

Detection and analysis of potential drug-drug interactions among patients admitted to the cardiac care unit in a tertiary care hospital

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Abstract. – OBJECTIVE: This study aimed to estimate how prevalent potential drug-drug interactions (pDDIs) were in patients with cardiovascular diseases who were hospitalized for more than 24 hours, and to determine the risk factors associated with these pDDIs.

PATIENTS AND METHODS: A prospective observational study was conducted on patients admitted to the cardiac care unit in a tertiary care hospital. We included two hundred medical records of cardiovascular disease patients who were prescribed more than one drug. These medical records were analyzed for pDDIs using the Micromedex drug interaction checker database. Data were analyzed using Descriptive statistics. Chi-square test and the Pearson correlation coefficient were applied.

RESULTS: PDDIs were prevalent in 95% of the analyzed medical records, with at least one detected pDDI per record. Within the 200 medical records, 430 potentially interacting drug pairs were identified, with the majority resulting in moderate and major interactions. Aspirin/clopidogrel (111), furosemide/aspirin (89), enoxaparin/clopidogrel (89) and Lisinopril/aspirin (60) were the most common interacting pairs. Whereas, aspirin, heparin, clopidogrel, furosemide, ranitidine and Lisinopril were the most frequently implicated drugs in DDIs.

CONCLUSIONS: PDDIs were common among hospitalized cardiovascular patients. PDDIs were associated with age and number of drugs prescribed. The routine integration of an online drug interactions screening tool may improve the ability of pharmacists to identify cardiac patients at higher risk of potential drug interactions and conduct appropriate interventions thereafter.

Key Words:

Hospitalized cardiac patients, Micromedex, Drug-related problems, Tertiary care hospital, pharmacist, Saudi Arabia.

Introduction

Drug-related problems (DRPs) remain a major challenge in clinical practice¹. Because of the adverse health outcomes and excess healthcare costs associated with these problems, identifying and addressing DRPs have become integral patient safety measures in healthcare systems^{2,3}.

There are different DRPs classification schemes. These schemes categorize DRPs into drug selection problems, inappropriate doses, therapeutic duplication, adverse drug reactions or allergies, drug interactions, adherence issues and other problems⁴. Potential drug-drug interactions refer to the possibility of a drug to interact with another when concurrently prescribed, regardless of whether adverse events occurred, i.e., pDDIs can be considered as precursors of DDIs. Hence, preventing, identifying, and addressing potential drug-drug interactions may improve patient safety⁵.

The reported prevalence of drug interactions varies significantly among studies. Moreover, some studies⁶⁻⁸ report incident DDIs, sometimes clinically significant DDIs, and others report pDDIs. This variability complicates the comparison of rates of DDIs among different settings or different populations. However, many studies^{6,9-14} suggest that cardiac patients are among the populations at highest risk of DDIs and that many cardiovascular medications are associated with high risk of potential and actual DDIs in various settings.

PDDIs are mostly predictable and preventable if proper monitoring is performed. Studies¹⁵⁻¹⁷ exploring the occurrence and characteristics of pDDIs may aid healthcare professionals in predicting and preventing these interactions. Clinical pharmacists are healthcare professionals

primarily concerned with optimizing medication management and minimizing potential or actual drug-related problems, including DDIs in different healthcare settings¹⁸⁻²⁰. Studies^{19,21-23} have shown that cardiology clinical pharmacists were able to reduce the occurrence of pDDIs and other DRPs in patients with cardiovascular diseases.

This study aimed to identify the prevalence and assess the severity of pDDIs in hospitalized cardiac patients in a tertiary care hospital at the Asir region of Saudi Arabia and assess the correlation between the number of prescribed drugs and association of certain comorbidities with the incidence of DDIs.

Patients and Methods

A cross sectional study was conducted over a period of three months, in a tertiary care hospital in the Asir region. Ethical approval was obtained from the Research Ethics Committee at King Khalid University (HA-06-B-001). The study included hospitalized cardiac patients aged 18 years or older who were taking more than one drugs during their hospital stay, including the PRN drugs (as needed). We excluded patients who were referred to the cardiology unit for assessment, were visiting on an outpatient basis or died during their hospital stay. A pre-defined form was used to collect data including patient demographics and medical information. The Patients' medication orders and electronic medication lists were evaluated. Micromedex interaction databases were used to objectively assess the presence and severity rating of pDDIs. PDDIs were classified as either major, moderate, or minor. After the Micromedex database detected a pDDI and identified its severity level, the clinical pharmacist recorded other drugs involved in the interaction, their doses, and routes of administration.

