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Cardiology

A PROSPECTIVE STUDY ON POTENTIAL DRUG INTERACTIONS AMONG HOSPITALIZED PATIENTS IN THE CARDIOLOGY DEPARTMENTS IN TERTIARY CARE HOSPITALS.

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ABSTRACT

OBJECTIVE

The aim of this study was to assess the potential drug interactions (pDIs) among hospitalized patients in cardiac department in 3 tertiary care hospitals.

METHODS

A prospective, observational study was carried out for a period of 12 months. A sample of 685 patients were assessed for pDDIs using Micromedex®- 2.7 and Drugs.com database.

RESULTS

A total of 685 patients were analyzed and it was found to be 524 (76.49%) cardiac patients had pDDIs, with potential drug-drug interactions (pDDIs) higher in male cardiac [298 (56.87%)] compared to females. Incidences of pDDIs were found to be higher in the age group of 60-70 years were [193(36.83%)] and incidences of interactions based on duration of (4-6 days) hospital stays were 380 (72.53%). Moreover, 51.90% patients were found to be prescribed with more than 7 drugs, with higher incidences of pDDIs. Some of the most common drug interacting pair was between aspirin and clopidogrel combination observed in 245 pDDIs in cardiac patients. Drug-food interactions (pDFIs) were found to be between atorvastatin – citrus fruits. The common potential drug – disease interaction (pDDIs) was found to be isosorbide dinitrate – myocardial infarction.

CONCLUSION

The present study found that incidence of pDDIs become associated with old age, male gender, number of medication given and increased duration of hospital stays. consequently, it is encouraged to do away with all drugs with out therapeutic benefit, goal and indication. food – drug interactions can produce negative results in safety and efficacy of drug therapy in addition to nutritional repute of patients. understanding of predictable or possible drug interactions is important for his or her well timed detection and prevention of associated morbidity.

KEYWORDS : Cardiac, pDDIs, aspirin and clopidogrel, atorvastatin and citrus fruits, ISDN – MI

INTRODUCTION

Drug Interaction occurs when one drug interacts with the other drug, food or disease condition to modify the pharmacological effect of drugs. These interactions can alter the effectiveness of drug or may produce any adverse drug events.

Drug-Drug interaction (DDI) is one of the kinds of drug related problems in which effects of one drug can be altered by the co-administration of another drug which may result in serious life threatening conditions. 56.4% of all ADR1 were due to DDI according to the estimation in 2011.Furthermore, ADR due to DDI accounts to about 2.8% hospital admission every year.2 The number and types of drugs as well as the effect of heart disease on drug metabolism makes the patients with cardiovascular disease at a higher risk. Potential drug interaction amongst cardiac drugs in hospitalised patients is 30.67%3 based on a prospected study conducted in 2011.

Drug-Food Interactions have significant impact on the compliance and success of drug therapy as it may delay or decrease drug absorption. Recommendation by The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is an ideal programme to prevent drug-food interactions by combined patient counseling and label system to select the most appropriate drug administration times and increase nurse and patient awareness of the potential for drug-food interactions.4

Drug-disease interaction occurs when a medication has the potential to make a pre-existing disease worse. Comorbidities and Polypharmacy makes the elderly patients susceptible to these interactions. A decrease in omeprazole plasma concentration was noted following tocilizumab administration to patients with Rheumatoid Arthritis.5

The Relevance of interaction studies are to determine the necessity of dosage adjustment in severe interactions; to determine whether the interaction calls for additional therapeutic monitoring; to determine whether there should be a contraindication to concomitant use when lesser measures cannot mitigate risk.

The purpose of the study is to assess the Potential Drug Interactions among Hospitalized patients in cardiology departments in tertiary care Hospitals.

MATERIALS AND METHODS:

The Research was conducted in a tertiary care hospital, Erode for a period of 8 months in the hospitalized cardiac patients. 685 cardiac cases were taken in for the study.

