Original Article

Impact of Clinical Pharmacist's Interventions on Potential Drug–Drug Interactions in the Cardiac Care Units of Two University Hospitals in Shiraz, South of Iran

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ABSTRACT

Objective: The main objective of this study aimed to assess drug–drug interactions (DDIs) in the cardiac care unit (CCU) and cardiac surgery units and the role of a clinical pharmacist in detecting and preventing the expected DDIs. **Methods:** This cross-sectional study was conducted in the CCU Units of Nemazee and Shahid Faghihi Hospitals, two referral hospitals in Shiraz, South of Iran, from August to February 2016. Patients older than 18 years, who were admitted and had received >24 h of inpatient services in these wards with two or more medication orders, were included in this study. All medication orders were evaluated by a pharmacist and DDIs were examined based on the Lexi-Interact™ software. In cases with serious DDIs (D or X), the physicians and nurses were informed, and intervention was conducted by a clinical pharmacist. **Findings:** A total of 3706 medical orders were evaluated. 6478 DDIs were detected, of which, 446 (6.88%) belonged to Classes D and X, and a total of 43.43% of all hospitalizations had at least one DDI. Factors with the most considerable influence on DDIs included an increased number of prescribed medications and patients underlying disease. The physicians accepted 62% of the interventions. The most frequent drugs responsible for interactions of Classes C, D, and X were aspirin, warfarin, and clopidogrel, respectively. **Conclusion:** This study shows that a significant number of clinical DDIs exist in hospitalized patients, especially among consumers of warfarin and aspirin. The role of a clinical pharmacist in preventing such interactions and safer pharmacotherapy management for hospitalized patients is essential.

Keywords: *Cardiovascular care unit, clinical pharmacist, drug–drug interactions*

Introduction

Drug–drug interactions (DDIs) are an essential class of medication errors common among both hospitalized patients and outpatients.[1] DDIs occur more prevalently in the cardiac care units (CCUs).[2,3] Besides the type of medications used, the mean age of the patients, the number of prescribed drugs, and comorbid diseases in a patient are other risk factors responsible for the high incidence of DDIs in CCUs.[4]

A prospective study carried out in one of the teaching hospitals in India showed that the incidence of potential DDIs in CCUs is 30.67%. Haji Aghajani *et al*. evaluated the DDIs in 203 patients in a teaching hospital in Tehran and found 3166 potential DDIs in a post-CCU ward.[5]

Although DDIs can lead to serious injury or even death, limited studies have been conducted to evaluate the different aspects of DDIs (including occurrence, complications, causes of occurrence, and cost) in the CCUs in Iran.[5] This study aimed to assess DDIs and their severity in CCU and cardiac surgery units in two

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large teaching hospitals in Shiraz, South of Iran, to determine their incidence and following complications. The novelty of this study is the clinical pharmacist's intervention after the detection of a life-threatening drug interaction.

Methods

We conducted a cross-sectional study in the Coronary Care Unit and Cardiac Surgery Ward of Nemazee and Shahid Faghihi hospitals, two referral University hospitals in Shiraz, South of Iran, from August to February 2016. These two hospitals have an overall of 68 beds in the CCU and cardiac surgery wards and are affiliated to the Shiraz University of Medical Sciences (SUMS). The local ethics committee of SUMS approved the study protocol (#IR.SUMS.REC.1390.4661).

Admitted patients older than 18 years, who received more than 24 h of inpatient services in the CCU and cardiac surgery wards with two or more medications, were included in the study. We recorded the demographic data and medication orders of the patients including the drug doses, frequencies, strength, and dosages and divided them according to their underlying diseases into two main categories: patients with ischemic heart disease (IHD) and patients without non-IDH events such as arrhythmia, structural heart diseases, thromboembolic diseases, and pulmonary edema.