Statistical Analysis

Demographic data like mean age and male to female ratio were described. Descriptive statistics were performed to develop a list of the most frequent and clinically significant pDDIs. Results were expressed as percentages for age, gender, diagnosis, number of drugs prescribed, severity and risk involved. A Chi-square test was done to study the potential association between the number of drugs prescribed, comorbidities, age and sex with the pDDI. Analysis was carried out using SPSS version 25 (IBM Corp., Armonk, NY, USA). The association between age and number of drugs prescribed and the number of pDDIs were analyzed using Pearson correlation. Continuous variables were expressed as means $\pm$ standard deviations (SD), while categorical variables were expressed as a count (percentage). *p*-value of <0.05 was considered significant.

Results

A total of 200 medical records of hospitalized cardiac patients were evaluated during the study period. Ninety three percent of the medical records contained drug combinations that exhibited moderate interactions; while 91.5% exhibited major interactions and 30.5% exhibited minor interactions (Table I).

Demographics and Clinical Characteristics

Of the 200 patients participating, a higher number of males [120 (60%)] were studied, compared to females (80 [40%]). The majority of patients were in the age group older than 70 years old [63 (31.5%)], followed by the age group 54-60 years [48 (24%)]. The most common diagnosis was hypertension [145 (72.5%)], followed by coronary artery diseases [97 (48.5%)] and congestive heart failure [58 (29%)]. Diabetes mellitus [121 (60.5%)], dyslipidemia [90 (45%)] and chronic

Table I. Prevalence of potential DDIs according to severity.

		Frequency	Percent	X ²	<i>p</i> -value
Major interaction	Yes	183	91.5	137.780	<i>p</i> < 0.001
	No	17	8.5		
Moderate interaction	Yes	186	93.0	147.920	<i>p</i> < 0.001
	No	14	7.0		
Minor interaction	Yes	61	30.5	30.420	<i>p</i> < 0.001
	No	139	69.5		

Table II. Patient's demographic and clinical characteristics.

Characteristics	N (%) or mean $\pm$ SD (range)
Gender	
Male	120 (60)
Female	80 (40)
Age (y)	62.8 $\pm$ 14.61
30-40	10 (5)
41-50	37 (18.5)
51-60	48 (24)
61-70	42 (21)
> 70	63 (31.5)
Number of drugs	10.9 $\pm$ 3.55
1-3	1 (0.5)
4-6	15 (7.5)
7-10	67 (33.5)
>10	117 (58.5)
Reason for hospitalization	
Hypertension	145 (72.5)
Coronary artery disease	97 (48.5)
Congestive heart failure	58 (29)
Atrial fibrillation	18 (9)
Cardiomyopathy	11 (5.5)
Valvular heart disease	2 (1)
Length of the hospital stay (days)	4.5 $\pm$ 1.3
< 3	10 (5)
3-5	129 (64.5)
> 5	61 (30.5)
Comorbidities	
Diabetes	121 (60.5)
Dyslipidemia	90 (45)
CKD	15 (7.5)
Respiratory disease	9 (4.5)
Gastrointestinal disease	3 (1.5)
Endocrine disease hypothyroidism	2 (1)

kidney disease (CKD) [15 (7.5%)] were the most common co-morbidities. The mean length of hospital stay was 4.5 $\pm$ 1.3 days, during which a majority of the patients received more than 10-drugs concurrently [117 (59%)], 7-10 drugs [67 (33.5%)] and 4-6 drugs [15 (7.5%)]. The anticoagulants and antiplatelet drugs [195 (97.5%)], antihypertensive [123 (77%)], angiotensin converting enzyme inhibitors (ACE inhibitors) [113 (56.5%)] and diuretic drugs [112 (56%)] were also used frequently (Tables II and III).

Prevalence and Severity of DDIs

Among the 200 checked prescriptions, 430 drug interactions were identified. The majority of the identified drug interactions were of moderate severity [186 (93%)], although nearly as many severe interactions [183 (91.5%)] were noted. Relatively few interactions of minor severity [61 (30.5%)] were found. The most common interacting drug pairs with severe consequences were aspirin/clopidogrel [111 (18.5%)], furosemide/aspirin [89 (10.5%)] and Heparin/aspirin [52 (7%)]. Among the moderate interacting drug pairs, Lisinopril, and aspirin [60 (12.3%)] was followed by Metoprolol and aspirin [58 (10.8%)], then insulin and aspirin [49 (10.3%)]. The interacting drug pairs of minor severity included ranitidine/aspirin [41 (58.5%)] and furosemide/hydralazine [24 (34.3%)] (Table IV).

Risk Factors

The prevalence of major and moderate DDIs increased in patients more than 70 years old

Table III. The most commonly prescribed drugs.

