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Original Article

Drug Interactions Among Hospitalized Patients in Intensive Care Units and Infectious Ward, Hamadan, Iran

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Abstract

Background: Drug interactions (DIs) are one of the problems caused by irrational drug use and includes the effects of drug, food, or anything that changes the pharmacokinetics or pharmacodynamics of a given drug. In this regard, DI is one of the causes of morbidity and mortality in patients. However, this problem is usually predictable and hence is required to be properly managed. The aim of the present study was to assess DIs in the patients hospitalized in the intensive care units and infectious ward of Sina hospital, Hamadan, Iran.

Methods: This cross-sectional study was conducted on the medical records of 500 patients hospitalized in ICUs and infectious ward of Sina hospital in Hamadan from March 2014 to February 2015. The inclusion criterion was the presence of at least one DI in the patients hospitalized in the intensive care units (ICUs) and infectious ward of the hospital for at least 24 hours. The potential DIs were classified based on the type and severity. Medical and demographic characteristics of the patients, including age, sex, duration of hospitalization, inpatient ward, and treatment results (death or advances in treatment) were collected using a checklist. Data were analyzed using SPSS software version 16.0.

Results: A total of 514 DIs were identified from which 5.05% were major and 41.82% were moderate interactions. The mean of DI per patient was 2.81 in the range of 1 and 23. The frequency of antibiotic/antibiotic and antibiotic/other drugs interactions were 7.97% and 28.98%, respectively. The average length of stay in hospital was 12.07 days, and 26.22% and 25.13% of the studied patients were hospitalized in general and infectious ICUs, respectively. The mean of DIs per patient was significantly higher in infectious ICU rather than other studied wards.

Conclusions: To sum up, although the percentage of major DIs were low, the prevalence of total DIs was high in the studied patients. Based on the results of this study, it seems that physicians must be aware of the presence of potential and harmful DIs. Moreover, working under the careful supervision of a clinical pharmacist in hospitals and continuous training around DIs and training the pharmacological care to physicians can be effective in the prevention of DIs.

Keywords: Drug-drug interaction, Infectious diseases, Major interaction, Minor interaction

Background

Patient safety is one of the fundamental concepts in health care system and in recent years a considerable attention has been given to this issue (1,2). Drug interactions (DIs) as one of the most important subgroups of drug errors can lead to unwanted reactions in the patients. DI occurs when a drug is affected by another drug pharmacodynamically or pharmacokinetically (3). This influence has led to the emergence of a concept called drug-drug interaction (DDI). However, in general, DI means the change in the behavior of a drug caused by another drug, foods, drinks, or other chemicals (4-6). The reactions to DIs can vary in a wide range from no response to treatment of serious and dangerous diseases (7-9). Although this interaction can be positive (increase drug efficacy) or negative (decrease drug efficacy or cause toxicity), it is undesirable in drug therapy (10).

In the United States, about 77 000 patients die or develop long-term complications because of the direct effects of DIs, which is more than the mortality from accidents (43 000 cases), breast cancer (42 000 cases), and HIV infection (16 000 cases) (11-13). According to the reports of Ministry of Health and Medical Education, several million dollars are annually spent on patient care because of drug errors and subsequent complications due to prolonged hospital stay (14). These problems make it necessary to change our attitude to drugs and their use. Although drugs are known as one of the necessary

technologies to provide therapeutic services, in cases of improper use, they can be a harmful and deadly agent. This is more apparent when the use of several drugs from different drug classes are inevitable because of the complex therapies which are required for the treatment of patients as seen in hospitalized patients (7,15,16).

Not all the DIs are preventable. However, the awareness of medical team from the incidence of DIs and the risk factors that increase the possibility of these interactions as well as their familiarity with the mechanisms of DIs can reduce their incidence, mortality, and treatment costs, and increase the patients' satisfaction (17).

Objectives

With these in mind, we undertook the present study to assess DIs in patients hospitalized in intensive care units (ICUs) and infectious ward of Sina hospital, Hamadan, Iran.

