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ORIGINAL ARTICLE

Assessment of potential drug–drug interactions and its associated factors in the hospitalized cardiac patients

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Abstract Drug–drug interactions (DDIs) may result in the alteration of therapeutic response. Sometimes they may increase the untoward effects of many drugs. Hospitalized cardiac patients need more attention regarding drug–drug interactions due to complexity of their disease and therapeutic regimen. This research was performed to find out types, prevalence and association between various predictors of potential drug–drug interactions (pDDIs) in the Department of Cardiology and to report common interactions. This study was performed in the hospitalized cardiac patients at Ayub Teaching Hospital, Abbottabad, Pakistan. Patient charts of 2342 patients were assessed for pDDIs using Micromedex® Drug Information. Logistic regression was applied to find predictors of pDDIs. The main outcome measure in the study was the association of the potential drug–drug interactions with various factors such as age, gender, polypharmacy, and hospital stay of the patients. We identified 53 interacting-combinations that were present in total 5109 pDDIs with median number of 02 pDDIs per patient. Overall, 91.6% patients had at least one pDDI; 86.3% were having at least one major pDDI, and 84.5% patients had at least one moderate pDDI. Among 5109 identified pDDIs, most were of moderate (55%) or major severity (45%); established (24.2%), theoretical (18.8%) or probable (57%) type of scientific evidence. Top 10 common pDDIs included 3 major and 7 moderate interactions. Results obtained by multivariate logistic regression revealed a significant association of the occurrence of pDDIs in patient with age of 60 years or more ($p < 0.001$), hospital stay of 7 days or longer ($p < 0.001$) and taking 7 or more drugs ($p < 0.001$). We found a high prevalence for pDDIs in the Department of Cardiology, most of which were of

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moderate severity. Older patients, patients with longer hospital stay and with elevated number of prescribed drugs were at higher risk of pDDIs.

1. Introduction

Drug related problems such as adverse drug reactions, drug–drug interactions, idiosyncratic reactions, and hypersensitivity reactions remained a major challenge in clinical practice (Krähenbühl-Melcher et al., 2007). Potential drug–drugs interactions (pDDIs) are observed to be one of the most frequently appearing challenge that may alter the pharmacokinetic and pharmacodynamics of the drugs thus alter the overall therapeutic response (Baxter and Preston, 2010; Rodrigues, 2013). Many adverse events can be prevented by identifying pDDIs (Hansten and Horn, 2007). However, certain conditions such as multiple disorders, chronic diseases and polypharmacy may increase the risk of pDDIs (Miranda et al., 2011). The consequences of pDDIs are highly variable from minor events to severe events that can be fatal (Baxter and Preston, 2010). Studies have shown that up to 27.0% of the patients admitted in hospital have complications that are the outcomes of DDIs (Janchawee et al., 2005). Studies have revealed that DDIs are a major clinical problem along with other adverse drug reactions especially in the hospitalized cardiac patients (Passarelli et al., 2005; Uijtendaal et al., 2014).

Various studies suggest that cardiovascular patients are more often reported with pDDIs as compared to patients with other diseases (Ismail et al., 2013a,b; Ismail et al., 2012a,b). The possible reason behind higher pDDI rate in cardiovascular diseases may include elder age, multiple drug regimen, and pharmacokinetic or pharmacodynamic nature of drugs used in cardiology (Faulx and Francis, 2008). Cardiovascular drugs are more often involved in pDDIs (Baxter and Preston, 2010; Mendell et al., 2011). For example the drug–drug interactions involving platelet inhibitors such as warfarin is often reported in clinical practice, which may cause fluctuations in prothrombin time (Tadros and Shakib, 2010). DDIs with anticoagulant drugs such as aspirin and clopidogrel are often result in reinfarction or bleeding (Juurlink et al., 2009; Yusuf et al., 2001). There are a few risk factors associated with pDDIs. It has been noticed in various studies that people with older age were at higher risk for exposure of more chronic conditions as this age group usually have multiple diseases and are prescribed with multiple number of medications as well (Gagne et al., 2008). A study reported that 558 (26.5%) of elder people taking medicines were exposed to at least one DDI (Secoli et al., 2010). Polypharmacy and longer hospital stay also influence the incidence rate of pDDIs (Gagne et al., 2008). It was reported that164 (75.9%) patients taking 7 or more drugs were having at least one pDDI while 76 (73.8%) patients with hospital stay of seven or more were at risk of DDIs (Ismail et al., 2011).

