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INTERPRETATION DRUG INTERACTIONS IN HOSPITALIZED CARDIAC PATIENTS

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Abstract:

Objective: *The present study is aimed to identify potential drug-drug interactions in cardiac patients and document any observed interaction. It was also planned to evaluate the demographics of patients and correlate it with drug drug interactions in Lahore General Hospital, Lahore.*

Methodology: *It is a prospective observational study conducted in inpatient setting. The data collected in pre design data collection form for 220 patients, who are assessed for the period of six months. The cardiac patients who were taking at least two cardiac drugs and had a hospital stay of 48 hours were considered for this study. The collected data included demographics; cardiac drugs usage pattern and safety analysis data. The data was compiled in excel and analysed using Micromedex.*

Result: *A total of 220 patients were included in the study out of which 140 patients prescriptions contains pDDI. A total of 234 pDDIs were identified during the study period with median of 1.67 potential drug-drug interactions. Extensive (97.85%) poly pharmacy was observed in study population. The median hospital stay was 7 days. The incidence rate was found to be 63.64%. Majority of interactions were of moderate severity, delayed onset, and pharmacodynamics in nature. Total 28 actual interactions were observed in the observed cases. Out 234 drug interactions, aspirin/clopidogrel (16) and clopidogrel/atorvastatin (16) were most common drug interaction pairs observed among prescribed medications. Of the 234 interventions proposed, the most frequent suggestion was on monitoring for adverse effect (44.01%) followed by dose adjustment (15.81%). 25.64% of interventions were accepted and therapy was changed. Most of the adverse drug interaction observed resulted in bleeding. The causality assessment as per Naranjo and WHO scale were probable in most of observed drug interactions.*

Conclusion: *The present study identified pDDIs and also documented interactions in cardiovascular patients. It was found that the incidence rate of pDDI was high and associated with old age, poly pharmacy and increased lengths of hospital stay. This study highlights the need for screening prescriptions of cardiovascular patients for pDDIs and proactive monitoring of patients who have identified risk factors; this helps in detection and prevention of possible adverse drug interactions.*

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INTRODUCTION:

Drug treatment that interferes with the patient achieving an optimum outcome of medical care.[2] They pose as a Cardiovascular diseases (CVDs) remain the biggest significant risk, leading to significant morbidity and cause of deaths worldwide**.** A WHO report (2012) mortality. In a review of international studies, it was estimated that 17.5 million people die of CVDs each year found that about 28% of all emergency department visits representing 31% of all deaths. Of these, about 7.4 were related to DRPs and 24% of them resulted in million are due to coronary heart disease and 6.7 million hospital admission. In a study conducted by Blix[3] et al due to stroke. By 2030, an estimated 23.6 million people in 2004, it was seen that about 87% of hospitalized will die from CVDs mainly from heart disease and patients have drug related problems. In another study stroke. These are projected to remain the single leading [1] conducted by Nascimento[4] et al in 2009, the incidence causes of death. of DRPs was reported as 91.7. An Pakistani study reported that the incidence of DRPs was found to be greater than Although pharmacotherapy in cardiovascular diseases quoted in developed countries. High incidence of can improve the well-being, its benefit can be inappropriate dosage and improper drug selection compromised by drug-related problems (DRPs). A drugobserved in the study was attributed to lack of standard related problem is any event or circumstance involving treatment protocols and the differing treatment patterns between the medical wards in each Pakistani hospital.[15] Cardiovascular drugs are one of the drug categories frequently involved in drug related problems. A study by Andreazza[5]et al in 2011 reported cardiovascular drugs to account for the majority of all DRPs. Detection and prevention of DRPs can save lives along with enhancing patients' quality of life and optimizing healthcare costs. Among DRPs potential drug-drug interaction is most important part in cardiovascular pharmacotherapy.

The role of drug-drug interaction during medicinal therapy can be considered a bivalent outcome which can be either beneficial or profoundly unintended and distressful. The identification of such unintended interaction is the primary goal of this research. As it has been already identified by Committee for Human Medicinal Product (CHMP) of European Medicines Agency that drug-drug interaction are a common problem during drug treatment and is major reason behind numerous hospitalization as a result of adverse drug reaction, sometimes serious or even fatal adverse events.[6] Drug-drug interaction may also result in decrease or completely inhibit treatment efficacy.

Many studies have proven the significance of pharmacists in identifying and resolving potential drugdrug interactions through timely interventions. Gattis 8et al observed that including a pharmacist as a member of a multidisciplinary heart failure (HF) team significantly reduced mortality and HF events. Studies assessing the prevalence of potential drug-drug interactions in hospitalized cardiac patients and the significance of pharmacist intervention in such cases are lacking in Pakistan.