DDIs have been examined based on the Lexi-Interact™ software (Lexi-Comp Inc., USA, 2016), and the type of interaction and the severity of their clinical effects were determined. All DDIs were classified into five groups based on their clinical significance (A, B, C, D, and X).[6]

In cases with serious DDIs (D or X), either in prescription or administration, physicians and nurses were informed, and intervention was conducted by a clinical pharmacist in charge of the study. All included patients were followed up to the end of the stay in the wards, and any occurred complication from DDI was recorded.

We have used descriptive statistics for presenting our continuous variables as mean ± standard deviation (SD) and summarized the categorical data in tables as percentages. Means of continuous variables were statistically analyzed using Student's *t*-test. Chi-square test was used to compare qualitative variables.

The relationship between the incidence of DDIs with others was analyzed using *t*-test and Pearson's correlation coefficient test. After reviewing each of the qualitative and quantitative variables associated with the DDIs in categories D and X, the effects of all variables on the occurrence of DDIs were examined by the logistic regression test. All analyses were performed using the SPSS statistical software (version 18.0, IBM, USA) and $P < 0.05$ was considered as statistically significant.

Results

A total of 495 patients were evaluated. One hundred and ninety-six patients (39.60%) were female. The mean ± SD age of the patients was 60.40 ± 16.60 years. On average, each patient was hospitalized for 6.0 ± 4.0 days. Three hundred patients (60.8%) were admitted due to IHD, and 39.20% (n = 194) were admitted due to non-IHD reasons.

A total of 3706 medical orders and 210 different drugs were studied. The average number of orders for each patient was 7.40 ± 4.80, and the mean number of medications prescribed for each patient during his/her hospital stay was 12.00 ± 4.00.

The four most commonly prescribed medications for the enrolled patients were aspirin (n = 422, 85.00%), atorvastatin (n = 404; 81.00%), nitroglycerin (n = 388; 78.00%), and metoprolol (n = 263; 53.00%). In total, 6478 DDIs were identified and categorized to C, D, and X types. The information about the DDIs in each category is shown in Table 1.

Tables 2 and 3 show the most interactions found, belonging to categories D and X with clinical pharmacist's interventions, respectively.

Warfarin had the highest interaction in the Category D, and clopidogrel had the highest drug interactions in the Category X. From a total of 446 potential DDIs, 221 interactions were moderate, 219 were major, and 6 were minor in case of their severity.

The assessment of reliability showed that 194 (43.50%), 165 (37.00%), and 87 numbers (19.50%) of the DDIs were fair, excellent, and reasonable, respectively.

The risk of DDIs increases with an increase in the number of drugs prescribed for the patient significantly in each DDIs' classification ($P < 0.001$). The same result was observed concerning the association between the number of medical orders and the risk of any DDI ($P < 0.00$).

The correlation between age and risk of DDIs in Classes D and X was statistically significant ($P < 0.00$, $r = 0.183$). The mean age of people who experienced at least one DDI in Classes D and X was 61.40 ± 17.90 years.

The mean number of hospitalization days in patients who had at least one DDI belonging to Class D or X

Table 1: Comparison between the frequency of drug-drug interactions in studied inpatients (*n*=495)

Total patients (*n*=495)	Total (C + D + X)	Type C interaction	Type D interaction	Type X interaction
Mean number of DDIs per patients (mean±SD)	4.3±2.4	12.2±7.2	0.88±0.06	0.02±0.00
Total number of DDIs	6478	6032	438	8
The maximum number of DDIs per patients	55	46	8	1

DDIs=Drug-drug interactions, SD=Standard deviation

Table 2: Most common interactions found, belonging to Category D with clinical pharmacist's interventions in studied inpatients (*n*=495)

