$16000 per hospitalization^[3-5]. While some adverse drug events are unpredictable (such as anaphylaxis from an unrecognized allergy), many others can be anticipated and prevented. Drug-drug interactions (DDIs) are a particularly important type of adverse drug events because they are often predictable based on previous reports, clinical studies, and an understanding of pharmacologic principles^[6-13]. Some adverse drug events have life-threatening consequences and may prompt the removal of popular medications from the marketplace^[14-21].

Adverse consequences of drug interactions have been shown in various studies. The prevalence of important DDIs varied in different countries. Studies conducted in various countries report rates of potential DDIs ranging from 1 to 66^[7,8,10,14-16,22-24].

Different factors are associated with the occurrence of potential DDIs. Polypharmacy is now common, and carries a high risk of DDIs and drug-disease interactions. These may cause adverse effects, or the therapeutic effects of the combined medicines may change, with serious consequences for health. In the United States 25% of ambulatory patients taking drug combinations were at risk for clinically important interactions^[25]. A European study of 1601 ambulatory elderly patients, taking an average of seven different drugs, found that 46.0% were at risk for at least one clinically important potential DDI^[22].

Furthermore, it has been reported that about 40% of hospitalized patients had at least one potential drug-disease interaction^[26]. Also the risk of potential drug interaction is higher in old patients^[17,22,23,27]. DDIs cause 4.8% of hospitalizations attributed to drugs in the elderly^[3].

It is possible that other risk factors for potential interactions exist, and these should be identified to establish successful methods for improving prescription practices. The prevalence of DDIs and the factors associated with it is not determined in inpatients' prescriptions in Iran. So the aim of this study was to estimate the prevalence and the factors associated with potential DDI in adult inpatients' prescriptions from wards of a general hospital in Zarand, Iran.

A retrospective study was performed using data of the prescriptions held at the pharmacy of an Iranian general hospital which is supervised by Social Insurance Organization (an Iranian general insurance organization). The hospital is a 200-bed general institution including different wards (internal, pediatric, surgery, obstetrics and gynecology) which is also a referral centre for hospital care in Zarand region with an estimated population of 150 000. Patients of both genders and 15 years-old or more were included in this study. Prescriptions with two or more drugs prescribed were selected during one year period 2010. All drug groups were accepted. Only one prescription from each patient during his/her hospitalization at ward during the study period was included.

Prescriptions with one or more potential DDI were identified by using a computerized DDI database system (Prescription Analyzer 2000, Sara Rayane Co., Iran). To estimate rates, results were expressed as odds ratios. All drugs were classified with Anatomical- Therapeutic-Chemical Classification (ATC code, level one – WHO, 2004). A total of 1000 randomly selected prescriptions were analyzed. Handwritten prescriptions with two or more drugs prescribed at wards during a one-year period (2010) were analyzed for potential DDI by using the information recorded on standard prescription forms. Only one prescription from each patient during his/her hospitalization at ward during the study period was included. The prescription forms include, patient characteristics [gender, age (more than 15 years old)], the number of drugs/prescription, drug name (generic or brand), and therapeutic drug classes. This protocol was approved by the Ethics Committee of Vice Chancellor of Research, Kerman University of Medical Sciences, Kerman, Iran (K/88/47).

DDIs were sorted by clinical relevance. Drug interactions are rated mild when they are not of clinical importance, or the effect of the interaction has not yet been established. Moderate interaction can cause possible changes in the therapeutic effects, or may cause adverse effects, but can be avoided adjusting the individual drug doses. A severe DDI is defined as drug interactions which can cause potential adverse effects; individual dose adjustment is difficult in these cases. Potential DDIs is defined as the moderate and severe drug interactions^[7].

Demographic data of patients and other data of prescriptions were presented as mean± standard deviation and percentage. Student's t, χ^2 (qui square) and Fisher's exact tests were performed. Probability (P) values of 0.05 or less were considered statistically significant. The data were processed and presented using EPI info statistical program software.

From 1000 prescriptions retrieved from hospital pharmacy for data analysis, at least 418 prescriptions (41.8%) were of inpatients of male ward (p=0.039). The average age of inpatients was 58.3±20.3 years old (range 15–89 years old).

The total number of medicines prescribed to the patients was 6400 with an average of 6.4±1.3

drugs per patient. The most frequent drugs prescribed were active on the cardiovascular system (38.6%). The next most common class of drugs was active on the infections and parasitic disease (25.8%); followed by drugs addressing gastrointestinal problems (18.7%), drugs active on the musculoskeletal and joint disorders (17.2%) and, finally, drugs affecting pulmonary diseases (9.6%) (Table 1).

The overall prevalence of DDI was 20.3%, which was significantly higher for inpatients who were women ($\chi^2=9.1$, p=0.003) or patients who were 60 years old or more ($\chi^2=112.1$, p=0.0) (Table 1).

About 22 (10.8%) of drug interactions were recorded in patients who were prescribed drug combinations with severe DDIs that should be avoided (Table 2). Most of drug interactions were drugs combinations of mild type 92 (45.3%) followed by moderate type 89 (43.8%) (Table 2). Severe DDIs were recorded in patients prescribed drugs combating cardiovascular diseases (10.8%). There was a significant statistical difference between age groups for DDIs and most of DDIs were in patients who were 60 years old or more was significant ($\chi^2=177$, p=0.00).