Methods

In this cross-sectional study, the medical records of 500 patients hospitalized in the ICUs and infectious ward of Sina hospital, Hamadan, west of Iran, were studied from March 2014 to February 2015. This duration was chosen because from February 2015 onwards, a clinical pharmacologist worked in Sina hospital to whom we arranged all consultations about DIs. The study protocol was compatible with the Declaration of Helsinki and was approved by Research Ethics Committee of Hamadan University of Medical Sciences.

Data were collected using a standard checklist pertaining to demographic characteristics including age and sex, the severity of DIs (minor, moderate, and major), the type of DIs (antibiotic/antibiotic, antibiotic/other drugs, and other drugs/other drugs), the duration of hospitalization, inpatient ward (general ICU, infectious ICU, and infectious ward), and treatment result (death or advances in the treatment).

DIs and their severity were investigated using up-to-date, drug interaction databases such as LEXI-COMP, and DI facts book (18). Based on these databases, major interaction is defined as the interaction that may be life-threatening or cause permanent damage; moderate interaction is defined as the patient's condition that may be deteriorated due to the interaction, require additional care or extended hospitalization. While minor interaction is defined as an interaction that is bothersome, but otherwise not medically detrimental (18).

The inclusion criterion was the hospitalization in the ICUs and infectious ward of Sina hospital, Hamadan, Iran, with at least one DI. Patients who had incomplete medical records and those who died or discharged from the hospital at the first 24 hours of the hospitalization were excluded from the study. After data collection, interactions were reviewed again using up-to-date prescriptions of the above-mentioned sources to confirm the accuracy of the data.

Data were analyzed at 2 levels of descriptive and analytical statistics. Descriptive analysis was performed using descriptive statistics, including mean, standard deviation (SD), and frequency. For analytical analysis, chi-square, Kolmogorov-Smirnov, Kruskal-Wallis, and Mann-Whitney U tests were used. Data were analyzed using SPSS software version 16.0. A *P* value less than 0.05 was considered statistically significant.

Results

Out of 500 studied medical records, 183 records (36.6%) contained at least one DI, from which 104 patients (56.83%) were male and 79 (43.16%) were female. The mean age of the patients was 60.27±19.61 years (age range: 16 to 95 years). A total of 514 DIs were observed in the studied medical records, out of which, 26 cases (5.05%) had major interactions, but 215 cases (41.82%) and 273 cases (53.11%) had moderate and minor interactions, respectively. In addition, 41 cases (7.97%) had antibiotic/antibiotic interactions, 149 cases (28.98%) had antibiotic/other drugs interactions, and 324 cases (63.03%) had other drugs/other drugs interactions.

The mean of DIs per patient was 2.81±2.28 interactions (ranged from 1 to 13). The average length of stay in hospital (ALOS) was 12.07±12.35 days (ranged from 2 to 90 days). Moreover, 48 (26.22%), 46 (25.11%), and 89 (48.63%) patients were hospitalized in general ICU,

Table 1. Comparison of Type, Number, and Severity of DIs Among Different Wards

Variables	NO. (%)/Mean ± SD			*P* value
	General ICU (n=133)	Infectious ICU (n=159)	Infectious Ward (n=222)	
DI severity				
Major	0 (0.00)	8 (5.30)	18 (8.10)	<0.001
Moderate	38 (28.57)	77 (48.42)	100 (45.04)	
Minor	95 (71.42)	74 (46.54)	104 (46.84)	
DI Type				
Ab-Ab	1 (0.75)	25 (15.72)	125 (56.30)	<0.001
Ab-OD	7 (5.20)	53 (33.33)	81 (36.48)	
OD-OD	125 (93.98)	81 (50.94)	118 (4.19)	
Mean of DI for each patient	2.77 ± 2.02	3.46 ± 2.52	2.49 ± 2.24	<0.05

Abbreviations: DI, drug interaction; SD, standard deviation, Ab, antibiotic; OD, other drugs.

infectious ICU, and infectious ward, respectively.

