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Research Article

THE INCIDENCE OF POTENTIAL DRUG-DRUG INTERACTIONS IN CARDIAC PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The aim of this study was to assess the potential drug-drug interactions (pDDIs) among hospitalized patients in cardiac department in tertiary care hospital.
Methods: A prospective, observational study was carried out for a period of 6 months. Samples of 425 patients were assessed for pDDIs using Micromedex®- 2.7.
Results: A total of 425 patients were analysed during these study periods. Out of 425 cardiac patients, 360 (84.70%) had found to be pDDIs, 856 pDDIs were found in 360 cardiac patients. With potential drug-drug interactions (pDDIs) higher in male [252 (70.00%)]patients, compared to females. Incidences of pDDIs were found to be higher in the age group of 60-70 years in cardiac [159 (44.16%)] patients and incidences of interactions based on duration of 4-6 days hospital stays in cardiac were 251 (69.72%). Moreover, 51.66% cardiac patients were found to be prescribed with more than 7 drugs causing higher incidences of pDDIs. Some of the most common drug interacting pair was aspirin and clopidogrel; causing major, pharmacodynamics interaction, with a frequency of 245.The prevalence of pDDIs in the cardiology was 53.27%, and majority of the prevalence were major severity. Out of 360 cardiology patients, there were 82 interacting pairs identified during the study. Among 856 pDDIs, 256 (29.90%) were due to pharmacokinetic interactions, and 456 (53.27%) were pharmacodynamics interactions. 71 (8.29%) showing both mechanisms and 73 (8.54%) were due to unknown mechanism.
Conclusion: The development of such data base in hospitals may help for the surveillance of pDDIs in hospitalized cardiac patients. The physicians should be aware of interactions among those drugs while prescribing for patients and thorough monitoring should be required for the patient safety by the implementation of admonitory guidelines and computer-based screening, which might help to prevent potentially harmful drug interactions.

INTRODUCTION

A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs or disease.[1] potential drug-drug interactions (pDDIs) that can result in toxicity, in an alteration of the desired therapeutic end point or at the very extreme in a life threatening situation.[2]Drug-drug interactions (DDIs) are an important sub group of Adverse Drug Events (ADE)[3] which are highly prevalent in patients receiving multiple-drug treatment.[4]The majority of the interactions occur because, either prescriber's do not consider them relevant[5,6] or prescriber may be receiving less information in the DDIs area. Polypharmacy, geriatric and patients with co-morbidities are considered as one of the major risk factors in pDDIs and drug-disease interactions.[5]The issue of drug interactions is a global concern, a study from US reported that 30.3% patients aware at risk of DDIs.[7]Recent study in Iran has reported that in 35.5% of the patients encountered with at least one pDDIs.[8]In India, a study identified 66% of DDIs in a medicinal department of a tertiary care hospital in Karnataka, India,[9] while another study in Chandigarh reported that 8.3% prescriptions had multiple DDIs.[10]It was estimated that about 46.3% drug interactions in an cross sectional study conducted in Karnataka and majority of the DDIs were moderate in severity and required therapeutic monitoring.[11] An exhaustive literature search did not reveal as many published report on DDIs, in chronic disorders in Indian population or other

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countries, however similar studies in other hospital wards has been done. The present study was instigated to determine the prevalence and Incidences of drug-drug interactions, type and severity in hospitalized patients. In view of above mentioned statistics, we purposefully conducted this study in a tertiary care hospital in Erode as there are no studies targeted this region of the country.

MATERIALS AND METHODS

The research was conducted in a tertiary care hospital, in Erode, for a period of 6 months at the hospitalized cardiac patients. 425 patients were taken in for the study, Exclusion criteria included out patients, patients less than 18 years of age, patients who are on Ayurveda, Siddha or other alternative system of medicine and prescription with less than 2 drugs prescribed. Inclusion criteria included hospitalized cardiac patients, Age groups above 18 years; prescriptions with two or more drugs prescribed during the hospitalization were only selected for the study. Consent was obtained from hospital authority and hospitalized patients. Demographic data (age and sex), length of hospital stay, diagnosis, number of medicine and details of comorbidities were obtained from the clinical records. All medications were prescribed, together with routine and pro-re-nata (as required) medications were screened for pDDIs.pDDIs were detected using the Drug Interactions Checker within Micromedex®-2.7.