Potential for drug interaction is higher with cardiac drugs11 and there are reports on potential DDIs in cardiology department from Pakistan.[13] There are no studies reporting actual incidence of DDIs in the Pakistan setting. Hence, the present study was designed to assess the incidence and pattern of DDIs in hospitalized cardiac patients in a tertiary care hospital, with the assessment of reaction characteristics, outcome, causality and pharmacist intervention.

MATERIALS AND METHODS:

Study Site:

Study was conducted in cardiology ward at Lahore General Hospital, Lahore. it is a 300 bedded hospital providing secondary health care to people.

Study Duration:

Study was conducted for a period of 6 months from October 2015 to March 2016.

Study Design:

It was a prospective observational study conducted in cardiac inpatient setting.

Ethical Clearance:

Hospital Ethical Committee, Lahore General Hospital, Lahore.

Sample Size:

220 prescriptions were evaluated out of which 140 prescriptions had pDDIs.

Study Criteria: Inclusion Criteria

All cardiac patients admitted in cardiac ward. - Patients who were taking at least two drugs and had a hospital stay of at least 48 hours.

Exclusion Criteria: Patients admitted to Pediatric and Obstetric and pregnancy ward

Material Used

- Case Record
- Treatment Chart
- Lab Master
- Physician Notes
- Patient Medication Rack
- Nurses Comment
- Site (Micromedex)

Method of Collection of Data:

The newly admitted case was randomly selected on daily basis and reviewed for the potential DDIs and followed up for the assessment of observed drug interaction effect.

Study Procedure:

The patient demographics and all medically relevant information was noted in a predefined data collection form. Alternatively, these case charts were reviewed for potential drug interactions, drugs involved in interactions (dose, route, frequency, therapy duration, indication), laboratory investigations, followed up for assessing observed adverse drug interaction and pharmacist's intervention. The changes and the daily notes in the case sheets were followed until the patient was discharged or shifted to other wards. The Micromedex, Medscape and references books were used as tools to review the prescription and case charts. The clinical pharmacist's intervention was done by suggesting physician about the drug related problems.

Adverse drug interactions occurred due to drug-drug interaction was recorded in an ADR *Reporting Form.* For each adverse drug reaction, the following information were recorded: type of adverse event, seriousness, onset and resolution, severity, casualty, action taken, and event outcome, and was analysed using the following methods: causality assessment by WHO and Naranjo scales, severity by Hartwig scale. Drug-drug interaction check was performed using Micromedex-2. According to this tool, drug interactions were categorized as minor, moderate or major which indicates the possible risks of occurrence of the potential drug interactions which can occur in patients, but not the actual severity of drug interactions. The data obtained was used to categorize interactions based on the mechanism as pharmacokinetic or pharmacodynamics. The pharmacokinetic drug interactions were further categorized into interactions based on absorption, distribution, metabolism and elimination. The severities of the interactions were assessed and categorized as major (can cause permanent damage or life risk), moderate (can cause harm and treatment is required) or minor (can cause small or no clinical effect, with no treatment required).The data were stored confidentially and subjected to further analysis using appropriate software.

Statistical analysis:

The data was subjected to descriptive analysis using Microsoft excel version 2013. Results were expressed in percentages and mean-standard deviation (SD).

RESULT AND DISCUSION:

DDI is always a matter of concern in the effective management of patient's illness. It may pose a significant health hazard to patients when risk-benefit ratio of combining interacting drugs is not accurately estimated.[16] Drug- drug interactions can result in anything from minor morbidities up to fatal consequences.[6, 3]

1. Patients Demographics:

The present study identified the pattern of pDDIs among patients admitted to cardiac unit of general medicine ward. The data of 220 patients admitted to inpatients ward during the period October 2015 and March 2016 were analysed for assessment of potential drug interaction. Among them 140 patients had at least one potential drug interactions.

This study enrolled 220 patients in which 140 patients prescriptions contains pDDI, Therefore 140 prescription was analyzed for pDDI, which showed that majority population was males (95). Mean age of the patients were 64.43 (±14.58) year. Among the study population 106(75.71%) were geriatric patients, 7(2.8%) were renal impairment patients and 3(2.14%) were hepatic impairment patients. Out of 140 study population, 83 (59.28%) had diabetes mellitus type 2 as major comorbidity.

Table 1: Primary cardiovascular diagnosis in study patients.

Main Diagnosis	Male		Fe male		Total	
Hypertension	58	41.42	33	23.57	91	65
MI	22	15.71	5	3.57	27	19.28
CHF	26	18.57	14	10	40	28.57
Atrial fibrillation	2	1.42	1	0.71	3	2.14
ACS	4	2.85	4	2.85	8	5.71
CVA	6	4.28	2	1.42	8	5.71

Table 2 Number of drug usage by study patients.

