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Investigation of Potential Drug Interactions in Hospitalized Cardiac Patients, Bhagwan Mahaveer Jain Hospital, Bangalore, India

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ABSTRACT

Objective: Drug-drug interaction (DDI) is of major concern in patients with complex therapeutic regimens. The involvement of cardiovascular medicines in drug interaction is even higher. However, reports of DDI between these groups of drugs are few. The present study was aimed to identify potential drug-drug interactions in cardiac patients and document any observed interaction in Bhagwan Mahaveer Jain Hospital, Bangalore, India. **Methodology:** The prospective observational study was conducted from January 2017 to July 2017 among hospitalized cardiac patients. The data collected in pre design data collection for 200 patients, Cardiac patients prescribed at least 2 drugs and having hospital stay of more than 24 hour duration were enrolled into the study. The collected data included demographics; cardiac drugs usage pattern and safety analysis data. The data was compiled in excel. **Result:** The incidence of potential DDIs was 98% with 200 prescriptions having at least one potential DDI and 130 patient prescriptions contain pDDI. The incidence rate was found to be 62.50%. Majority of interactions were of moderate severity, delayed onset, and pharmacodynamics in nature.Total28actual interactions were observed in the observed cases. Out 200 drug interactions, aspirin/clopidogrel and clopidogrel/atorvastatin were most common drug interaction pairs observed among prescribed medications. Of the 200 interventions proposed, the most frequent suggestion was on monitoring for adverse effect (42.01%) followed by dose adjustment (16.83%). 27.55% of interventions were accepted and therapy was changed. Most of the adverse drug interaction observed resulted in bleeding. **Conclusion:** Drug–drug interaction in patients was common in this resource limited set-up. Proper therapeutic planning, routine monitoring of cardiac in-patients and usage of online DDI database will avoid potentially hazardous consequences in cardiac in-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.

INTRODUCTION

Drug-drug interactions (DDIs) are defined as two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered. The irrational use of medication is a major worldwide public health problem, with a great impact on clinical, economic, and humanistic outcomes. It is estimated that prescription errors can lead to an increase of 50 to 70% in the government funds for medication. However, when used properly, medications are the most cost effective therapeutic resources. The activities developed by the clinical pharmacist play a key role in promoting better medication use, ensuring that patients receive appropriate pharmacotherapy, thus minimizing the risk of unfavourable outcomes of pharmacotherapy and consequently reducing costs. Among these activities, the review of medication orders is extremely important, and it enables identifying, solving and preventing the emergence of potential drug-drug interaction.[14]

Many studies have proven the significance of pharmacists in identifying and resolving potential drug-drug interactions through timely interventions. Gattis et al. [9] 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 India.

Pharmacotherapy for the cardiovascular disease has grown more complex with the introduction of new drugs. The complex regimen increases the risk of drug interaction to a great extent. Drug-Drug Interactions (DDIs) defined as pharmacokinetic or pharmacodynamic influences of drugs on each other, which may result in undesired effects, reduced efficacy or increased toxicity. DDIs result in many adverse clinical outcomes; they are responsible for 5% of all hospital admissions. [6]

DDI is said to occur when the effect of one drug is altered by the concurrent administration of other [12.] It can occur either pharmacokinetically or pharmacodynamically. Pharmacokinetic interaction occurs when either of the concurrently administered drugs has potential to alter other's pattern of absorption, distribution, metabolism and excretion. Similarly, pharmacodynamic interaction occurs if concurrently administered drugs have similar or opposite effects [3.] DDI is said to account for a number of severe adverse drug reactions (ADR) resulting in hospitalizations and emergency department visits. It is estimated that DDI

contribute to about 6-30% of all ADRs [8]. Furthermore, ADR due to DDI accounts for about 2.8% of hospital admission every year.

Patients with cardiovascular disorders are even at higher risk of DDI due to the number and types of drug they receive and the influence of heart disease on drug metabolism [10]. The potential of cardiovascular drug in the involvement of DDI is relatively higher as shown in the studies conducted worldwide. A prospective study [17] conducted in one of the teaching hospitals in India indicated that the incidence of potential drug interaction amongst cardiac drugs in hospitalized patients is 30.67%. A study in Palestine among patients receiving antihypertensive medications came up with 433 different unique pairs of potential drug interactions among 867 patients[17]. Another study conducted in Nepal to evaluate the pattern of DDI amongst diabetic outpatients also found that 47.5% of medications potentially interacting with antidiabetics were cardiovascular drugs. [5]