Out of 183 hospitalized patients, 72 patients (39.43%) died and 111 patients (60.65%) discharged from the hospital. Furthermore, out of 514 DIs, 133 cases (25.87%) were in general ICU, 159 cases (30.93%) were in infectious ICU, and 222 (30.93%) were in infectious ward.

Table 1 shows the type and severity of DIs in the studied wards. Statistically significant differences were observed in the type, number, and severity of DIs between the wards ($P<0.05$).

Out of 514 DIs, 7 cases (1.36%), 95 cases (18.48%), 149 cases (28.98%), 165 cases (32.10%), and 98 cases (19.06%) were observed in the patients within the age ranges of 1-20, 21-40, 41-60, 61-80, and 81-100 years, respectively (Table 2). A statistically significant difference was noted for the type of DI between the age groups ($P<0.05$). On the contrary, no significant differences were found for the number and severity of DIs ($P>0.05$). However, the difference in the severity of DIs between the groups tended to be significant ($P=0.074$).

The type, number, and severity of DIs of the male and female patients are indicated in Table 3. Two hundred and ninety-six DIs (57.58%) and 218 DIs (42.41%) were observed in male and female patients, respectively. There was no statistically significant difference between the male and female patients ($P>0.05$). However, the difference in the severity of DIs between them tended to be significant ($P=0.091$).

The type and severity of DIs were significantly different between died and discharged patients ($P<0.05$); however, no significant difference was observed in the number of DIs ($P>0.05$) (Table 4). Out of 514 DIs, 265 (51.55%), 161 (31.32%), 52 (10.11%), and 36 cases (7.00%) were observed in the patients with the duration of hospitalization of 1-10, 11-20, 21-30, and >30 days, respectively (Table 5). Furthermore, only the severity of DIs was statistically significant between different durations of hospitalization ($P<0.05$). The difference in the number of DIs between the groups was statistically significant ($P=0.052$).

The most frequent medication interactions in all wards were 23 minor interactions of aspirin/dipyridamole (17 in general ICU and 6 in infectious ward), 22 minor interactions of heparin/dipyridamole (17 in general ICU, 2 in infectious ICU, and 3 in infectious ward), aspirin/heparin (16 in general ICU, 2 in infectious ICU, and 4 in infectious ward), and pantoprazole/rifampin (9 in infectious ICU, and 13 in infectious ward), 17 moderate interactions of phenytoin/pantoprazole (7 in general ICU, 6 in infectious ICU, and 4 in infectious ward), 13 moderate interactions of dexamethasone/rifampin (1 in infectious ICU and 12 in infectious ward), 11 minor interactions of digoxin/metoral (2 in general ICU and 9 in infectious ICU), 9 moderate interactions of rifampin/pyrazinamide (7 in infectious ICU and 2 in infectious ward), 8 moderate interactions of azithromycin/

Table 2. Comparison of Type, Number, and Severity of DIs Among Different Age Groups

Variables	Age Groups (y)					*P* Value
	1-20 (n=7)	21-40 (n=95)	41-60 (n=149)	61-80 (n=165)	81-100 (n=98)	
DI severity						
Major	0 (4.52)	8 (6.83)	7 (5.76)	7 (0.0)	4 (4.08)	<0.05
Moderate	4 (45.28)	43 (40.99)	75 (34.61)	59 (30.55)	34 (34.69)	
Minor	3 (50.18)	44 (52.17)	65 (59.61)	99 (69.44)	60 (61.22)	
DI type						
Ab-Ab	0 (0.00)	8 (8.42)	3 (11.40)	10 (6.06)	6 (6.12)	<0.001
Ab-OD	4 (28.57)	38 (40.00)	11 (35.57)	33 (20.00)	21 (21.42)	
OD-OD	3 (42.85)	49 (51.57)	38 (53.02)	122 (73.93)	71 (72.44)	
Mean of DI for each patient (Mean ± SD)	2.33 ± 2.30	2.88 ± 2.72	3.23 ± 2.44	2.53 ± 2.06	2.80 ± 2.05	>0.05

Abbreviations: DI, drug interaction; SD, standard deviation, Ab, antibiotic; OD, other drugs.

