Brief Communication

Assessment of Potential Drug–Drug Interactions in Hospitalized Cardiac Patients of a Secondary Care Hospital in the United Arab Emirates

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Abstract

Objective: To identify the types, severity, and documentation grades of potential drug–drug interactions (pDDIs) and to identify the predictors of pDDIs among hospitalized cardiac patients. **Methods:** This was a cross-sectional study. All the patients who were admitted for >24 h in a cardiology ward of a general hospital of the United Arab Emirates and prescribed with cardiac medications were included. The occurrence of any pDDI between cardiac medications and other coprescribed medications was identified using Micromedex database 2.0® and graded and documented based on the severity and documentation. **Findings:** A total of 842 pDDIs were identified in 155 patients. The overall relevant frequency for the occurrence of pDDIs was found to be 87.74%. A total of 79 pairs of pDDIs were identified. Among identified pDDIs, 41.33% and 56.65% were major and moderate severity type, respectively, whereas 12.32% were excellent and 36.81% were good documentation grade. The majority of pDDIs were between aspirin-bisoprolol (11.64%). Patients taking more than seven drugs (odds ratio [OR] = 9.90; 95% confidence interval [CI]: 2.28–42.99), polypharmacy (OR = 3.86; 95% CI: 0.93–16.08), and number of medical conditions (OR 0.25; 95% CI: 0.09–0.68) were significant predictors of pDDIs. **Conclusion:** The study fosters the importance of regular and close monitoring for pDDIs among cardiac patients. Thus, multicenter interventional studies are required to determine the exact nature and types of pDDIs in the local population.

Keywords: *Adverse drug reactions, cardiology, hospitalized patients, potential drug–drug interactions*

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Introduction

Drug–drug interactions (DDIs) appear to be the most frequently encountered challenge that may alter overall therapeutic response and may result in increased hospital stay and health care cost. Studies suggest that cardiovascular disease (CVD) patients more repeatedly encounter DDIs than patients with other disease states, probably due to associated risk factors such as age, polypharmacy, and pharmacokinetic and pharmacodynamic profile of the drugs.[1]

The literature states that up to 1% of hospitals' admissions and 16% of admissions due to adverse drug reactions (ADRs) are owing to DDIs.[2] The reported prevalence rate of potential DDIs (pDDIs) in CVD patients is found to be 65%–99.2%.[1,3-6] Studies have reported a higher prevalence of DDIs in CVD patients than other disease group population.[7]

Not much data are available in the Gulf Cooperation Council countries regarding the incidence or prevalence of pDDIs among cardiac patients. There are few published data regarding the incidence or prevalence and pattern of DDIs among United Arab Emirates (UAE) CVD patients. Hence, this study aims to find out the frequency, types, severity, documentation

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grades, and predictors of pDDIs among hospitalized cardiac patients.

Methods

This was a cross-sectional clinical study conducted at a cardiac inpatient setting of a secondary care ministry hospital from January 2017 to May 2017. One hundred fifty-five patients were included using a convenience sampling technique. Patients of >18 years of age of both genders, diagnosed with any CVD, and admitted under direct cardiac care for a minimum of 1 day and prescribed with a minimum of two medications were included. However, patients referred to the cardiology department for the assessment and visited as outpatients were excluded.

The cases were identified by the principal investigator by attending clinical ward rounds at the study site. All the required information such as demographic parameters, number of drugs prescribed, length of hospital stay, primary diagnosis, and the number of comorbidities and laboratory investigations was collected from the medical records and entered into a data collection form.

The prescriptions of in-patients were reviewed for the presence of pDDIs when two or more drugs were prescribed by entering the prescribed drugs in the Micromedex® 2.0 database. The drug interactions tool (DRUG-REAX®) of this database helps to check for interacting drugs, their effects, and clinical significance (Truven Health Analytics Inc., Michigan, USA). The identified pDDIs were classified according to the severity and documentation grade system of the database. Drug interaction probability scale (DIPS) was used to assess the probability of pDDIs.[8]

All ADRs noted by treating cardiologist/s, reported by patients, and occurred during the hospital stay as a consequence of pDDIs were documented. A reported ADR was included and documented only when the suspected drug was involved in the pDDIs and the ADR corresponds to the description of the interaction effect cited in Micromedex®. Naranjo and WHO probability scale were used to assess the causality assessment of documented ADRs.[9,10] Hartwig *et al*. scale was implemented to determine the severity.[11] However, Modified Schumock and Thornton Scale and predictability criteria were used to assess the preventability and predictability of ADRs.[12]

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM, Armonk, New York, USA). Multivariate logistic regression analysis was done to assess the predictors of pDDIs. Chi-square test was used to assess the association between categorical variables and pDDIs. Odds ratio (OR) with 95% confidence interval (95% CI) was performed. Pearson correlation test was done to assess the relationship between the number of DDIs and continuous demographic variables (age, number of comorbidities, number of medication, and duration of hospital stay). A $P < 0.05$ and $P < 0.01$ were considered as statistically significant and highly significant, respectively.

