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A PROSPECTIVE OBSERVATIONAL STUDY ON DRUG-DRUG INTERACTIONS IN CARDIAC PATIENTS AT A TERTIARY CARE HOSPITAL

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Abstract:

Aim:*To study the occurrence, frequency and severity of significant drug-drug interactions in cardiac patients.*

Method: *This study was carried out for duration of 6 months at the inpatient department of General medicine in Osmania general hospital, Afzalgunj, Hyderabad. The data of 75 patients was collected and the frequently occurring drug-drug interactions among the selected patients were noted.*

Results: *The study identified various drug-drug interactions in cardiac patients with minor drug interactions being more common (52%). The subjects were distributed on the basis of age, gender, diagnosis and number of drugs used. The cardiovascular drugs prescribed were Anticoagulants (25.7%), Anti hyper lipidemics (21.3%), Diuretics (16.9%) and Calcium channel blockers (13.2%), ACE-inhibitors (9.5%), Vasodilators (6.6%) and Angiotensin receptor blockers (6.6%).*

Conclusion: *The present study shows that DDI's are frequent among hospitalized cardiac patients and highlights the need to screen prescriptions of cardiovascular patients for DDI's, as this helps in detection and prevention of possible adverse drug interactions.Thus, this study assists in understanding the factors associated with DDI's that can help in safe and effective use of drugs in future.*

Key words: *Drug-drug interactions, cardiovascular, patients, adverse drug.*

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INTRODUCTION:

Drug interactions:

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. Interactions between drugs (drug–drug interactions) may be beneficial or harmful. The net effect of the combination may manifest as an additive or enhanced effect of one or more drugs, antagonism of the effect of one or more drugs, or any other alteration in the effect of one or more drugs.

These interactions can be either pharmacokinetic or pharmacodynamic.

Pharmacokinetic interaction is said to occur when one drug affects the effect of other drug by change in absorption, distribution, metabolism or excretion of another drug. On the other hand, Pharmacodynamic interaction is seen when the two drugs either exhibits synergism or antagonism in their mechanism of action. There is paucity of data highlighting potential drug-drug interactions in cardiac patient in India Elderly patients are especially vulnerable – with a strong relationship between increasing age, the number of drugs prescribed, the frequency of potential drug–drug interactions, hospitalized for a longer period of time.

Maybe due to comorbid conditions, chronic therapeutic regimens, polypharmacy, and frequent modification in therapy, hospitalized patients are more likely affected by potential drug–drug interactions (pDDIs). Knowing how drug–drug interactions occur and how to manage them is an important part of clinical practice.

DIs can be predicted and avoided through the knowledge of their mechanism; by identifying the enzymes responsible for the particular drug metabolism; and by identifying the enzymes transporters and modulators. This is followed by the use of clinical expertise to determine whether inhibition or induction of these factors will lead to clinically significant DI or not. [1]

Reducing the risk of drug interactions:

Principles of Drug Interactions Management

The consequences of drug interactions may be

- Major: life threatening
- Moderate: deterioration of patient's status
  Minor: bothersome or little effect.

The risk of drug interactions is a challenge that embraces a number of considerations.

The following are guidelines to reduce and manage drug interactions.

1. Identify patient risk factors such as age, the nature of the patient's medical problem (e.g., impaired renal function), dietary habits, smoking, and problems such as alcoholism influence the effect of certain drugs.
2. Take thorough drug history and maintain complete patient medication records.
3. Keep knowledge about actions (both primary and secondary pharmacological actions) of drugs being utilized.
4. Consider therapeutic alternatives.
5. Avoid complex therapeutic regimens where possible.
6. Educate the patient to comply with instructions for administering medications. They should be encouraged to ask questions about their therapy and to report any excessive or unexpected responses.
7. Monitor therapy: Any change in patient behavior should be suspected as drugrelated until that possibility is excluded.
8. Individualize therapy: priority should be assigned to the needs and clinical response of the individual patient, rather than to the usual dosage recommendations, standard treatment, and monitoring guidelines.
9. Involve the patient as a partner in health care. If the optimal benefits of therapy are to be achieved with minimal risk, each participant must be knowledgeable about and diligent in fulfilling his responsibilities.