Table 3. Comparison of Type, Number, and Severity of DIs Between Males and Females

Variables	Gender		*P* value
	Male (n=296)	Female (n=218)	
DI Severity			
Major	16 (5.40)	10 (4.58)	>0.05
Moderate	135 (45.60)	80 (36.69)	
Minor	145 (48.98)	128 (58.16)	
DI Type			
Ab-Ab	26 (8.73)	15 (6.88)	>0.05
Ab-OD	91 (30.74)	58 (26.60)	
OD-OD	179 (59.45)	145 (66.51)	
Mean of DI for each patient (Mean ± SD)	2.84 ± 2.17	2.77 ± 2.43	>0.05

Abbreviations: DI, drug interaction; SD, standard deviation, Ab, antibiotic; OD, other drugs.

Table 4. Comparison of Type, Number, and Severity of DIs Based on Clinical Outcomes

Variables	Clinical outcomes		*P* value
	Mortality (n=201)	Discharged (n=313)	
DI Severity			
Major	3 (1.49)	23 (7.43)	<0.001
Moderate	68 (33.83)	147 (46.96)	
Minor	130 (64.67)	143 (45.68)	
DI Type			
Ab-Ab	26 (8.73)	15 (6.88)	<0.001
Ab-OD	91 (30.74)	58 (26.60)	
OD-OD	179 (59.45)	145 (66.51)	
Mean of DI for each patient (Mean ± SD)	2.79 ± 1.87	2.82 ± 2.52	>0.05

Abbreviations: DI, drug interaction; SD, standard deviation, Ab, antibiotic; OD, other drugs.

Table 5. Comparison of Type, Number, and Severity of DIs Based on Duration of Hospitalization

Variables	Duration of Admission (Day)				*P* Value
	1-10 (n=265)	11-20 (n=161)	21-30 (n=52)	≥30 (n=36)	
DI severity					
Major	12 (4.52)	11 (6.83)	3 (5.76)	0 (0.0)	>0.05
Moderate	120 (45.28)	66 (40.99)	18 (34.61)	11 (30.55)	
Minor	133 (50.18)	84 (52.17)	31 (59.61)	25 (69.44)	
DI type					
Ab-Ab	24 (9.05)	14 (8.69)	3 (5.76)	0 (9.05)	<0.01
Ab-OD	88 (33.20)	49 (30.43)	11 (21.15)	1 (2.77)	
OD-OD	153 (69.44)	98 (60.86)	38 (73.07)	35 (97.22)	
Mean of DI for each patient (Mean ± SD)	2.42 ± 1.87	3.32 ± 2.68	4.00 ± 3.44	3.30 ± 1.88	>0.05

Abbreviations: DI, drug interaction; SD, standard deviation, Ab, antibiotic; OD, other drugs.

ciprofloxacin (4 in infectious ICU and 4 in infectious ward), 6 minor interactions of digoxin/lasix (1 in general ICU, 2 in infectious ICU, and 3 in infectious ward), 6 minor interactions of isoniazid/rifampin (5 in infectious ICU and 1 in infectious ward), 6 moderate interactions of diazepam/phenytoin (4 in general ICU, 1 in infectious ICU, and 1 in infectious ward), and 6 moderate interactions of azithromycin/levofloxacin (3 in infectious ICU and 3 in infectious ward).

Discussion

Regarding the importance of DIs, the present study was conducted on the improvement of the quality of drug therapy, prevention of drug side effects, and reduction of mortality and treatment costs in the patients hospitalized in ICUs and infectious ward in Sina hospital, Hamadan, Iran.

In the present study, out of 500 studied medical records, 183 (36.60%) had at least one given DI and a total of 514 DIs were identified (2.8 interactions per patient). About 5.05%, 41.82%, and 53.11% of the DIs were major, moderate, and minor, respectively. In other words, the most frequent DIs were minor ones. Durrence et al reported at least one potential DI for 17% of hospitalized patients which is much lower than that in our study (19). In the study of Khouri et al in Gorgan, Iran, the prevalence of DIs in the physicians' prescriptions was 8.72%. However, major, moderate, and minor DIs were 8.72%, 69.26%, and 22.02%, respectively.