Drug–drug interactions can be difficult to identify. Although altered concentrations of drugs can be objectively measured for most medications in research settings, it is more difficult to describe the clinical impact. Often, there are very few data about the clinical effects of sub- or supra-therapeutic concentrations of drugs in humans. Additionally, commercial bioassays are only available for selected medications, making many DDI "theoretical" or reliant on presentation of clinical sequelae before suspicion is raised. In contrast, some DDI produce measurable pharmacokinetic or pharmacodynamic changes, but these have little effect on clinical outcomes. Large-scale, prospective clinical assessments examining the impact of DDI are rare [7]. DDI in patients receiving multidrug therapy is a major concern as in cardiovascular disease. Such interactions may lead to an increased risk of hospitalization and higher health care costs [11]. The incidence of actual occurrence of drug interactions [15] has been reported to be much smaller, ranging from 0 to 1.3%. Some studies have found that up to 11% of patients experience symptoms associated with DDIs and that DDIs are responsible for up to 2.8% of hospital admissions. [13]

MATERIALS AND METHODS

Study Site:

Study was conducted in cardiology ward at Bhagwan Mahaveer Jain Hospital, Bangalore, India.

Study Duration:

Study was conducted for a period of 6 months from January 2017 to July 2017.

Sample Size:

200 prescriptions evaluated out of which 130 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 24 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 were 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 Form. For each adverse drug reaction, the following information was 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.

RESULT AND DISCUSSION

A total of 230 cardiac inpatients that fulfilled the inclusion and exclusion criteria were enrolled into the study. Among them, prescriptions of 200 patients were found to have at least one potential interacting drug.

A. Demographic profile

The present study identified the pattern of pDDIs among patients admitted to cardiac unit of general medicine ward. The data of 200 patients admitted to inpatients ward. Among them, 130 patients had at least one potential drug interactions.

The average number of drugs per prescription is an important index of a prescription audit. It is preferable to keep the number of drugs per prescription as low as possible to minimize the risk of drug interactions and hospital costs. The mean number of drugs received by patients in the present study (9.81) was higher compared to report from another study in 2012 which recorded a mean of 7.34 drugs [2.] This may be related to the physician's tendency to polypharmacy and also multi-diagnosed prescriptions written for some patients. Polypharmacy is defined as concomitant use of five or more drugs and it could enhance drug interactions and drug related problems [4.] Extensive polypharmacy (97.85%) that is more than five drugs were prescribed in all the patients. In contrast to this study, another study showed 86.4% of polypharmacy[2] Polypharmacy in some instance becomes necessary especially when the patient has some co-morbid conditions and older in age.

B. Potential Drug-Drug Interaction

Out of 200 prescriptions analysed, 130 prescriptions comprised of potential drug interactions and it was found that 220 drug interactions were present. The incidence of potential drug interaction was 62.50%. This study showed the median number of 1.67 pDDIs in the cardiac patients. Of the total pDDIs identified, the interacting combination of moderate severity (58.11%) constituted majority of pDDI. Major severity interacting combination identified was 40.59%. This finding is similar to most of the DDI studies conducted worldwide.

Table 1 pDDI in study area

pDDI pair	Effect	Male		Female		Total	
		N	%	N	%	N	%
Aspirin/Clopidogrel	bleeding	13	5.55	3	1.28	16	6.83
Clopidogrel/atorvastatin	Decreased efficacy	11	4.70	5	2.13	16	6.83
Atorvastatin/amiodarone	rhabdomyolysis	7	2.99	0	0	7	2.99
Aspirin/Acenocoumarol	bleeding	3	1.28	3	1.28	6	2.56
Atorvastatin/Azithromycin	rhabdomyolysis	5	2.13	1	0.42	6	2.56
Atorvastatin/Clarithromycin	rhabdomyolysis	3	1.28	3	1.28	6	2.56
Acenocoumarol/Clopidogrel	bleeding	3	1.28	2	0.85	5	2.13
Carvedilol/aspirin	Decreased efficacy	3	1.28	2	0.85	5	2.13
Insulin/aspirin	hypoglycaemia	3	1.28	2	0.85	5	2.13
Ramipril/Spironolactone	hyperkalaemia	3	1.28	2	0.85	5	2.13

This study found some factors related with pDDIs that include patient's age, polypharmacy and long hospital stay. Significant associations of pDDIs with various factors have also been found in different other studies. It was reported in this study that old age is a risk factor for pDDIs.