Management options of drug interaction include:

Avoiding the combination entirely: For some drug interactions, the risk always outweighs the benefit, and thus the combination should be avoided. Because drug classes are usually heterogeneous with regard to drug interactions (as described above), one can often select a no interacting alternative for either the object drug or the precipitant drug. [2]

Adjusting the dose of the object drug: Sometimes, it is possible to give the two interacting drugs safely as long as the dose of the object drug is adjusted.

Spacing dosing times to avoid the interaction: For some drug interactions involving binding in the gastrointestinal tract, to avoid the interaction one can give the object drug at least 2hour before or 4 hour after the precipitant drug. In this way, the object drug can be absorbed into the circulation before the precipitant drug appears.

Monitoring for early detection: In some cases, when it is necessary to administer interacting drug

combinations, the interaction can be managed through close laboratory or clinical monitoring for the evidence of the interaction. In this way, the appropriate dosage change scan be made, or the drug's discontinued if necessary.

Continue medication as before: if interacting drugs are the optimal therapy for a condition orif the interaction is not clinically significant.

Provide information on patient risk factors that increases the chance of an adverse outcome: It is clear from the clinical experience of physicians and pharmacists as well as published studies that most patients who take interacting drug combinations do not manifest adverse consequences. Substantial evidence from both the clinical experience of physicians and pharmacists as well as published studies suggest that the risk of statin-induced myopathyincreases with increasing serum concentrations of the statin.

Improve computerized screening systems: the computerized drug interaction screening systems have not been as successful as one hoped. [3]

Studies have revealed that DDIs are a major clinical problem along with other adverse drug reactions especially in the hospitalized cardiac patients. Cardiovascular patients are more often reported with potential drug-drug interactions (pDDIs) as compared to patients with other diseases. The possible reason behind higher pDDI rate in cardiovascular diseases mayinclude elder age, multiple drug regimen, and pharmacokinetic or pharmacodynamic nature of drugs used in cardiology. [4]

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels.CVD includes coronary artery diseases (CAD) such as angina and myocardial infarction(commonly known as a heart attack).Other CVDs include stroke, heart failure, hypertensiveheart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heartdisease, valvular heart disease, myocarditis, aortic aneurysms, peripheral artery disease,thromboembolic disease, and venous thrombosis. [5]

According to the Global Burden of Disease study age-standardized estimates, nearly quarters (24.8%) of all deaths in India are attributable to CVD. The age standardized CVD death rate of 272 per 100 000 population in India is higher than the global average of 235 per 100000population. However, there is a major gap in knowledge, especially regarding the causes of death in rural India; Global Burden of Disease estimates are based on smaller community based studies. [6]

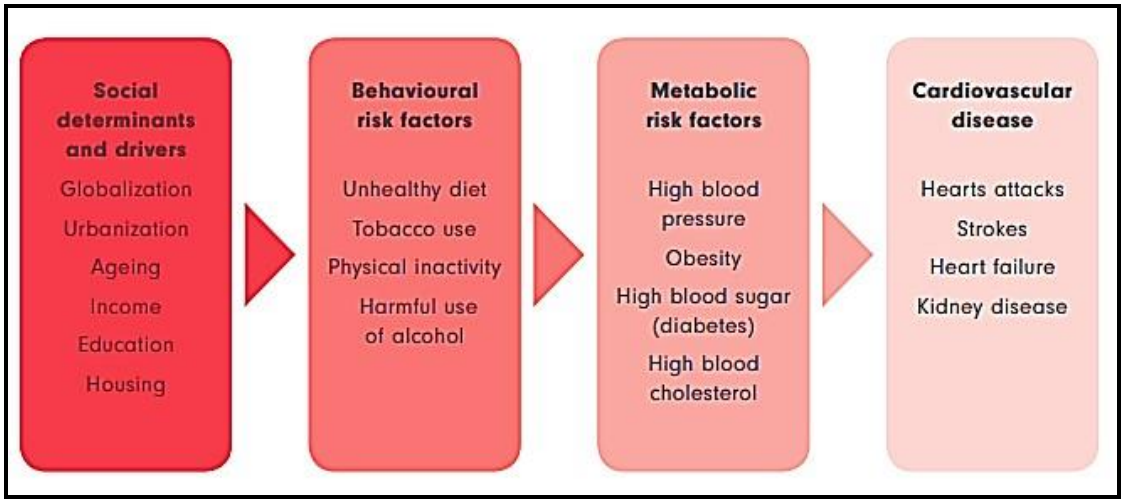

Figure 1: Risk factors for the cardiovascular diseases [7]

Aim and objectives:

- To study the occurrence, frequency and severity of significant drug-drug
- interactions in cardiac patients.
- To identify and evaluate the impact of significant drug-drug interactions in cardiac patients.
- Assessing the possible risk factors associated with the drug-drug interactions.
- To intervene strategies from pharmacist perspective to promote rational and efficacious use of drugs in order to improve therapeutic outcomes and quality of life of patient.