In the present study, the most prevalent DIs were minor interactions, while in the study of Khouri et al, the most frequent DIs were moderate interactions (20). In the study of Abbasi et al in Golestan, Iran, the prevalence of DI in the physicians' prescriptions were very low (0.66%), which is much lower than that in our study. However, 35.5% of the DIs were major, which are much higher than that in our study (21). Rashidi et al reported that 8.5% of the physicians' prescriptions contained DIs; this percentage is lower than that in our study. However, in the study of Rashidi et al, more prevalent DIs were moderate (42.6%), major (15.6%), and minor (41.8%), respectively. In comparison with our results, the major DI in that study was higher than that in our study (22).

The high prevalence of total DIs in the present study can be explained, at least in part, by the fact that the studied hospital was an educational one and medical students were working in the wards of hospital. In addition, the lack of any course on DIs for medical students, enough supervision on administered medications and on pharmacist are other possible causes. In addition, in the present study, DIs were studied in hospitalized patients while in majority of the above-mentioned studies, the prescriptions by physicians in a province or city, or insurance prescriptions were studied. Several studies have reported high prevalence of DIs in hospitalized patients, particularly in ICU (3,21,23-26). In addition, simultaneous administration of multiple drugs is common in infectious patients which in turn could result

in the possible increase of DIs in these patients (17). In this regard, Almedia et al stated that patients hospitalized in ICU are at high risk of DI because of the number and type of prescribed drugs and their medical conditions (23). In agreement with the above statement, the study of Rahimi et al on ICU wards in Urmia, Iran, showed that the frequency of DIs was 73.6% and the mean of DIs (the number of interactions per patient) was 4.07 (27).

Based on the results from the study of Rodrigues et al on the ICU, DIs were seen in 89% of the studied prescriptions and 67% of the DIs were major (24). The prevalence of total DIs and major interactions were much higher than those of our study. In majority of the previous studies, the prevalence of moderate and minor interactions was higher than that in our study. This result may be attributed to the physicians' awareness of the potentially severe DIs, the risk factors that increase the possibility of DIs, and their familiarity with DIs. These results may converge on the assumption that the physicians avoided simultaneous administration of the drugs with potentially severe interactions. In addition, physicians may be unaware of the incidence of minor and moderate DIs. It is noteworthy that the presence of DIs is not definite indicator of their harmfulness and many DIs can be useful. It seems that a few number of the studied DIs are useful. However, whether the DI is useful or harmful was not the aim of the present study and only the presence or absence of interactions was investigated (27).

In the present study, the mean number of DIs (DI per patient) was significantly different between the wards. Similarly, Almedia et al and Lima et al found that patients hospitalized in ICU were at higher risk of DI than those in other wards (23, 25). In addition, Brunton et al reported that infectious patients were inherently at the risk of DIs because of their need for multiple drugs (17) as was seen in our study, in which the patients hospitalized in infectious ICU were at higher risk of DIs than those in general ICU.

It is plausible that a number of limitations may have influenced our results. The first limitation of our study is that it was done in 2 wards of Sina hospital, so the results might not be extrapolated to other wards or hospitals. The second limitation is that we did not assess physicians' compliance and were not able to consider possible cofactors in the study. Therefore, further multi-center studies are required to find out the details of potential DIs in the hospitalized patients.

Conclusions

Taken together, although in the present study, the majority of DIs were minor, the moderate interactions were also considerable. Moreover, although all potential DIs did not actually happen, the high prevalence of DIs could ring a bell about the actual DIs in the patients hospitalized in ICU. Being aware of DIs, replacing the drugs that frequently cause interaction with other drugs, reducing the number of drugs in prescriptions, attending the prescriptions more than before especially when multiple drugs are co-administered, the limited use of drugs of each drug class, and further familiarity with the drug issues could prevent DIs and their consequences. In addition, the presence of at least one medical pharmacist in each hospital is recommended.

Conflict of Interests

Authors do not have any conflict of interest.

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