Although drug–drug interactions are common in the cardiac patients, but there exists no practical mechanism for reporting a drug–drug interaction in government hospitals of Pakistan (Ismail et al., 2013a,b; Ismail et al., 2012a,b).

1.1. Aim of the study

The main objectives of our study were to identify pDDIs in the patient charts of cardiac patients admitted in a teaching hospital, to find the prevalence and types of pDDIs in The Department of Cardiology ATH, to make list of most common pDDIs in the hospitalized cardiac patients and to determine the risk factors associated with pDDIs in cardiology.

1.2. Ethical approval

The study protocol was approved by the Ethical Committee of the Department of Pharmacy, COMSATS Institute of Information Technology Abbottabad, Pakistan. Permission to conduct this study in the Department of Cardiology was also obtained from hospital administration of Ayub Teaching Hospital Abbottabad.

2. Methods

This is a cross-sectional descriptive study carried at the Department of Cardiology of the Ayub Teaching Hospital (ATH), Abbottabad for a one year period from 01.01.2013 to 31.12.2013. There is no computerized hospital system at ATH for dispensing of medicines or for reduction of medication errors. Unfortunately the pharmacists appointed at ATH are not assigned proper duty of providing pharmaceutical care or medication management for the patients.

2.1. Study population

A total of $N = 3043$ patient charts were screened for the male and female patients admitted in the Department of Cardiology, ATH during the year 2013. A minimum one day hospital stay with at least two prescribed drugs was outlined as the main criteria for the inclusion of the patient prescription to the study sample. All the patients not complying these two main criteria's were excluded from the study. In addition, all those patients who had incomplete data such as gender, age, diagnosis, duration of hospital stay, date of admission and discharge were excluded from our study. Upon applying the inclusion and exclusion criteria, a sample of $n = 2342$ patient charts was considered for the assessment. Hospital administration of ATH maintains patient record on their forms called patient charts. Our concerned data were obtained from patient charts. The data obtained included patient age, gender, hospital stay, number of drugs used, main diagnosis, and all prescribed drugs during his/her stay at the hospital. Most of the drugs were prescribed with their trade names. We used Pharmaguide to determine generic names of such drugs (Neeshat, 2013).

2.2. Study measures

Patient charts were screened for pDDIs using *Micromedex®* free version for Microsoft Windows 8 *by Truven Health Analytics Inc*. We considered all drugs given to patients including all regular and PRN (pro re nata: as required) during their whole hospital stay, that is, from their admission to discharge in the hospital. Based on the severity, pDDIs were classified into three main types;

- **Contraindicated:** The drug-pair is contraindicated for the patient.
- **Major:** Such interaction may have risk of death and/or may result in some serious negative outcome.
- **Moderate:** It may have harmful effect on patient's condition and can require change in the prescription.

Furthermore the scientific evidence of the pDDIs was documented using the following three classifications

- **Established:** Research conducted under well controlled studies have strongly demonstrated the existence of interaction.
- **Theoretical:** Researchers suggest that the interaction exists but there is no proof of well-controlled studies.
- **Probable:** There is no strong evidence present, but health care professionals suspect that there may have interaction on the basis of their observations or pharmacology of drugs.

2.3. Data analyses

Frequencies and percentages are used to represent gender, age group, duration of hospital stay and number of drugs used by the patients. Median and ranges are also used accordingly. Multivariate logistic regression analysis is done to determine the association of occurrence of potential drug–drug interactions with specified risk factors including gender, age, hospital stay and number of drugs prescribed. *P*-value of 0.05 or less was deemed statistically significant. SPSS for Windows version 20 (SPSS, Inc., Chicago, IL, USA) was employed for all statistical analyses.