Number of Drug Dispensed	Male		Female		Total	
3-5	2	1.42	1	0.71	3	2.14
6-10	58	41.42	26	18.57	84	60
>10	35	25	18	12.85	53	37.85

Among 140 study population, most of the patient had hypertension (65%) as a major diagnosis. Other main diagnosis were CHF(28.67%) and MI(19.28%). The N=140

A total of 1374 drugs were prescribed, and thus the average number of drugs per patient was 9.81. Among studied patients 60% were using 6-10 medication followed by 37.85% of patients using more than 10 medications. Extensive (97.85%) polypharmacy was observed in study population. The number of drug dispensed is given in Table 2.

2. Potential Drug-Drug Interaction Out of 220 prescriptions analyzed, 140 prescriptions comprised of potential drug interactions and it was found that 234 drug interactions were present. The incidence of potential drug interaction was 63.64%. Other studied showed the incidence rate of 30.67% from South Pakistani Hospital[16], 91.6% from Pakistan[42]. Among 234 drug interaction 90 types of interaction combinations were identified.

Out of 220 prescriptions analyzed, 140 prescriptions comprised of potential drug interactions and it was found that 234 drug interactions were present. The pattern of primary cardiovascular disorder is shown in Table 1.

incidence of potential drug interaction was 63.64%. Among 234 drug interaction 90 types of interaction combinations were identified. The studied prescription comprised 58.11% moderate interaction, 40.59% major drug interactions and 1.28 minor drug interactions. Among them 57.26% were pharmacodynamic drug interactions followed by 36.75% of pharmacokinetic interaction and 5.98% of unknown mechanism interactions. In most patients of the cases one potential drug interaction were identified with median of 1.67 potential drug-drug interactions. Among them 30% of prescription had two potential drug-drug interactions.

The classification of potential drug-drug interactions were made based on their mechanism like pharmacodynamic, pharmacokinetic or unknown. Among 234 drug interactions, 57.26% were pharmacodynamic, 36.75% were pharmacokinetic and 5.98% were unknown. Among pharmacokinetics 23.98% were metabolism interaction. The mechanism of pDDIs is shown in Table 3.

Table 3: Mechanism of potential drug interaction.

Mechanism		Male		Female		Total	
Pharmacokinetic	Absorption	2	0.85	0	0	2	0.854
	Distribution	16	6.83	7	2.99	23	9.82
	Metabolism	39	16.66	17	7.26	56	23.93
	Excretion	1	0.42	4	1.70	5	2.13
Subtotal		58	24.78	28	11.96	86	36.75
Pharmacodynamic	Synergism	67	28.63	35	14.95	102	43.58
	Antagonism	18	7.69	14	5.98	32	13.67
Subtotal		85	36.32	49	20.94	134	57.26
Unknown		7	2.99	7	2.99	14	5.98

Decreased efficacy was the commonest clinical clinical effect of interaction. Clinical effect of pDDIs is consequences in 56(23.93%) cases. Bleeding (21.36%) summarized in Table 4. and hypo or hyperglycemia (19.23%) was other common

Table 4: Clinical effect of pDDI.

Clinical effect	Male		Female		Total	
Bleeding	33	14.10	17	7.26	50	21.36
Decreased efficacy	31	13.24	25	10.68	56	23.93
Hypotension	4	1.70	5	2.13	9	3.84
Rhabdomyolysis	20	8.54	7	2.99	27	11.53
Increased Toxicity	21	8.97	13	5.55	34	14.52
Hypo or hyperglycaemia	32	13.67	13	5.55	45	19.23
QT prolongation	9	3.84	4	1.709	13	5.55

The drug interaction software by Micromedex-2 showed that monitoring for the adverse drug effects 173(73.93%) was the most popular intervention followed by dose adjustment 32(13.67%) and use of alternative 24(10.25%) following potential drug-drug interactions. The detailed management of potential drug interaction is listed in Table 5.

Table 5: Management of pDDI.

Management of pDDI	Male		Female		T otal	
Avoid concurrent use	0	0	1	0.42	1	0.42
Use of alternative drug	15	6.41	9	3.84	24	10.25
Discontinuation of drug	3	1.28	1	0.42	4	1.70
Dose adjustment	17	7.26	15	6.41	32	13.67
Continue with monitoring	115	49.14	58	24.78	173	73.93

3. Pharmacists Intervention

Of the 234 interventions proposed, the most frequent suggestion was on monitoring for adverse effect (44.01%) followed by dose adjustment (15.81%). 25.64% of interventions were accepted and therapy was changed. A study conducted in Coimbatore reported 251 interventions which is higher than this study. Of the 251 intervention, most common were related to drug interaction followed by doing changes. This higher result might be due to more of sample size than this current study.[1] Result of pharmacist intervention shown that table 6.