RESULTS

A total of 425 patients were analysed during these study periods. Out of 425 cardiac patients, 360 (84.70%) had found to be pDDIs, 856 pDDIs were found in 360 cardiac patients. With potential drug-drug interactions (pDDIs) higher in male [252 (70.00%)] patients, compared to females. Incidences of pDDIs were found to be higher in the age group of 60-70 years in cardiac [159 (44.16%)] patients and incidences of interactions based on duration of 4-6 days hospital stays in cardiac were 251 (69.72%). Moreover, 51.66% cardiac patients were found to be prescribed with more than 7 drugs causing higher incidences of pDDIs. Some of the most common drug interacting pair was aspirin and clopidogrel; causing major, pharmacodynamics interaction, with a frequency of 245.The prevalence of pDDIs in the cardiology was 53.27%, and majority of the prevalence were major severity.

Table 1 Demographic profile of cardiac patients

S.No	Parameters	Cardiac total no. of. patients (n=360)
1.	**Gender wise distribution**	
	Male	252 (70.00%)
	Female	108 (30.00%)
2.	**Age wise distribution**	
	18-30	11 (03.05%)
	31-45	39 (10.85%)
	46-59	94 (26.11%)
	60-70	159 (44.16%)
	Above 70	57 (15.83%)
3.	**Number of hospital stay (In days)**	
	<3	74 (20.55%)
	4 – 6	251 (69.72%)
	>7	31 (08.61%)
4.	**Number of prescribed drugs per day**	
	<4	29(08.05%)
	5-6	145 (40.27%)
	>7	186 (51.66%)

Out of 360 cardiology patients, there were 82 interacting pairs identified during the study. Among 856 pDDIs, 256 (29.90%) were due to pharmacokinetic interactions, and 456 (53.27%) were pharmacodynamics interactions. 71 (8.29%) showing both mechanisms and 73 (8.54%) were due to unknown mechanism.

Table 2 Types of diseases in each department

Cardiology (n=360)	
Type of diseases	No. of. Patients
Myocardial Infarction	57 (15.83%)
Angina + Diabetes mellitus	91 (25.27%)
Hypertension	131 (36.38%)
Ischaemic Heart Disease	36 (10.00%)
Coronary Artery Disease	24 (06.66%)
Chronic Heart Failure	21 (05.83%)

On average, each patient had one or two coded diagnosis in which hypertension was the most common condition 165 (36.38%), followed byangina with diabetes mellitus 111 (25.27%) in cardiac patients.

Table 3 Highest potential drug-drug interaction combinations in cardiology

PDDI Combination	Type	Severity	Frequency (n=856)	Percentage (%)
T. Aspirin + T. Clopidogrel	PD	Major	245	28.62%
T. Aspirin + T. Enalapril	PD	Moderate	69	8.06%
T. Atorvastatin + T. Clopidogrel	PK	Moderate.	78	9.11%
T. Aspirin + T. Atenolol	PD	Moderate	25	2.92%
T. Clopidogrel +T. Amlodipine	PK	Moderate	80	9.34%
T. Atenolol + T. Metformin	PK	Major	25	2.92%
T. Spironolactone +T. Enalapril	PD	Moderate	18	2.10%
T. Enalapril + T. Metformin	Unknown	Major.	15	1.75%
T. Enalapril + T. Furosemide	PD	Moderate	12	1.40%
T. Aspirin + T. Spironolactone	PD	Major	41	4.78%

Table 4 Interactive effect, M.O.A, clinical management of common potential drug-drug interactions in cardiology

pDDIs combination	Mechanism of action	Anticipated effect	Clinical Management
T. Aspirin +T. Clopidogrel	Increased risk of bleeding.	Additive Effect	Monitor for blood counts if co-administration is needed
T. Aspirin + T. Enalapril	Decreased effectiveness of enalapril.	Antagonistic Effect	Weigh benefit and risk
T. Atorvastatin +T. Clopidogrel	Decreased formation of the clopidogrel active metabolite resulting in higher on-treatment platelet reactivity.	Metabolism	Discontinue the statin and substitute a statin that is not metabolized by CYP3A4 (i.e, pravastatin or rosuvastatin)
T. Aspirin +T. Atenolol	Decreased antihypertensive effect.	Antagonistic Effect	Monitor for the patient's blood counts and dose adjustment for beta blockers if necessary
T. Clopidogrel +T. Amlodipine	Decreased antiplatelet effect and increased risk of thrombotic events.	Inhibit CYP3A (Metabolism)	The addition of cilostazol may reduce the potential harmful interactions
T. Atenolol +T. Metformin	Result in hypoglycemia or hyperglycemia	Altered glucose Metabolism	Monitor for patient's glucose level
T. Spironolactone +T. Enalapril	Result in hyperkalemia.	Additive Effect	Monitor for serum potassium level
T. Enalapril +T. Metformin	Increased risk of hypoglycemia.	Unknown Mechanism	Avoid concurrent use
T. Enalapril +T. Furosemide	Result in postural hypotension	Synergistic Effect	Discontinue the diuretic 2 or 3 days prior to ACEI
T. Aspirin +T. Spironolactone	Result in hyperkalemia, or possible nephrotoxicity.	Additive Effect	Avoid aspirin doses of greater than 650mg daily in adults receiving spironolactone