Approval for the conduct of the study was obtained from the institutional and regional research and ethics committee (MOHP/RAK/SUBC/NO-372016-PG-P).

Results

A total of 155 patients were recruited and screened for the pDDIs during the study period, among which majority (128 [82.6%]) were male. The mean age of the study patients was found to be 58.8 ± 14.3 years. Most of the study patients were expatriates (120 [77.4%]) followed by UAE nationals (35 [22.6%]). The average length of hospital stay of the patients screened was found to be 4.8 ± 2.7 days. The mean number of drugs administered was 9.1 ± 2.8 per patient.

The overall relevant frequency for pDDIs among the study patients was found to be 87.74%. A total of 842 pDDIs and 79 pairs of interacting drugs were identified among 155 patients. A total of 136 (87.7%) of the patients had a minimum of single DDI, irrespective of severity. Severity, documentation grades, mechanism, onset, and probability assessment of pDDIs are shown in Table 1.

A total of 79 different pairs of interacting drugs associated with the use of cardiovascular medicines were detected. Aspirin with bisoprolol (98 [11.64%]) followed by aspirin with clopidogrel (95 [11.28%]) was the most commonly documented pDDIs. The most common 15 pairs of pDDIs are mentioned in Table 2.

A total of 12 ADRs were reported among 155 patients as a possible outcome of pDDIs. Thus, the relevant frequency of suspected ADRs, as a possible outcome of pDDI, was found to be 7.74%. Majority (n = 11) were males. Higher number (n = 9) of ADRs documented in expatriates. Bleeding was the most commonly suspected ADR (n = 6) followed by hyperkalemia (n = 3), bradycardia (n = 1), hypokalemia (n = 1), and raised prothrombin time (n = 1). Tenecteplase was the most commonly involved drug in ADR (6 [50%]) followed by perindopril (n = 2) and enoxaparin, losartan, furosemide, and diltiazem (n = 1) each. In the majority of cases (n = 7), withdrawal of suspected medication was done, while (n = 5) patients were managed by the alteration in the prescribed dose of medication.

Table 1: Severity, documentation grades, mechanism, onset, and probability assessment of the potential drug-drug interactions in the studied patients

pDDI	*n* (%)
Number of pDDIs per patient (*n*=155 patients)	
None	19 (12.25)
1-2	6 (3.87)
3-5	53 (34.19)
≥6	77 (49.67)
Severity of pDDIs (*n*=842)	
Contraindicated	3 (0.35)
Major	348 (41.33)
Moderate	477 (56.65)
Minor	14 (1.66)
Documentation of pDDIs (*n*=842)	
Excellent	103 (12.32)
Good	310 (36.91)
Fair	429 (50.9)
Mechanism of pDDIs (*n*=842)	
Pharmacodynamic	526 (62.74)
Pharmacokinetic	85 (10.10)
Multiple mechanism	142 (16.86)
Unknown	89 (10.57)
Onset of pDDIs (*n*=79 pairs)	
Rapid	10 (12.66)
Delayed	24 (38.38)
Unknown	45 (56.96)
DIPS (*n*=842)	
Highly probable	128 (15.9)
Probable	149 (17.69)
Possible	437 (51.89)
Doubtful	128 (15.2)

pDDI=Potential drug-drug interaction, DIPS=Drug interaction probability scale

No treatment was given to eight patients except drug withdrawal, and the remaining (2 [16.66%]) patients were treated symptomatically, while two patients were treated with specific treatments. Majority of the suspected ADRs (n = 10) were recovered.

Naranjo causality assessment of ADRs reveals that majority of the suspected ADRs were probable (n = 7) followed by possible type (n = 5). While a majority of the suspected ADRs were possible (n = 5) in nature followed by probable type (n = 7) by WHO probability assessment. Majority of the suspected ADRs were mild in nature (7 [58%]) followed by moderate (n = 2) and severe (n = 3). Seven ADRs were of the predictable type and (n = 5) were not predictable. Majority of the suspected ADRs (n = 8) were of probably preventable type followed by definitely preventable (n = 2) and not preventable type (n = 2).