Drug pairs	Risk rating of DDIs class	Observed number (%)	The number of DDIs requiring intervention	The number of accepted interventions	Clinical pharmacist intervention
Warfarin--aspirin	D	63 (14.38)	41	25	Attention to the INR and the symptoms of bleeding and, if necessary, change the dose or discontinue aspirin until the bleeding is stopped
Amiodarone-atorvastatin	D	50 (11.41)	30	16	Attention to symptoms such as muscle aches and liver function tests, and atorvastatin dose reduction if needed
Spironolactone-- potassium chloride	D	39 (8.90)	7	5	Attention to hyperkalemia symptoms, especially in people with renal impairment and, if necessary, change the dose of potassium chloride
Clopidogrel--omeprazole	D	25 (5.71)	16	11	Discontinue the use of omeprazole and use of pantoprazole or antagonist H2
Amiodarone--warfarin	D	23 (5.25)	17	9	INR monitoring closely
Digoxin--amiodarone	D	21 (4.79)	13	4	Measure digoxin plasma concentrations, especially in patients with renal impairment, and evaluate the signs and symptoms of digoxin toxicity
Carvedilol- - β2 -adrenergic agonists	D	14 (3.2)	12	9	Changing carvedilol to metoprolol or if the patient has an established active airway disease, discontinue of beta-blocker
Warfarin--diclofenac	D	11 (2.5)	11	3	Attention to the symptoms of bleeding and, if possible, use of another analgesic, such as acetaminophen
Atorvastatin--fluconazole	D	4 (0.91)	4	4	Discontinuation of fluconazole due to lack of evidence for antifungal treatment according to culture and clinical symptoms of the patient
diltiazem amiodarone	D	3 (0.68)	2	1	Regarding the two-sided interaction of these drugs, in case of toxicity with any of the drugs or the symptoms of bradycardia, reduction of cardiac output or Sinoatrial block, reduction of diltiazem, or amiodarone dosage
Atorvastatin--Gemfibrozil	D	1 (0.22)	1	1	Attention to symptoms of muscle pain and taking two drugs at a time interval of 12 h or replacing gGemfibrozil with fenofibrate

DDIs=Drug--drug interactions

was 7.00 ± 4.00 days, and in patients who did not have any potential DDIs was 5.80 ± 2.20 days ($P < 0.001$).

In total, 215 patients experienced at least one Class D or X DDI. 50% of women and 39.40% of the men who were included in our study experienced at least one drug interaction of Class D or X ($P = 0.017$). It is noteworthy that there was no significant difference in sex in Category C of interactions ($P = 0.71$).

In our study, 60.80% of the patients were hospitalized due to IHD, and 33.50% of them had at least one drug

Table 3: Most common interactions found, belonging to Ccategory X with clinical pharmacist interventions in studied inpatients (*n*=495)

Drug pairs	Risk rating of DDIs class	Observed, *n* (%)	The number of DDIs requiring intervention	The number of accepted interventions	Clinical pharmacist intervention
Fluconazole--clopidogrel	X	3 (0.68)	3	3	Discontinuation of fluconazole due to lack of evidence for antifungal treatment according to culture and clinical symptoms of the patient
Clopidogrel--sertraline	X	1 (0.22)	1	0	Discontinuation of sertraline and replace with citalopram
Clopidogrel--fluoxetine	X	1 (0.22)	1	0	Discontinuation of fluoxetine and replace with citalopram
Clopidogrel--gemfibrozil	X	1 (0.22)	1	0	Discontinuation of gGemfibrozil and replace with fFenofibrate
Clopidogrel--ticlopidine	X	1 (0.22)	1	1	Discontinuation of ticlopidine and replace with aspirin

DDIs=Drug--drug interactions

interaction of Class D or X, whereas 58.70% of patients hospitalized due to non-IHD, experienced at least one drug interaction of Class D or X ($P < 0.001$).

Logistic regression analysis showed that only two variables, the number of drugs being used (odds ratio [OR] = 2.77, 95% confidence interval [CI]: 1.780–4.312) and the underlying disease (OR = 3.53, 95% CI: 2.289–5.473) are significantly effective in increasing the risk of DDIs of the two Classes D or X.

The most common complications that occurred due to DDIs in our study are shown in Table 4.