3. Results

More than three thousand patients were admitted in the Department of Cardiology during the study period. Among them 2342 patients were studied. Among the studied patients 1291 (55.1%) were male and 1051 (44.9%) were female; median age was 62 years; median hospital stay was 6 days and median number of prescribed medications was 8 (Table 1). Most common diagnosis was myocardial infarction followed by acute coronary syndrome and coronary artery disease (Table 1).

Upon analysis, a total of 5109 numbers of pDDIs and 53 types of interacting combinations were identified. Overall, 2145 (91.1%) patients had a minimum of one pDDI regardless of type of severity; 2021 (86.3%) and 1979 (84.5%) patients were having at least one pDDI of major and moderate severity, respectively (Table 2). Contraindicated types of pDDIs were not found in any patient. In most of the cases 1–2 pDDIs per patients were identified with median of 2 pDDI. The identified pDDIs were classified on the basis of severity and scientific evidence. Table 3 shows these types for 5109 numbers of pDDIs. Among 5109 pDDIs, most were of moderate (2810, 55%) or major severity (2299, 45%); probable (2912, 57%), established (1238, 24.2%) or theoretical (959, 18.8%) type of scientific evidence.

Table 1 General patient characteristics.

Patient characteristics	Frequency (%)
Gender	
Male	1291 (55.1)
Female	1051 (44.9)
Age (years)	
⩽14	17 (0.7)
15–30	62 (2.6)
31–45	200 (8.5)
46–59	945 (40.4)
⩾60	1118 (47.7)
Median (years)	62
Range (years)	12–100
Hospital stay (days)	
⩽3	497 (21.2)
4–6	1030 (44)
⩾7	815 (34.8)
Median (days)	6
Range (days)	1–20
Number of prescribed medications	
⩽4	44 (1.9)
5–6	682 (29.1)
⩾7	1616 (69)
Median (drugs)	8
Range (drugs)	1–18
Main diagnosis	
Myocardial Infarction (MI)	770 (32.9)
Coronary Artery Disease (CAD)	531 (22.7)
Acute Coronary Syndrome (ACS)	427 (18.2)
Others*	614 (26.2)

Table 2 Prevalence of pDDIs in the department of cardiology.

Type of prevalence	Frequency: *n* (%)
Severity of pDDIs	
Overall[a]	2145 (91.6)
Major[b]	2021 (86.3)
Moderate[b]	1979 (84.5)
Number of pDDIs per patient	
None	197 (8.4)
1–2	1704 (72.8)
3–5	339 (14.5)
⩾6	102 (4.4)
	Total pDDIs (*n* = 5109)
Median	2
Range	1–14

[a] Overall prevalence stands for occurrence of at least one pDDI despite of severity-type.
[b] A single prescription may contain both type of interactions i.e. at least one major and at least one moderate interaction as well.

Table 3 Levels of identified pDDIs.

Level	Frequency: *n* (%)
Severity	
Major	2299 (45.0)
Moderate	2810 (55.0)
Documentation (Scientific Evidence)	
Established	1238 (24.2)
Theoretical	959 (18.8)
Probable	2912 (57.0)

In addition, about fifty-three interacting drug-combinations were also identified during the pDDIs. Few of the most frequently occurring pDDIs despite of their clinical significance found in our study are presented in Table 4. Top 10 frequently occurring pDDIs included 3 major and 7 moderate types of pDDIs. Furthermore to identify predictors of pDDIs, a multivariate logistic regression analysis for the association of pDDIs with various risk factors (Table 5) was used. It was revealed that patient age of sixty years or more ($p = < 0.001$; OR = 0.263; 95% Cl = (0.167–0.353)) was significantly associated with pDDI events. Moreover, hospital stay of seven days or longer ($p = < 0.001$; OR = 0.230; 95% Cl = 0.150–0.354) and those patients taking 7 or more drugs ($p = < 0.001$; OR = 0.063; 95% Cl = 0.043–0.093) were also found significantly associated with pDDI events.