Table 5 Highest percentage of potential drug-drug interaction combinations

SI.NO	Disease condition	pDDIs Combination
1.	Myocardial Infarction	T.Aspirin +T.Clopidogrel, T.Atorvastatin+T.Clopidogrel.
2.	Hypertension	T.Aspirin+ T.Enalapril, T.Aspirin+T.Atenolol
3.	Ischaemic Heart Disease	T.Atorvastatin + T.Clopidogrel
4.	Coronary Artery Disease	T. Spironolacton +T.Enalapril
5.	Chronic Heart Failure	T.Aspirin+T.Spironolactone, T.Spironolactone+T.Enalapril

In this study had identified, the highest percentage of pDDIs combinations were in Myocardial Infarction was found to be T. Aspirin + T. Clopidogrel, T. Atorvastatin + T. Clopidogrel, followed by hypertension was found to be T. Aspirin + T. Enalapril, T. Aspirin + T. Atenolol in cardiology department.

Table 6 Prevalence of pDDIs

Sl.No.	Type of prevalence	Cardiology
	Severity of pDDIs	Frequency (n=856)
1.	Major	456 (53.27%)
2.	Moderate	251 (29.33%)
3.	Minor	149 (17.40%)

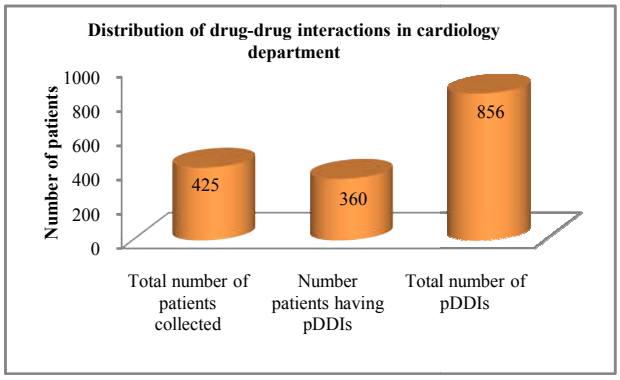

Figure 1 Distribution of drug-drug interactions in cardiology department

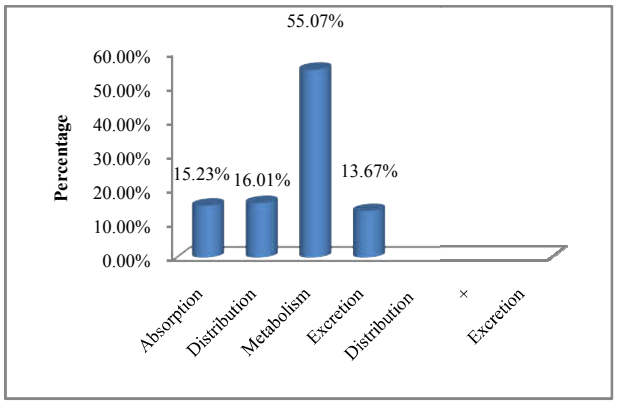

Figure 2 Classification of PK Interactions

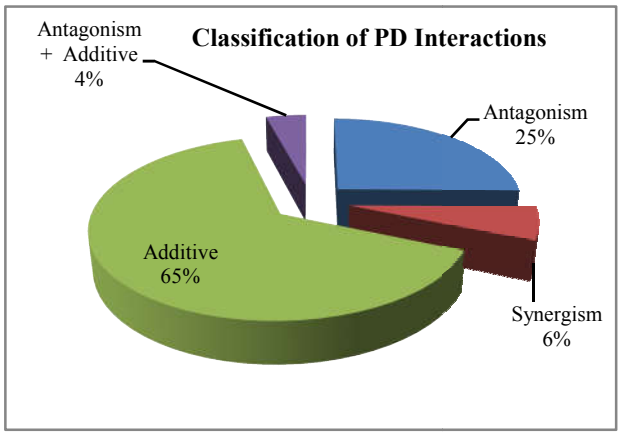

Figure 3 Classification of PD Interactions

DISCUSSION

DIs are a major area of concern these days for the effective management of patient illness. It may create a considerable health hazard to the patients when the risk-benefit ratio of combining interacting drugs is not accurately estimated. It has already been approximated that the effect of drug interactions can range from any minor morbidity to fatal consequences. The study of drug-drug, interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is expected to improve drug safety and will enable individualized drug therapy.