A significant ($P < 0.05$) association was documented between nationality ($\chi^2 = 4.722$; $P = 0.041$), length of hospital stay ($\chi^2 = 6.126$; $P = 0.021$), number of medical conditions diagnosed ($\chi^2 = 10.379$; $P = 0.015$), and occurrence of pDDIs. However, a highly significant ($P < 0.01$) association was documented for number of drugs prescribed ($\chi^2 = 35.18$; $P < 0.01$) and polypharmacy ($\chi^2 = 32.06$; $P < 0.01$). It was noted that patients taking seven or more drugs ($P = 0.002$; OR 9.90; 95% CI = 2.28–42.99), polypharmacy ($P = 0.063$; OR = 3.86; 95% CI = 0.93–16.08), and number of medical conditions ($P = 0.006$; OR 0.25; 95% CI = 0.09–0.68) were significant predictors of pDDIs. A statistically highly significant ($P < 0.01$) positive linear correlation was observed between number of drugs prescribed and total number of pDDIs ($r = 0.547$; $P < 0.01$).

Table 2: Most common pair of potential drug-drug interactions in the cardiology department's patients

Type of pDDIs	*n* (%)	Severity	Documentation
Aspirin-bisoprolol	98 (11.64)	Moderate	Good
Aspirin-clopidogrel	95 (11.28)	Major	Fair
Atorvastatin-clopidogrel	89 (10.57)	Moderate	Excellent
Clopidogrel-enoxaparin	82 (9.74)	Major	Fair
Aspirin-perindopril	78 (9.26)	Moderate	Fair
Aspirin-furosemide	43 (5.11)	Major	Good
Aspirin-insulin	41 (4.87)	Moderate	Fair
Bisoprolol-insulin	32 (3.80)	Moderate	Good
Insulin-perindopril	29 (3.44)	Moderate	Good
Aspirin-tenecteplase	24 (2.85)	Moderate	Good
Enoxaparin-tenecteplase	23 (2.73)	Major	Fair
Furosemide-perindopril	17 (2.02)	Moderate	Good
Aspirin-spironolactone	14 (1.66)	Major	Good
Aspirin-metformin	11 (1.31)	Major	Fair
Amlodipine-clopidogrel	9 (1.07)	Major	Excellent

pDDI=Potential drug-drug interaction

Discussion

The higher occurrence of pDDIs in males in our study is consistent with previously published reports.[13-15] The average number of drugs prescribed/patient in our study was also similar to other studies.[13,14] The similarities in observations could be due to similarities in the prescribing pattern of the medications in CVD patients. There was a variance in the reported number (higher and lesser) of pDDIs documented in other studies compared to our study.[3,6,13] The difference in the number of pDDIs and interacting pairs of a drug can be because of the number of drugs, classes of drug, and drugs prescribed for other comorbidities. CVD patients often have multiple comorbidities, for which they use many drugs other than cardiac medication giving rise to more pDDIs.

Majority of the pDDIs were of moderate severity in our study. This observation of ours is consistent with

a study conducted by Murtaza et *al.*, which reported a higher number of moderate (55%) followed by major severity (45%) pDDIS.[1] The slight difference in severity grades of pDDIs is not validated and can be possible due to the difference in resources/database used for identification of pDDI.

As far as documentation grades are concerned, half of the pDDIs were fair followed by good and excellent. Ismail *et al.* reported most interaction to be good and fair in documentation similar to our study.[16] However, Shakeel *et al.* reported slight different documentation grades; almost half were good followed by fair, then excellent documentation.[17] The difference in the documentation grade reporting could be due to the difference in the type of drugs prescribes for patients in different study settings, availability, and affordability of medications, local and international treatment guidelines, and prescribers' preference based on their experience.

The incidence rate of pDDIs in the current study falls within this reported range of other studies.[1,3-7] A wide variation of the occurrence of pDDIs among cardiac patients may be because of various factors such as age, polypharmacy, and comorbidities which affects the potential of DDIs.

A majority (58.3%) of the interactions were pharmacokinetic in nature as reported by Sharma *et. al.* This was in contrast to the findings of our study, which documented a higher number of pharmacodynamic interactions.[15] The onset of pDDIs in our study was found to be unknown for most. Similar results were reported by Shakeel *et al*.[17] The possibility of a high number of unknown onset can be due to underreporting of pDDIs or not observed or noticed promptly.