A clinical pharmacist intervention was conducted on 446 DDIs of Categories D and X as follows: administration intervention (with nurses, n = 58) and prescription intervention (with physicians, n = 388). All of the administration interventions (100%) were accepted by the nursing staff. One hundred and eighty-two DDIs needed no intervention because the dose of the drugs was adjusted based on clinical findings and laboratory setting by the physicians. Therefore, 206 prescription interventions were done that 51.90% (n = 107) of them were accepted. Due to the prescription interventions made, drug interactions (Types D and X) in 27 cases (7.5% drug interactions) were prevented.

Table 4: Complications of drug-drug interactions in studied inpatients (*n*=495)

Complication of DDIs	*n* (%)
Systolic blood pressure <100 mmHg	133 (26.9)
Hyperkalemia (potassium >5 mmol/L	65 (13.1)
Bradycardia (HR <60 beats/min)	40 (8.1)
The elevated INR more than therapeutic range	40 (8.1)
BUN >23 mg/dl	40 (8.1)
SCr >1.2 mg/dl	27 (5.4)
PTT greater than >1.5-2 of normal	22 (4.4)
Bleeding	19 (3.8)

DDIs=Drug--drug interactions, HR=Heart rate, INR=International normalized ratio, BUN=Blood urea nitrogen, SCr=Serum creatinine, PTT=Partial thromboplastin time

Discussion

Nowadays, pharmacotherapy is an essential part of medical care. In health-care settings, different errors regarding medication prescription can be observed, one of them are DDIs.[7] In recent years, the necessity to becoming more evident due to the increase in mortality rates and hospital costs.[8]

In the course of this study, 6478 DDIs occurred, however, in Haji Aghajani *et al*.'s study,[5] 3360 DDIs occurred in a post-CCU ward. One of the reasons for this difference is that a more significant number of patients have been enrolled in this study (503 vs. 203) and also we have studied two major teaching hospitals, whereas in the mentioned study, only one hospital was recruited. In Aparasu's study[9] that was performed in the outpatient group of patients in the United States, most of the DDIs (about 92%) were related to anticoagulants. Furthermore, in a study conducted in 2011 in several hospitals and medical clinics in Pakistan, most of the interactions observed were between warfarin and aspirin. Relevant to these results, the most potential DDIs in our

study (belonging to categories D and X), were related to anticoagulants, especially warfarin.

There are various results regarding the impact of sex on DDIs, as in some studies a higher percentage was seen in men[10,11] and others it was the opposite.[4] The cause of this difference may be due to the study of sex factor on inpatients or outpatients or the average life expectancy being greater in women.[12] In the female population, having a longer lifespan brings about possible comorbid diseases which may increase the number of medication used and therefore increases possible DDIs.[11] In our study, logistic regression analysis showed that there was no significant difference between genders in the rate of DDIs. Our study was limited to CCU and cardiac surgery units which are expected to have men patients than women considering the higher risk of cardiovascular diseases in men, compared to women in premenopausal age.[13] In our study, the mean age of men and women was >60 years, and the risk of cardiovascular events was the same in both genders.

The next effective variable was the underlying diseases of patients. The risk of DDIs Type D or X in patients with known IHD was 3.5 times than that of patients with IHD (95% CI, 2.289–5.473). An explanation to this outcome can be that the most common Type D drug interactions were related to warfarin and 33% of patients admitted because of non-IHD were taking warfarin, whereas the percentage of warfarin consumers in IHD patients was only 7.40% ($P < 0.00$). Other studies have also shown that anticoagulants had the most influence on the rate of DDIs.[2,14] In our study, the incidence of DDIs had a significant relationship with the number of medications prescribed. 95.00% of patients had more than seven medications per day. Based on the descriptive analysis, DDIs of Types D and X, had a normal distribution, when the patient was taking 12 or more medications. Therefore, this number was selected as the cutoff point, and logistic regression showed that the risk of DDIs in patients who were taking 12 or more drugs, was 2.77 times more than patients who were taking <12 drugs at the same time (OR = 2.77, 95% CI = 1.780–4.312). These results are similar to other studies.[15]