Inclusion criteria patients of both gender, aged more than 18 years, admitted and received more than 24 hours inpatient services with two or more medications. Exclusion criteria were outpatients, patients with less than 24 hours in patient services as well as patients less than 18 years old, and patients who are on ayurveda, siddha or other alternative system of medicine. Consent form was obtained from hospital authority and hospitalized patients. The data were collected from case sheets of Hospitalized patients and direct patient interview from cardiac department. The data collection includes age, gender, data prescriptions, diagnosis, name of the each medication, dosage form, frequency, quantity dispensed, co-morbidity, and types of food taken by the patients. pDDIs were detected using the Drug Interactions Checker within Micromedex®-2.7 and www.drugs.com database.

RESULTS

A total of 685 patients were admitted in the department of cardiology during the study period. Among these, 685 patients, 524(76.49%) had found to be pDDIs, 856 pDDIs were found in 524 cardiac patients. It was found that patients were confirmed with minimum one or two pDDIs in cardiac department. Out of which 298(56.87%) cardiac male were found to be higher pDDIs, compared to females. Incidences of pDDIs were found to be higher in the age group of 60-70 years [193(36.83%)] patients and incidences of interactions based on duration of (4-6 days) hospital stay were 380 (72.53%). 51.90% patients prescribed with more than 7 drugs in cardiac patients were found to have developed a higher number of pDDIs.

Table 1: Demographic profile of cardiac patients

S.No	Parameter	Total number of patients (n=524)	Percentage%
1.	**Gender wise distribution**		
	Male	298	56.87%
	Female	226	43.13%
2.	**Age wise distribution**		
	18-30	21	4.00%
	31-45	69	13.17%
	46-59	164	31.29%
	60-70	193	36.85%
	Above 70	77	14.69%
3.	**Number of hospital stay (In days)**		
	<3	83	15.83%
	4 – 6	380	72.53%
	>7	61	11.64%
4.	**Number of prescribed drugs per day**		
	<4	94	17.93%
	5-6	158	30.15%
	>7	272	51.90%

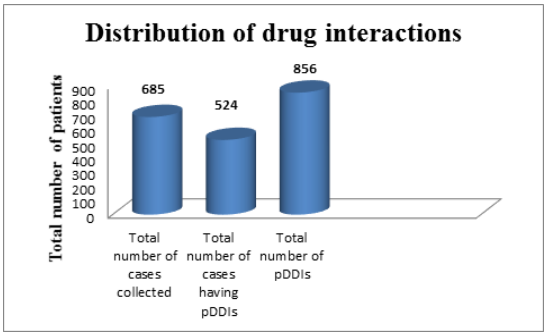

Figure 1: Distribution of drug interaction

Table 2: Distribution of diseases in cardiology department

S.No	Cardiology type of diseases	Total number of Patients (n=524)	Percentage %
1.	Myocardial Infarction	87	16.60%
2.	Angina + Diabetes mellitus	111	21.18%
3.	Hypertension	165	31.48%
4.	Ischaemic Heart Disease	46	08.77%
5.	Coronary Artery Disease	34	06.48%
6.	Chronic Heart Failure	81	15.45%

On average, each patient had one or two coded diagnosis in which hypertension was the most common condition 165 (31.48%), followed by Angina with Diabetes mellitus 111 (21.18%) in cardiac patients (Table 2).

Table 3: Highest potential drug-drug interaction combinations

Note: PD= Pharmacodynamics, PK= Pharmacokinetics

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%

Out of 524 cases, there was 82 interacting pair identified during the study. There were 685 pDDIs found. Among 685 pDDIs, 256 (29.90%) were pharmacokinetic interactions, 456 (53.27%) were pharmacodynamic interactions. 71 (8.29%) showing both mechanisms and 73 (8.54%) were unknown mechanism. Among 456 (53.27%) pharmacodynamic interaction 28 (6.14%) were synergistic, 115 (25.21%) were antagonistic, 294 (64.47%) were additive and 19 (4.18%) with both additive and antagonistic effect. Among 256 (29.90%) pharmacokinetic drug interactions 39 (15.23%) were due to absorption, 41 (16.01%) were due to distribution, 141 (55.07%) were due to metabolism and 35 (13.67%) were due to excretion. Prevalence of potential drug-drug interactions in these patients was found to be 53.27%.