Age, gender, length of stay, number of drugs received/polypharmacy, comorbidities, and other patient characteristics are known to be as the potential predictors of DDIs. Our findings are almost in accordance with the findings of Crucial-Souza and Thomson, which documented some medications and comorbidities as the significant predictor of DDIs in patients.[7] Moreover, Jain *et al*. identified age and polypharmacy having a positive correlation with the drug interaction.[18] Polypharmacy, length of stay, and concurrent illness are the most crucial determinants of pDDIs.[15] Predictors of pDDIs. Our findings are similar to Murtaza *et al.*, which revealed age, length of stay, and number of drug prescribed to be positive predictors of pDDIs.[1] However, in Sharma *et al*.'s study, length of hospital stay, number of medications, and concurrent illness were associated risk factors.[15] It is well-known fact that more extended length of hospital stay and concurrent illness contributes to increased exposure to drugs, which might lead to higher prevalence of pDDIs.[4]

The reason for a low occurrence of ADRs in our study could be possibly due to the short length of stay of patients as our study was conducted in a secondary care hospital. Bleeding, bradycardia, and abnormal serum potassium levels were the most commonly documented ADR in our study. Almost similar types of clinical outcome of pDDI have been documented in a study conducted by Kovačević *et al*. However, in their study, the most common most common potential clinical outcome was cardiovascular related.[4]

The strengths of our study are that the pharmacist was involved in the monitoring of pDDIs. Further, we used the DIPS for assessing the probability of pDDIs, which is not documented in many previous studies and the study also documented that ADRs occurred as a possible consequence pDDIs. The main limitations of our study were short study duration, small sample size, noninternational, and conducted in a single center.

In conclusion, the study fosters the possible role of the pharmacist in regular monitoring of cardiac patients receiving different medications. Multicenter interventional studies are required to assess the effect of interventions in preventing and managing pDDIs, which further improves patient outcomes.

Authors' Contribution

Muhammad Zeeshan Khan, Sathvik Belagodu Sridhar and Pradeep Kumar Gupta contributed in designing, conducting the study, acquisition of data, analysis, and interpretation of the data. All authors read and approved the manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. 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.
2. Roblek T, Trobec K, Mrhar A, Lainscak M. Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. Arch Med Sci

2014;10:920-32.
3. Reis AM, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics (Sao Paulo) 2011;66:9-15.
4. Kovačević M, Vezmar Kovačević S, Miljković B, Radovanović S, Stevanović P. The prevalence and preventability of potentially relevant drug-drug interactions in patients admitted for cardiovascular diseases: A cross-sectional study. Int J Clin Pract 2017;71:e13005.
5. Uddin MB, Nipa N, Ahmed S, Haider B, Hasan SB, Yousuf A. Possibility of drug-drug interaction through prescription analysis at the national institute of cardiovascular disease (NICVD), Bangladesh. Peertechz J Clin Pharmacol Clin Pharmacokinet 2016;2:7-10.
6. Sepehri G, Khazaelli P, Dahooie FA, Sepehri E, Dehghani MR. Prevalence of potential drug interactions in an Iranian general hospital. Indian J Pharm Sci 2012;74:75-9.
7. Cruciol-Souza JM, Thomson JC. Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. J Pharm Pharm Sci 2006;9:427-33.
8. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother 2007;41:674-80.
9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
10. The Use of the WHO-UMC System for Standardized Case Causality Assessment. Accessed from: http://www.WHO-UMC.org/graphics/4409.pdf. [Last accessed on 2016 Jul 18].
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
12. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27:538.
13. Marusic S, Bacic-Vrca V, Obreli Neto PR, Franic M, Erdeljic V, Gojo-Tomic N, *et al.* Actual drug-drug interactions in elderly patients discharged from internal medicine clinic: A prospective observational study. Eur J Clin Pharmacol 2013;69:1717-24.
14. Shanbhag AD, Hema NG, Sadananda KS. Potential drug-drug interactions among hospitalized cardiac patients. Int J Basic Clin Pharmacol 2016;5:2251-6.
15. Sharma S, Chhetri HP, Alam K. A study of potential drug-drug interactions among hospitalized cardiac patients in a teaching hospital in Western Nepal. Indian J Pharmacol 2014;46:152-6.
16. Ismail M, Iqbal Z, Javaid A. Khan TM. Potential drug-drug interactions in cardiology ward of a teaching hospital. Health Med 2012;6:1618-24.
17. Shakeel F, Khan JA, Aamir M, Shareef R, Shah N. Identification of clinically significant drug-drug interactions in cardiac intensive care units of two tertiary care hospitals in Peshawar, Pakistan. Trop J Pharm Res 2016;15:2289-95.
18. Jain S, Jain P, Sharma K, Saraswat P. A prospective analysis of drug interactions in patients of intensive cardiac care unit. J Clin Diagn Res 2017;11:FC01-4.