The present study identified a total of 425 patients admitted at the department of cardiology during the study period. Out of 425 cardiology patients, 360 (84.70%) had found to be pDDIs, 856 pDDIs were found in 360 cardiology patients (Figure 1).In our study male (70.00%) population shown more drug interactions than female (30.00%) population, it may be due to the fact that more hospital admissions were seen in male patients. Similar to the study conducted by Sharma *et al*[12]. Another study conducted by Murtaza *et al*.,[13] also reports that male patients are higher in cardiology (50.94%) department (Table 1).Another reason possibly will be the greatest risk of cardiovascular, disorders among male gender when compared to female and hence there is a need for multiple drugs which ultimately result in drug interactions.

According to our study most of the patients, were of age group between 60 - 70 (44.16%) years (Table 1).Study conducted by Fita *et al*.,[14] reported that the majority of patients ages were between 70-74 yrs. Older people are at high risk of developing an ADR due to pDDIs for several reasons. They are likely to have higher comorbidities and thus take several prescriptions and over the counter drugs.

The study revealed a hospital stay between 4-6 days in 69.72% of cardiac patients (Table 1). The likelihood of getting the multiple drugs increases with the increased length of hospital stay which in turn will increase the likelihood of pDDI. Lubinga *et al*.,[15] conducted a study which showed that the majority of the cases, the number of hospital stay were less than 6 days. In our study, 51.66% in cardiology patients were prescribed with more than 7 drugs. Similar study conducted by de Andrade *et al*.,[16] which have shown 40.6% cases were reported to be prescribed between 13 to 16 drugs.

The most common interacting pair at the cardiology department was found to be aspirin - clopidogrel; causing major pharmacodynamic interaction, with a frequency of 245 (Table 3). Followed by aspirin - enalapril; causing moderate pharmacodynamic interaction, with a frequency of 69.Similar to the study conducted by Murtaza *et al*.,[13] in which most common interacting pair was identified as aspirin - clopidogrel followed by clopidogrel - fondaparinux.

The prevalence of pDDIs in the cardiology was 53.27%, and majority of the prevalence were major severity (Table 6). Similar study was performed by Ismail *et al*.,[17] showed an overall 77.5% pDDI prevalence rate among randomly selected patients. Out of 360 cardiology patients, there were 82 interacting pairs identified during the study. Among 856 pDDIs, 256 (29.90%) were due to pharmacokinetic interactions, and 456 (53.27%) were pharmacodynamics interactions. 71 (8.29%) showing both mechanisms and 73 (8.54%) were due to unknown mechanism. Among 256 pharmacokinetic drug interactions in cardiology department, 141 (55.07%) were due to metabolism, followed by 41 (16.01%) were due to distribution (Figure 2). Among 456

pharmacodynamics interactions in cardiology department, 294 (65.00%) were due to additive effects, followed by 115 (25.00%) were due to antagonism (Figure 3). A study conducted by Chavda *et al*.,[18] were 67.44% were synergistic followed by 30.7% antagonistic.

Limitation

- The study was carried out in a hypothetical way of approach to find the incidence of drug-drug interactions.
- The active possibilities of DDIs respect to the time of drug administration, half-life of drugs, elimination time were not assessed.
- The study also could not assess the outcomes of pDDIs in the selected patients.

CONCLUSION

Our study concluded that the overall incidence of pDDIs was very high in cardiology department. The pDDIs were found to be more in males compared to females, it was found that incidence of pDDIs was associated with old age, polypharmacy and increased lengths of hospital stay. The majority of interactions were pharmacodynamics in nature, having major severity. The most of the common pDDIs were between aspirin and clopidogrel. The development of such data base in hospitals may help for the surveillance of pDDIs in hospitalized cardiac patients.

The physicians should be aware of interactions among those drugs while prescribing for patients and thorough monitoring should be required for the patient safety by the implementation of admonitory guidelines and computer-based screening, which might help to prevent potentially harmful drug interactions.

Authors Contributions

The entire author has contributed equally.

Conflict of Interests

All authors have no conflicts of interest to declare.

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