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

PDDI combination	Mechanism of action	Interactive 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: 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%)

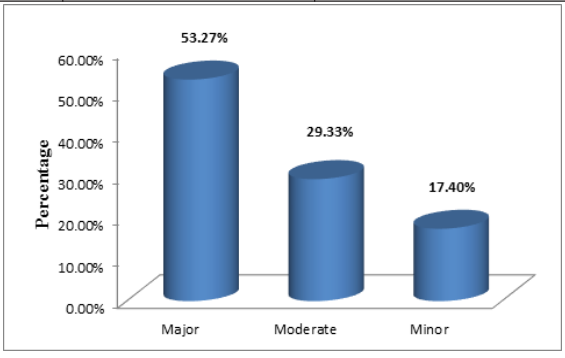

Figure 2: Prevalence of pDDIs

Table 7: Distribution of potential drug- food interactions

Drug-food	Interactive Effect	Type of DFI	Severity	Frequency (n=457)
T. Atorvastatin with Citrus fruits	Decreased first pass metabolism and increased bioavailability	PK	Moderate	144 (31.50%)
T. Enalapril with Banana	Hyperkalaemia	Unknown	Moderate	47(10.28 %)
T. Atenolol with Orange Juice	Decrease the mean peak plasma concentration of atenolol; excretion of drugs in urine decreased	PK	Moderate	79 (17.28%)
T. Diazepam with Tea / Coffee	Antagonistic Effect. Caffeine generally antagonized the diazepam induced ratings of sedation and impairment of psychomotor performance	PD	Minor	83 (18.16%)
T. Bisacodyl with Milk	Increase the risk of stomach upset and nausea.	Unknown	Minor	91 (19.91%)
T. Paracetamol with Cabbage	Decrease effectiveness of the drug.	PK	Moderate	38 (8.31%)

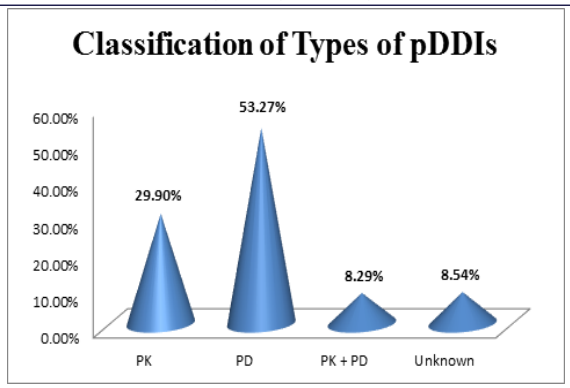

Figure 3: Classification of Types of pDDIs

Table 8: Distribution of Potential Drug disease interactions in cardiology

Drug-disease	Interactive Effect	Severity	Frequency (n=289)
T. ISDN with MI	Systemic hypotension and tachycardia	Major	42(14.53%)
Inj. Furosemide with Diabetes Mellitus	(Latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test)	Moderate	56(19.37%)
T. Atenolol with DM	Inhibit catecholamine-mediated glycogenolysis, thereby potentiating insulin-induced hypoglycemia and delaying the recovery of normal blood glucose levels.	Major	24(8.30%)
T. Enalapril with CHF	Oliguria and/or progressive azotemia and, rarely, renal failure, myocardial ischemia and death.	Major	28(9.68%)
T. Amlodipine with CAD	Unknown Mechanism	Major	18(6.22%)

Note: ISDN= Isosorbide dinitrate, MI= Myocardial Infarction, DM= Diabetes mellitus, CHF= Congested heart failure, CAD= Coronary artery diseases

DISCUSSION:

Dis are a major area of problem in recent times for the effective management of patient illness. It can create an extensive health risk to the patients when the risk –benefit ratio of combining interacting drugs isn't always correctly anticipated. It has already been approximated that the effect of drug interactions can range from any minor morbidity to fatal consequences. The observe of drug-drug, drug-food, and drug-disease interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is predicted to enhance drug protection and could allow individualized drug therapy.