Table 6: Result of Pharmacist intervention.

Recommendation	Result	
Suggestion accepted and therapy changed	60	25.64
Suggestion accepted and therapy not changed	74	31.62
Neither suggestion accepted nor therapy changed	100	42.73

4. Adverse drug-drug Interaction

The incidence rate of adverse drug interactions was found to be 20%. This rate is similar to the study conducted in Iran.[15] Another study reported 17.53% of observed drug interaction which is lower than this study.[16] The most common drug interaction pair resulting in adverse drug reaction was aspirin/clopidogrel (5). Bleeding was the most important interaction in 8 cases followed by hypoglycaemia (4) and QT-interval prolongation (4). The most common objective drug is aspirin and precipitant drug is clopidogrel. Similarly, Bleeding was most common clinical effect of observed drug interaction in South Pakistani study.[16]

During the study period, a total of 28 adverse drug reactions were recorded among 234 pDDIs identified. The incidence rate of adverse drug interactions was found to be 20%. The study revealed that male patients 21(75%) predominated over females 7(25%) in ADR occurrence.

Of the reported adverse drug interactions moderate reactions accounted for 11(39.28%) followed by mild reactions 10(35.71%) and major reactions 5(17.85%). The causality assessment of reported ADRs as per the Naranjo scale revealed that 17(60.71%) were probable and 11(39.28%) were possible. As per WHO scale revealed that 16(57.14%) were probable and 12(42.85%) were possible. The detailed description of adverse drug reaction with severity and causality assessment is summarized in Table 7.

Table 7: Details of Observed drug interaction (adverse drug interaction).

Interacting drug	No.	Effect	WHO causality	Naranjo Causality	Severity
Enalapril/Spironolactone	2	Hyperkalemia	probable	Probable	Mild
Aspirin/Clopidogrel	6	bleeding	probable	Probable	Major
Amiodarone/atorvastatin	1	Muscle pain	possible	Possible	Mild
Clopidogrel/Acenocoumarol	2	bleeding	probable	Probable	Moderate
Venlafaxine/Ivabradine	1	QT prolong	possible	Possible	Moderate
Furosemide/Hydrocortisone	2	Hypokalemia	probable	Probable	Mild
Aspirin/Acenocoumarol	3	Bleeding	possible	Probable	Moderate
Domperidone/Cilnidipine	2	QT prolong	possible	Possible	Mild
Insulin/aspirin	1	Hypoglycemia	probable	Possible	Moderate
Aspirin/Heparin	1	bleeding	possible	Possible	Moderate
Aspirin/Telmisartan	1	Increase creatinine	possible	Proable	Mild
Insulin/nebivolol	1	hypoglycemia	probable	Probable	Moderate
Domperidone/Atorvastatin	1	QT prolong	possible	Probable	Mild
Amiodarone/nebivolol	1	bradycardia	possible	Probable	Moderate
Spironolactone/aspirin	1	hyperkalemia	probable	Probable	Moderate
Metformin/Ramipril	2	hypoglycemia	possible	Possible	Mild

CONCLUSION:

This study attempted to assess the potential drug-drug interaction in the prescription of cardiac patients in inpatient hospital setting. This study also examined patient, drug characteristics, causality and severity of pDDIs. This study shows that DDIs are frequent among hospitalized cardiac patients. About 234 drug interactions were reported during study period with median number of 1.67 pDDIs in the cardiac patients. It was found that incidence of pDDIs was associated with old age, polypharmacy and increased lengths of hospital stay. Polypharmacy

was high in the present study which can be minimized by the appropriate use of the medication. This study emphasizes the need to consider pDDIs during therapeutic planning, protect patients from consequence of drug interactions. In addition, providing DDI related information to the prescribers and drug interaction alert software to the dispensing pharmacist can play a vital role in minimizing the incidence rate of DDI.

The majority of interactions were pharmacodynamic in nature, having moderate severity. Anti-platelets and anticoagulants were commonly implicated in many PDDIs in this study and therefore require intensive monitoring during therapy. The most common management plan found in present study for most of the drug interaction was monitoring and dose adjustment. The study reported that about 26% of intervention proposed were accepted by physician. The current study demonstrated the importance of routine medication review and the need of a pharmacist in a multidisciplinary team.

The incidence rate of adverse drug interactions was found to be 20%. The results provided an insight to the healthcare providers on the importance of monitoring and reporting of adverse drug interactions. The active involvement of a well-trained clinical pharmacist for detecting the adverse drug interactions and delivering the awareness classes for the healthcare professionals regarding the need of reporting the incident could improve the scenario in under-reported hospitals.

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