Of the total pDDIs identified, the interacting combination of moderate severity (58.11%) constituted majority of pDDI. Major severity interacting combination identified was 40.59%. This finding is similar to most of the DDI studies conducted worldwide. The studies in MTH, India [17] and Palestineshowed similar results. [20]

Of the pDDIs identified, 60.25% were of not specified and 31.19% were of delayed onset in nature. This implies that even if there was an interaction occurring during the concomitant administration, it may not manifest itself immediately. If these combination of drugs were to be continued on an outpatient basis, this could potentially lead to decreased efficacy leading to therapeutic failures or potential for delayed adverse events. Hence the duration of concomitant drug use should also be taken into account when prescribing relevant interacting drugs. Most of interactions were documented as good (44.4%). This suggested that most of the interaction rating were reliable in nature.

Table 2 Top 10 moderate pDDI

Object Drug	Precipitant Drug	Effect	Documentation	Frequency	Management
Aspirin	Furosemide	Decreased efficacy	good	4	Monitor BP
Aspirin	Spironolactone	toxicity	excellent	4	Monitor for toxicity
Atorvastatin	amiodarone	Rhabdomyolysis	good	7	Monitor for toxicity
Atorvastatin	azithromycin	Rhabdomyolysis	good	6	Monitor for toxicity
Atorvastatin	phenytoin	Decreased efficacy	good	4	Dose adjustment
Atorvastatin	Domperidone	QT prolong	fair	4	Monitor ECG
Carvedilol	Aspirin	Decreased efficacy	good	5	Monitor BP
Clopidogrel	atorvastatin	Decreased efficacy	excellent	16	Alternative therapy
Insulin	Aspirin	Hypoglycaemia	fair	5	Monitor blood glucose
Ramipril	Aspirin	Decreased efficacy	fair	4	Monitor BP

Among moderate drug interaction, clopidogrel/atorvastatin (16) was most commonly observed. The common moderated drug interaction is listed in Table 2.

C. Pharmacists Intervention

Of the 200 interventions proposed, the most frequent suggestion was on monitoring for adverse effect (43. 1%) followed by dose adjustment (14.51%). 26.4% of interventions were accepted and therapy was changed. A study conducted in Coimbatore reported 240 interventions which are higher than this study. Of the 240 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].

A study conducted in Brazil reported 76.32% acceptability of the interventions by Clinical pharmacists, which is higher compared to this study [19]. It is important to consider that, in our

study, pharmacist recommendations to physicians regarding pharmacotherapy monitoring were registered only as educational actions, therefore without a measure of acceptability. This aspect may have led to a reduction in the acceptability rate of the study.

Table 3 Types of pharmacist intervention to prevent pDDI

Types of intervention	Total	
	N	%
Substitution	20	10.25
Stop/avoid/dose adjustment	30	15.81
Monitoring	90	44.01
No change	60	29.91

D. Adverse drug-drug Interaction

During the study period, a total of 28 adverse drug reactions were recorded among 200 pDDIs identified. The incidence rate of adverse drug interactions was found to be 20%. The study revealed that male patients 21 person (75%) predominated over females 7 person (25%) in ADR occurrence.

Of the reported adverse drug interactions, moderate reactions accounted for 11 people (39.28%) followed by mild reactions 10 person (35.71%) and major reactions 5 person (17.85%). The causality assessment of reported ADRs as per the Naranjo scale revealed that 17 people (60.71%) were probable and 11 person (39.28%) were possible. As per WHO scale revealed that 16 person (57.14%) were probable and 12 person (42.85%) were possible.

Table 4 Adverse drug-drug interaction

Object Drug	Precipitant Drug	No. of ADI	Adverse outcome
Enalapril	Spironolactone	2	Hyperkalemia
Aspirin	Clopidogrel	6	GI bleeding
Amiodarone	atorvastatin	1	Muscle pain
Clopidogrel	Acenocoumarol	2	bleeding
Venlafaxine	Ivabradine	1	QT prolong
Furosemide	Hydrocortisone	2	Hypokalemia
Aspirin	Acenocoumarol	3	Bleeding
Domperidone	Cilnidipine	2	QT prolong
Insulin	aspirin	1	Hypoglycemia
Aspirin	Heparin	1	bleeding
Clopidogrel	atorvastatin	2	thrombocytopenia
Aspirin	Telmisartan	1	Increase creatinine
Insulin	nebivolol	1	hypoglycemia
Domperidone	Atorvastatin	1	QT prolong
Amiodarone	Nebivolol	1	bradycardia
Spironolactone	aspirin	1	hyperkalemia
Metformin	Ramipril	2	hypoglycemia

The most common drug interaction pair resulting in adverse drug reaction was aspirin/clopidogrel (5person). Bleeding was the most important interaction in 8 cases followed by hypoglycaemia and QT-interval prolongation. The most common objective drug is aspirin and precipitant drug is clopidogrel. The result is presented in Table 4.

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 200 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. Antiplatelets 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 was 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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