The present study identified a total of 685 patients were admitted in the department of cardiology during the study period of tertiary care hospital. Our study shows that 298(56.87%) male patients were found to be higher pDDIs, when compared to female patients (Table 1), which are similar to the study conducted by Sharma et. al6. More number of male patients when compared to female in the present study may be the primary reason. Another reason possibly will be the greater risk of cardiovascular disorders among male gender when compared to female.

The study showed that the majority of the incidences of pDDIs were found to be higher in the age group of 60-70 years in cardiac 193 (36.85%) (Table 1). A study conducted by Chelkeba et. al.,8 reported an age group of 59 – 69 yrs whereas study conducted by Fita et. al.,9 reported that 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, 72.53% of cardiac and 62.31% of pulmonary cases and that the number of hospital stay was between 4-6 days (Table 1). Lubinga et. al.,10 conducted a study which showed that majority of the cases, the number of hospital stay were less than 6 days. The likelihood of getting the multiple drugs increases with the increased length of hospital stay which in turn will increase the likelihood of PDDI.

In our study, 51.90% patients prescribed with more than 7 drugs in the cardiology department (Table 1). The study conducted by Andrade et. al.,11 which have shown 40.6% cases have been reported as the prescribing between 13 to 16 drugs. The more the medications that are prescribed, the more the possibility of polypharmacy. 12 The most common interacting pair in the present study was found to be between Aspirin and Clopidogrel . The study is similar to the study conducted by Murtaza et. al.,7 in which most common interacting pair were identified as aspirin – clopidogrel followed by clopidogrel–Fondaparinux. Another study conducted by Patel et. al.,13 observed an increased risk when aspirin combined with other thrombolytic agent.

Among 856 pDDIs, major was pharmacodynamics 456 (53.27%) with additive 294 (64.47%) being reason for most of the interactions, According to Chavda et al.,14 where pharmacodymanic interactions being the majority. The reason may be due to modification of the action of one drug at the target site by another drug, independent of a change in its concentration. This may result in enhanced response (synergism), an attenuated response (antagonism) or an abnormal response.

The most common interacting pair was found to be between Aspirin and Clopidogrel; which is a major pharmacodynamic interaction, with a frequency of 245 (Table 3). The study is similar to the study conducted by Murtaza et al., 7 in which most common interacting pair was identified as aspirin–clopidogrel followed by clopidogrel-Fondaparinux.

In our study, prevalence of pDDIs was 53.27% (Table 7) more in major severity. Fokter et. al., 16 reported pDDIs of major severity in 13% patients and Ismail et. al.,15 in 24.25% patients. Prevalence of pDDIs of moderate severity was 48%.Patel et. al.,13 reported moderate severity to 60.3% patients. This study contrasts the other studies which reports moderate severity. These potential DDIs suggest that there is a need for modification or alteration of therapy such as dosage adjustment.

According to our study, most of the cases have Atorvastatin – Citrus fruits interaction which may cause decreased first pass metabolism and increased bioavailability of Atorvastatin that further results in muscle breakdown, liver damage, digestive problems, increased blood sugar and neurological side effects. The reason for these interactions is due to furanocoumarins. The interaction between citrus fruits and medications poses dangers only if a drug is taken orally because the interaction occurs in the digestive tract.

The most common drug–disease interaction was found between ISDN with MI (Table 10). The interaction may result in systemic hypotension and tachycardia. It may also exacerbate myocardial ischaemia.

CONCLUSION

The present study found that incidence of pDDIs becomes associated with old age, male gender, number of medication given and increased duration of hospital stays. Consequently, it is encouraged to do away with all drugs without therapeutic benefit, goal and indication. Food – drug interactions can produce negative results in safety and efficacy of drug therapy in addition to nutritional repute of patients. Understanding of predictable or possible drug interactions is important for his or her well timed detection and prevention of associated morbidity.

AUTHORS CONTRIBUTIONS

All the author has contributed equally.

CONFLICT OF INTERESTS

All authors have no conflicts of interest to declare.

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