In our study, no significant relationship between age and incidence of DDIs was observed by logistic regression analysis. Since 78.60% of our patients had >50 years of age, distribution of age was not wide enough to serve as an influencing factor between age groups. Other studies show that older people are more susceptible to DDIs because they are more sensitive to pharmacokinetic effects, and often due to concomitant illnesses, these patients are taking more than two drugs at a time.[16]

The logistic regression analysis showed that the incidence of DDIs had no significant relationship with the length of stay in the hospital in our study. However, in some reports, it increased with more extended stay,[17] and in another, it decreased.[18] In a study by Patel *et al*.[19] and another study by Bertoli *et al*.,[20] the incidence of DDIs increased with length of stay, but in a study conducted by Reimche *et al*.,[15] the same as our study, the risk of DDIs was reduced with the length of hospital stay. One of the causes of this difference can be the availability of clinical pharmacy services in our study and also hospitals in which the study of Reimche was conducted. The presence of clinical pharmacy services in a hospital can be a means to provide the necessary information on drug interactions to the physician staff.

In our survey, 62.50% of 264 interventions with health team members (physicians and nurses), were accepted. In a study conducted in 2007 in Switzerland, 80.50% of the intervention were accepted.[21] The difference goes back to the doctor's decision to accept or reject the drug interactions and whether to rely on the pharmacist's knowledge/practice or not.

In our study, the occurrence of 27 DDIs was prevented after clinical pharmacist's intervention. Klopotowska *et al*., also reported that the adverse drug events significantly decreased after intervention by hospital pharmacists.[22]

One limitation of this study was that patients are studied only while they are hospitalized in the mentioned wards. Therefore, any complications occurring after patients' discharge from their wards were not documented. OTC drugs, herbal products, and home remedies were not considered in the study. There are many different databases of drug interactions for the detection of DDIs, and there are some differences between these databases regarding the classification of DDIs. We only used one software for the detection of DDIs according to the previous studies,[23] while it is suggested that using two or more software, improvement can be made in the precision of detecting DDIs.

In almost half of the study population (44%), at least one DDI was detected. The number of medications used by a patient and the underlying diseases were associated with the incidence of clinically significant DDIs. Considering this fact, the risk of drug interactions in patients who are using 12 or more medications at the same time, is twice more than patients who are taking <12 drugs. However, the critical point is that DDIs are preventable. About 62% of the interventions made during the study were accepted by nurses and physicians and probable life-threatening conditions due to DDIs were prevented.