Table 5 Predictors associated with pDDIs.

Variable	Total number of patients: $n = 2342$		Multivariate	
	Interaction present ($n = 2145$)	Interaction absent ($n = 197$)	OR (95% Cl)	*P*-value
Patient age (years)				
<60	1069	155		
≥60	1076	42	0.243 (0.167–0.353)	<0.001
Gender				
Female	965	86		
Male	1180	111	0.857 (0.616–1.193)	0.361
Hospital stay (days)				
<7	1359	168		
≥7	786	29	0.230 (0.150–0.354)	<0.001
Number of drugs				
<7	564	162		
≥7	1581	35	0.063 (0.043–0.093)	<0.001

OR = Odds ratio; CI = Confidence interval.
Exposure to potential drug–drug interactions (pDDIs) was the dependent variable in the model (0 = absent, 1 = present). The following variables were included in the model as predictors of pDDIs: patient's age (1 = below 60 years, 0 = 60 years or older), gender (1 = male, 0 = female), hospital stay (1 = less than 7 days, 0 = 7 days or above), and number of drugs (1 = less than 7 drugs, 2 = 7 or above).
$p = < 0.001$ was considered statistically significant.

4. Discussion

The prevalence of pDDIs in our study was very 91.6%. Few years ago, a similar study was performed in the Department of Cardiology, Hazara, Pakistan which showed overall 77.5% pDDI prevalence rate among randomly selected cardiac patients (Ismail et al., 2012b). A study in the south Indian hospital showed that prevalence rate for pDDIs was 30.67% among the studied cardiac patients (Patel et al., 2011). According to a study carried out in the cardiac ward of a hospital in Nepal 32 out of the 150 studied cardiac patients had at least one pDDI with prevalence rate of 21.3% (Sharma et al., 2014). 43.4% prevalence rate for pDDIs was observed during the study in the cardiac patients at an Iranian hospital (Namazi, 2012). Few other studies also suggest that cardiac patients are at higher risk of pDDIs as a number of cardiac drugs are associated with pDDIs as these patients are more vulnerable to pDDIs due to complexity of disease and multiple drug therapy (Albadr et al., 2014; Smithburger et al., 2010; Straubhaar et al., 2006). Researchers have found that the drugs commonly involved in pDDIs include cardiac glycosides, NSAIDs, diuretics and calcium channel blockers (Queneau et al., 2007). These studies show that pDDIs are one of most important issues in cardiac patients.

Our study reported the median number of two pDDIs in the cardiac patients. A study held earlier at ATH reported similar median number of pDDIs in cardiac patients (Ismail et al., 2012b). The median number of pDDIs in our study was in accordance with previous studies. Some other studies found similar median for pDDIs in cardiac patients (Bacic-Vrca et al., 2010; Straubhaar et al., 2006). It was revealed in our study that 55% of pDDIs in cardiac patients were of moderate severity and 45% with major severity. A previous study in cardiac patients at ATH also found a number of pDDIs.

Table 4 Top 10 pDDI combinations.

pDDI Combination	Severity	Documentation	Frequency
Aspirin + Clopidogrel	Major	Probable	489
Clopidogrel + Fondaparinux	Major	Theoretical	423
Aspirin + Fondaparinux	Major	Theoretical	414
Aspirin + Bisoprolol	Moderate	Probable	380
Aspirin + Ramipril	Moderate	Established	268
Aspirin + Nitroglycerin	Moderate	Probable	230
Hydrochlorothiazide + Ramipril	Moderate	Probable	180
Aspirin + Furosemide	Moderate	Probable	146
Aspirin + Lisinopril	Moderate	Established	142
Atorvastatin + Clopidogrel	Moderate	Established	128

Most of the pDDIs were of moderate severity, while others had major severity (Ismail et al., 2012b). Majority of cardiac patients in Croatia were also found with moderate pDDI severity (Bacic-Vrca et al., 2010).