		Frequency	Percent	Chi-Square	p-value
Anticoagulants and antiplatelet	Yes	195	97.5	183.322	< 0.001
	No	4	2.0		
Diuretics	Yes	112	56.0	2.880	0.090
	No	88	44.0		
Antihypertensive	Yes	123	61.5	10.580	0.001
	No	77	38.5		
Calcium channel blocker	Yes	30	15.0	97.090	< 0.001
	No	169	84.5		
ACE inhibitors	Yes	113	56.5	3.663	0.056
	No	86	43.0		
Adrenergic inhibitors	Yes	116	58.0	5.472	0.019
	No	83	41.5		
Vasodilators	Yes	57	28.5	36.307	< 0.001
	No	142	71.0		
ARB	Yes	17	8.5	135.838	< 0.001
	No	181	90.5		
Inotropic agents	Yes	16	8.0	140.146	< 0.001
	No	183	91.5		

p-value is significant at $p < 0.05$.

Table IV. The most common drug pairs involved in pDDIs.

Risk rating	Interacting drug pairs	Frequency	Percent	Effect	Type
Severe	Aspirin and Clopidogrel	111	18.5	Aspirin, clopidogrel. Either increases toxicity of the other by pharmacodynamics synergism	PD
	*Aspirin and Furosemide	89	10.5	aspirin increases and furosemide decreases serum potassium	PD
	Clopidogrel and Enoxaparin	89	10.5	Either increases effects of the other	PD
	Clopidogrel and Omeprazole	69	8.1	Decreased Clopidogrel effect	PK
	Aspirin and Heparin	52	7	Aspirin, heparin. Either increases toxicity of the other by anticoagulation	PD
	Spironolactone and Aspirin	29	11.5	Aspirin decreases effects of spironolactone and both increase the potassium level	PD
	Ticagrelor and Aspirin	18	2.1	Increased risk of bleeding	PD
	Heparin and Clopidogrel	16	3.6	Bleeding	PD
	Lisinopril and Aspirin	60	9.3	Co administration may result in a significant decrease in renal function	PD
	Metoprolol and Aspirin	58	10.8	Aspirin decreases effects of metoprolol	PD
Moderate	Insulin and Aspirin	49	10.3	Hypoglycemia aspirin increases effects of insulin	PD
	Carvedilol and Aspirin	40	5.3	Aspirin decreases effects of carvedilol	PD
	Lisinopril and furosemide	32	5.0	pharmacodynamic synergism	PD
	Insulin and Lisinopril	27	4.2	lisinopril increases effects of insulin	PD
	Enalapril and Aspirin	26	6.7	Coadministration may result in a significant decrease in renal function. Decreased efficacy	PD
	Levofloxacin and Aspirin	16	7	Coadministration may result in a significant stimulation of the central nervous system	PD
	Clopidogrel and Atorvastatin	12	1.9	Decreased efficacy	PK
	Ranitidine and Aspirin	41	58.5	Reduce the absorption of aspirin	PK
	Furosemide and Hydralazine	24	34.3	Increase the Furosemide renal clearance	PK
	Dobutamine and Metoprolol	2	2.8	Metoprolol decreases effects of Dobutamin by pharmacodynamic antagonism	PD

*The interaction depends on the dose.

(58% and 59%, respectively), patients taking a higher number of drugs (more than 10 drugs) and patients having diabetes mellitus. No association was found between gender and the prevalence of pDDIs (Tables V and VI).

Discussion

We found that pDDIs were highly prevalent among hospitalized cardiac patients in a tertiary care hospital (95%), and that pharmacodynamic interactions were more common than pharmacokinetic ones.

The Micromedex database was used to detect pDDIs. Among the 200 prescriptions analyzed, 430 potential drug interactions were identified, with a prevalence rate of 95%. Our results are in accordance with many previous studies^{1,16,24,25},

which also indicated a high prevalence rate of pDDIs among hospitalized cardiac patients. The study done by Kovačević et al²⁴ reported a prevalence of 94.7%, while Murtaza et al¹ reported 91.6% and Shakeel et al²⁵ reported 96.9% prevalence of pDDIs in their studies. By contrast, a study¹⁶ in a South Indian hospital showed a low prevalence rate for pDDIs (30.67%) among the cardiac patients studied. The high variability of reported prevalence rates among different studies may be attributed to the use of different methods to detect pDDIs^{16,25}.

The majority of the identified pDDIs in our study were moderate in severity, followed by those major in severity. These results are in accordance with previous studies^{1,26} which also reported a high prevalence of pDDIs of moderate severity among cardiac patients.

Table V. Prevalence of potential DDIs, according to patient demographics and clinical characteristics.