Authors' Contribution

Mojtaba Shafiekhani, Soha Namazi, Negin Moosavi, and Dena Firouzabadi conceived and planned the experiments. Soha Namazi, Negin Moosavi, and Mojtaba Shafiekhani performed the measurements. Mojtaba Shafiekhani, Soha Namazi, and Dena Firouzabadi contributed to sample preparation and interpretation of the results. All authors discussed and provided critical feedback for the results and contributed to the manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. Expert Opin Drug Saf 2012;11:83-94.
2. Nabovati E, Vakili-Arki H, Taherzadeh Z, Hasibian MR, Abu-Hanna A, Eslami S. Drug-drug interactions in inpatient and outpatient settings in Iran: A systematic review of the literature. Daru 2014;22:52.
3. Dunn SP, Holmes DR Jr., Moliterno DJ. Drug-drug interactions in cardiovascular catheterizations and interventions. JACC Cardiovasc Interv 2012;5:1195-208.
4. Rafieii H, Arab M, Ranjbar H, Arab N, Sepehri G, Amiri M. The prevalence of potential drug interactions in intensive care units. J Crit Care Nurs 2012;4:191-6.
5. Haji Aghajani M, Sistanizad M, Abbasinazari M, Abiar Ghamsari M, Ayazkhoo L, Safi O, *et al.* Potential drug-drug interactions in post-CCU of a teaching hospital. Iran J Pharm Res 2013;12:243-8.
6. Makiani MJ, Nasiripour S, Hosseini M, Mahbubi A. Drug-drug interactions: The importance of medication reconciliation. J Res Pharm Pract 2017;6:61-2.
7. Bertsche T, Pfaff J, Schiller P, Kaltschmidt J, Pruszydlo MG, Stremmel W, *et al.* Prevention of adverse drug reactions in intensive care patients by personal intervention based on an electronic clinical decision support system. Intensive Care Med 2010;36:665-72.
8. Ahmadizar F, Soleymani F, Abdollahi M. Study of drug-drug interactions in prescriptions of general practitioners and specialists in Iran 2007-2009. Iran J Pharm Res 2011;10:921-31.
9. Aparasu R, Baer R, Aparasu A. Clinically important potential drug-drug interactions in outpatient settings. Res Soc Adm Pharm 2007;3:426-37.
10. Shafiekhani M, Karimi S, Ali Davarpanah M, Vazin A. Evaluating drug interactions, adverse drug reactions, and level of adherence to highly active antiretroviral therapy regimen amongst HIV-positive patients who referred to an AIDS healthcare center in fars, Southern Iran: The first multifaceted study from Iran. HIV AIDS Rev Int J HIV Relat Probl 2017;16:24-31.
11. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995-2010. BMC Med 2015;13:74.
12. Wastesson JW, Canudas-Romo V, Lindahl-Jacobsen R, Johnell K. Remaining life expectancy with and without polypharmacy: A register-based study of swedes aged 65 years and older. J Am Med Dir Assoc 2016;17:31-5.
13. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis 2015;241:211-8.
14. Shah S, Naqvi BS, Ale-Zehra AZ, Ali D, Saeed R, Naqvi GR. Quantitative analysis of drug-drug interactions of OTC drugs with other prescribed drugs collected from different hospitals and clinics of Karachi, Pakistan. Jordan J Pharm Sci 2011;4:1-24.
15. Reimche L, Forster AJ, van Walraven C. Incidence and contributors to potential drug-drug interactions in hospitalized patients. J Clin Pharmacol 2011;51:1043-50.
16. Mukker JK, Singh RS, Derendorf H. Pharmacokinetic and pharmacodynamic considerations in elderly population. Developing Drug Products in an Aging Society. New York: Springer; 2016. p. 139-51.
17. Murtaza G, Khan MY, Azhar S, Khan SA, Khan TM. Assessment of potential drug-drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharm J 2016;24:220-5.
18. Nobili A, Licata G, Salerno F, Pasina L, Tettamanti M, Franchi C, *et al.* Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. Eur J Clin Pharmacol 2011;67:507-19.
19. Patel VK, Acharya LD, Rajakannan T, Surulivelrajan M, Guddattu V, Padmakumar R. Potential drug interactions in patients admitted to cardiology wards of a South Indian teaching hospital. Australas Med J 2011;4:9-14.
20. Bertoli R, Bissig M, Caronzolo D, Odorico M, Pons M, Bernasconi E. Assessment of potential drug-drug interactions at hospital discharge. Swiss Med Wkly 2010;140:w13043.
21. Bond CA, Raehl CL. Clinical pharmacy services, pharmacy staffing, and hospital mortality rates. Pharmacotherapy 2007;27:481-93.
22. Klopotowska JE, Kuiper R, van Kan HJ, de Pont AC, Dijkgraaf MG, Lie-A-Huen L, *et al.* On-ward participation of a hospital pharmacist in a dutch intensive care unit reduces prescribing errors and related patient harm: An intervention study. Crit Care 2010;14:R174.
23. Armahizer MJ, Kane-Gill SL, Smithburger PL, Anthes AM, Seybert AL. Comparing drug-drug interaction severity ratings between bedside clinicians and proprietary databases. ISRN Crit Care 2012;2013:1-6.