The type of drug combinations showing DDIs are shown in Table 2. The most frequent severe drug interactions were the combination of digoxin and furosemide (5.91%) followed by the combination of angiotensin converting enzyme inhibitors (ACEIs) + potassium-sparing diuretics (1.47%). The combination of ACEIs + thiazide diuretics (13.3%) was the most frequent moderate

TABLE 1: RELATIONSHIP BETWEEN PATIENT'S AND PRESCRIPTION'S CHARACTERISTICS AND POTENTIAL DRUG-DRUG INTERACTIONS IN AN IRANIAN GENERAL HOSPITAL

Variables	Patients with at least one potential DDIs in their prescription n (%)
Gender (female)	123(60.6)
Patient age ≥ 60	116(57.1)
Cardiovascular disease	78(38.6)
Gastrointestinal disease	38(18.7)
Endocrine, and metabolic disease	33(16.3)
Pulmonary disease	20(9.6)
Infections and parasitic disease	53(25.8)
Musculoskeletal and joint disorders	35(17.2)

DDIs is drug-drug interactions. n=203

TABLE 2: POTENTIAL DRUG-DRUG INTERACTIONS IN AN IRANIAN GENERAL HOSPITAL

Interactions	Patients n (%)
Severe	
ACE inhibitors + Potassium-sparing diuretics	3(1.47)
Digoxin+ Furosemide	12(5.91)
Verapamil + Erythromycin	3(1.47)
Warfarin + Phenobarbital	2(0.98)
Potassium + Potassium-sparing diuretics	2(0.98)
Total	22(10.8)
Moderate	
ACE inhibitors + Thiazide diuretics	27(13.30)
Fluoroquinolones + Antacids	22(10.83)
NSAIDs + β blocking agents	11(5.42)
β blocking agents + Calcium channel blockers	6 (2.94)
Bronchodilators + β blocking agents	5 (2.46)
β blocking agents + α -Blockers	5(2.46)
Insulin + Antihypertensives	4(1.98)
ACE inhibitors + Low dose ASA	3(1.47)
Furosemide + ACE inhibitors	2(0.98)
Tetracyclines + Antacids	2(0.98)
Potassium + Triamtrene - H	2(0.98)
Total	89(43.8)
Mild	92(45.3)

ACE is angiotensin-converting enzyme; ASA is acetylsalicylic acid; NSAIDs is non-steroidal antiinflammatory drugs, Triamtrene- H is triamtrene+ hydrochlorothiazide. n=203

drug interactions followed by the combination of, fluoroquinolones + antacids (10.83%) and non-steroidal antiinflammatory drugs (NSAIDs) and β blocking agents (5.42%).

Various studies have shown that potential drug-drug interactions are frequent when patients receive multiple prescriptions. This is true for both ambulatory and hospitalized patients, and, in many cases, causes adverse effects and changes in therapeutic efficacies of the combined medicines, with consequent poor control of the diseases under treatment^[14,15,24]. The results of this study showed that the occurrence of potential DDI was significantly higher in women and the patients aged over 60 years old, cardiology patients and having digoxin prescribed which is comparable to other studies^[23,27].

In the present study, we found that the total frequency of potential drug-drug interactions (both severe and moderate DDIs) in prescriptions in general hospital in Zarand City was almost 59.1%, which is higher than the frequency in Europe^[22] (46.0%) , in ambulatory patients over 59 years of age in the

United States (25.0%)^[25], Thailand (49.7%)^[17] and a Brazilian teaching hospital (49.7%)^[15]. Severe DDIs were recorded in patients prescribed drugs combating cardiovascular diseases (10.8%). The frequency of severe drug interactions (10.8%) (which should be avoided) in our work, is almost comparable with some other studies the type D (very severe DDIs) frequency was 10.0% in an European study^[22]. However it is significantly higher the value recorded in north Italy (4.7%)^[29].

Digoxin and ACEIs were the most commonly prescribed drugs which showed severe and dangerous DDIs. These data are comparable with many other studies which reported that drugs with a narrow therapeutic range or low therapeutic index such as digitals and warfarin. ACEIs are more likely to be the objects for serious drug interactions, especially in elderly patients^[3,23,25,27,30]. Object drugs for moderate DDIs were ACEIs (15.75%), β blocking agents (13.3%), fluoroquinolones (12.8%) and antacids (10.8%) which is comparable to some other studies^[27,31-33].

Fluoroquinolones adverse effects and interactions can be considered as mild, moderate and severe, and their incidence is irrespective of the gender. Fluoroquinolones can interact with a variety of drugs: antacids, non-steroid antirheumatics, xanthines, warfarin, and others^[31,33].

It is possible to conclude that the high frequency of prescription of drugs with potential drug interactions is not acceptable in clinical practice; the easiest way to reduce the frequency of them is to decrease the number of medicines prescribed. Nevertheless, sometimes it is difficult to reduce the number of drugs prescribed for patients with multiple chronic conditions; therefore, to lower the frequency of potential interactions it could be necessary to make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events. It is recommended that the health professionals along with the pharmacist, has a duty to aware the nurses and the patients for the signs and risk of possible side effects.

We should declare the limitations of our study. We used administrative data. We had no direct measure of drug levels, renal function, or adherence

to medications, and the accuracy of the dispensed and used drugs. Also the data shows the possible drug interactions only in internal medicine, surgery, obstetrics and gynecology departments, however, the data did not include cardiology, intensive care units and psychiatric patients which are more prone to reveal potential DDIs^[16,28].

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