Risk rating	Major			Moderate			Minor		
	N	p-value	X ²	N	p-value	X ²	N	p-value	X ²
Gender									
Male	113	0.098	X ² = 2.743	114	0.175	X ² = 1.483	38	0.661	X ² = 0.193
Female	70			72			23		
Age									
30-40	6	0.04	X ² = 14.484	6	0.001	X ² = 18.697	1	0.556	X ² = 3.011
41-50	36			35			10		
51-60	44			47			14		
61-70	39			39			15		
> 70	58			59			21		
Number of drugs prescribed									
4-6	11	0.001	X ² = 13.66	12	0.013	X ² = 8.702	2	0.135	X ² = 4.002
7-10	60			63			18		
> 10	112			111			41		
Comorbidities									
Diabetes	112	0.505	X ² = 13.66	112	0.764	X ² = 16.45	41	0.198	X ² = 1.76

A significant association was found between polypharmacy and the prevalence of pDDIs. We found a high prevalence of pDDIs in patients who received more than 10 drugs, as well as by those who received 7-10 drugs. Moreover, the results of this study indicated a high prevalence of moderate and severe interactions in the elderly patients. Many other studies^{1,24,27,28} have proposed polypharmacy pDDIs, especially among cardiac and elderly patients. For example, Schuler et al¹¹ found a high prevalence of pDDIs among their elderly patients, with a mean number of 7.5±3.8 drugs taken.

Patients diagnosed with diseases like hypertension, diabetes mellitus, heart failure and atrial fibrillation – which are more common in the elderly population – end up receiving at least 6 different drugs which promotes the practice of polypharmacy¹¹. Nevertheless, other studies²⁵ reported that the association between age and prevalence of pDDIs is not consistent after the adjustment of polypharmacy and the management of co-morbidities. Sometimes, the use of polypharmacy is essential in the management of patients with multiple co-

morbidities, and it is a major challenge for the healthcare system and professionals to optimize medication management and avoid adverse drug reactions (ADRs) and DDIs¹⁰.

In our study, no association was noted between gender and pDDIs. This result is similar to some previous studies^{1,2,4,12,14} performed in different countries. However, other studies^{17,29,30} have previously shown contradictory results. For instance, the study by Ismail et al¹⁷ demonstrated a significant association between the male gender and the prevalence of pDDIs. Another study carried out by Mateti et al²⁹ noted a significant association between females and the prevalence of pDDIs, as did Shanbhag et al³⁰ study.

Drugs used for the management of cardiovascular disease (CVD) are usually prescribed in combinations, which increases the likelihood of pDDIs²⁴. In our study, the most commonly prescribed drug pairs that were found to be associated with pDDIs were anticoagulants and antiplatelets, followed by antihypertensives and diuretics. Our study is in accordance with previous studies³¹ which stated that the drugs used for CVD, inflammation, diabetes, and infection were the major factors for hospitalization due to adverse drug reactions and drug-related problems. The consequences of the pDDIs reported in our study included bleeding, effects on heart rate and blood pressure, decreased renal function, disturbance in the potassium level and impaired glucose level.

Finally, the decision to use the drug pairs which cause pDDIs depends on several factors, such as the patient's condition and the risk/ben-

Table VI. Risk factor correlation with pDDIs.

Risk factor	r	p-value
Age	0.247**	0.001
Number of drugs prescribed	0.658**	0.001

p-value calculated using Pearson correlation; significant at $p < 0.05$.

efit ratio. If the potential benefits outweigh the risks, the physician may prescribe them together and monitor the patient closely. For example, in our study, the combination of aspirin and clopidogrel was the highest reported drug pair identified as a pDDI that may result in bleeding. However, physicians frequently prescribe them to prevent thromboembolisms as they are class I recommendation in multiple guidelines to prevent major adverse cardiac events (MACE).

Limitations

This study has several limitations. A single hospital was used as the study site, so the patient pool was limited. The monitoring of pDDIs was based on drug interaction screening software, which checks only the interactions; therefore, the consequences of these interactions are not considered. Future studies to monitor the actual adverse consequences of the identified pDDIs are recommended.

Recommendations

Healthcare professionals are encouraged to use screening software programs for the detection of pDDIs. The clinical pharmacist should be consulted in order to minimize medication errors, including the detection and prevention of pDDIs.

Conclusions

Patients having CVD are at high risk for pDDIs. Most of the detected pDDIs in this study were of moderate and high severity. The presence of diabetes mellitus, advanced age, and polypharmacy are the major risk factors for pDDIs. These factors can be used as triggers for more careful prescription and monitoring of DDIs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

Ethical approval was obtained from the Research Ethics Committee at King Khalid University.

Informed Consent

Written informed consent was obtained for all participants.

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