Our study found some factors related with pDDIs that include patients' age, polypharmacy and long hospital stay. Significant associations of pDDIs with various factors have also been found in different other studies. Our findings regarding association of pDDIs with elder patients are supported by other studies as well (Bacic-Vrca et al., 2010; Mallet et al., 2007). It was reported in our study that old age is a risk factor for pDDIs ($p < 0.001$). A study performed at Switzerland in cardiovascular patients also showed that patients with old age were at higher risk for pDDIs (Egger et al., 2007). Another study carried out in patients taking antihypertensive drugs in Medicaid population also found significant association of pDDIs with increase in age (Carter et al., 2002).

Long hospital stay is another factor associated with occurrence of pDDIs as reported in our study ($p < 0.001$). According to the results obtained from a study conducted at Brazil in hospitalized patients, it was found that patients with longer hospital stay had significant association with pDDIs (Riechelmann et al., 2005). Some other studies found similar association which support our findings which suggest that longer hospital stay may increase the chances of pDDI occurrence (Moura et al., 2009; Patel et al., 2011). Patients taking multiple drugs in our study were at higher risk of pDDIs ($p < 0.001$). A study held at Switzerland in a cardiac ward found that incidence of pDDIs increased with increase in number of drugs prescribed (Egger et al., 2007). Another study performed at USA in patients with hypertension reported similar association (Carter et al., 2004). Few other studies have also found similar association of polypharmacy with incidence of pDDIs (Chatsisvili et al., 2010; Cruciol-Souza and Thomson, 2006b; Gagne et al., 2008; Janchawee et al., 2005; Riechelmann et al., 2005).

There was no significant association of pDDIs with specific gender in our study. Various studies have found different results regarding association of any gender with risk of pDDIs. A study held in cardiac patients of ATH had found significant association of pDDIs with male patients (Ismail et al., 2012b). On the other hand, a significant association of pDDIs was found with female patients in another study performed in Brazil (Cruciol-Souza and Thomson, 2006a). There are many studies which support our findings. A study in Italy revealed that pDDIs are not associated with any specific gender (Nobili et al., 2009). Our findings suggest that pDDIs are associated with elder patients, increased number of drugs and patients with longer hospital stay.

The pharmacist role regarding clinical outcomes of various adverse events is very important as pDDIs are a significant factor for hospitalization of patients. A clinical pharmacist can help in the improvement of pharmacotherapy. A clinical pharmacist can find factors that may result in irrational prescriptions. Such factors are called "drug related problems" and may alter the desired effects of drugs (Azhar et al., 2009; Hanlon et al., 2004; Viktil and Blix, 2008). The role of pharmacist in the developed world is well recognized but this profession is not well established in the developing countries including Pakistan. The lack of proper role of pharmacist in less developed countries is leading patients with higher ratio of adverse drug events. If pharmacists are assigned with their proper role it may result not only in avoiding adverse drug events but also in reducing cost of hospitalization as well (Albadr et al., 2014; Azhar et al., 2009).

4.1. Limitations

Limitation of this study is its duration which is just for one year without any intervention component. In addition, another issue that might have affected the results of current study is a strict inclusion criteria due to which, approximately a quarter of medical chart was excluded. It is possible that the cases excluded might be representing a relevant subpopulation of patients, and using missing value imputations authors have assessed the predictors of pDDIs for this sample in a better way. However, in the current situation it was not possible for the researcher to predict how the excluded cases might have influence the current results of study. Future studies addressing the similar question should consider adding such case and analysis using missing value imputations can give a better understanding about the predictors for the pDDIs among hospitalized patients. Moreover, the absence of in vitro models in our study representing the actual physiological environment also limits our ability to accurately find the predictors in vivo environment where multiple drugs are co-administered.

5. Conclusion

Our study concluded that the overall incidence of pDDIs was very high in the Department of Cardiology. It was found that incidence of pDDIs was associated with old age, polypharmacy and increased lengths of hospital stay. The development of such data base in hospitals may help for the surveillance of pDDIs in hospitalized cardiac patients.

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