Need for study:

Patients with cardiovascular diseases are particularly vulnerable to DDIs due to their advanced age, polypharmacy and the influence of heart disease on drug metabolism. The DDI potential for a particular cardiovascular drug varies with the individual, the disease being treated, and the extent of exposure to other drug.

Detection of drug-drug interactions remains a substantial clinical challenge and this study aims to detect interactions so as to promote rational and safe use of drugs.

- The study is designed to evaluate the incidence and pattern of drug interactions in cardiac patients.
- To analyze and correlate the clinical data for better management.
- To evaluate the incidence of drug-drug interactions and their association with risk factors.

Therefore assessment of patients at risk for clinically important DDIs will be useful in minimizing medication-related problems and improving pharmaceutical care.

METHODOLOGY:

A Prospective and Observational study was carried out in the Department of General Medicine, at Osmania General Hospital.Hyderabad, Telanagana State.for a period of 6 months with a sample size of 100 patients.

MATERIALS AND METHODS:

- Suitable Data collection forms were prepared and the data collection was done in the prepared forms.
- The Data is Collected using Prepared forms
- Follow up of Patients is done to Evaluate
- Assessment and Rationality of Prescription
- Assessment and Classification of Collected Data
- Evaluation and Analysis of Collected Data

Data analysis:

- Data Analysis is done based on the Parameters assessed and analyzed.
- The data is represented and the results are made by Graphical Data Representation

Plan of work:

Suitable Data Collections forms were prepared/ Modified to collect the details on following

↓

The Data is collected using Prepared forms

↓

Followup of Patients is done to Evaluate

↓

Assessment and Rationality of Prescription

↓

Assessment and Classification of Collected Data

↓

Evaluation and Analysis of Collected Data

Table 1: Distribution of subjects based on age

AGE GROUP	NO. OF PATIENTS	PERCENTAGE
<45	19	25%
45-60	39	52%
>60	17	23%

Figure 2: Pie chart showing distribution of gender based on DDI's.

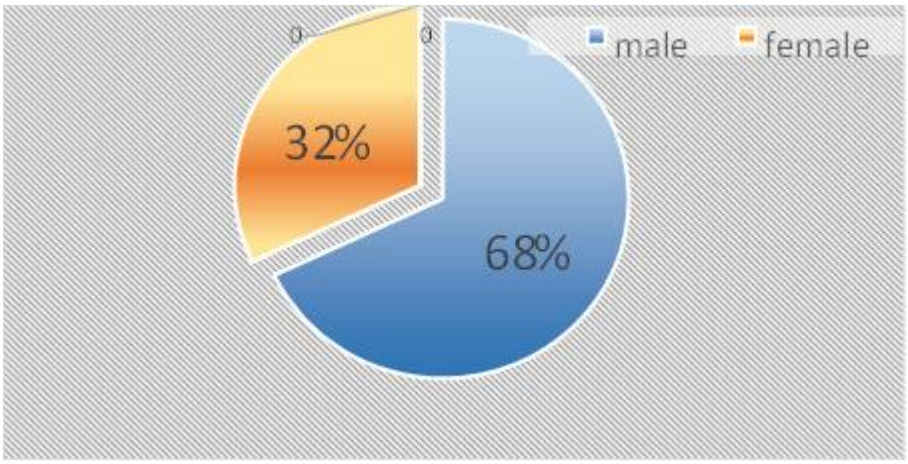

Table 2: Number of drugs prescribed per patient

NO. OF DRUGS	PRESCRIBED PER PATIENT	PERCENTAGE
<5	29	38%
5-10	46	62%

Figure 3: Pie chart showing distribution of subjects based on diagnosis

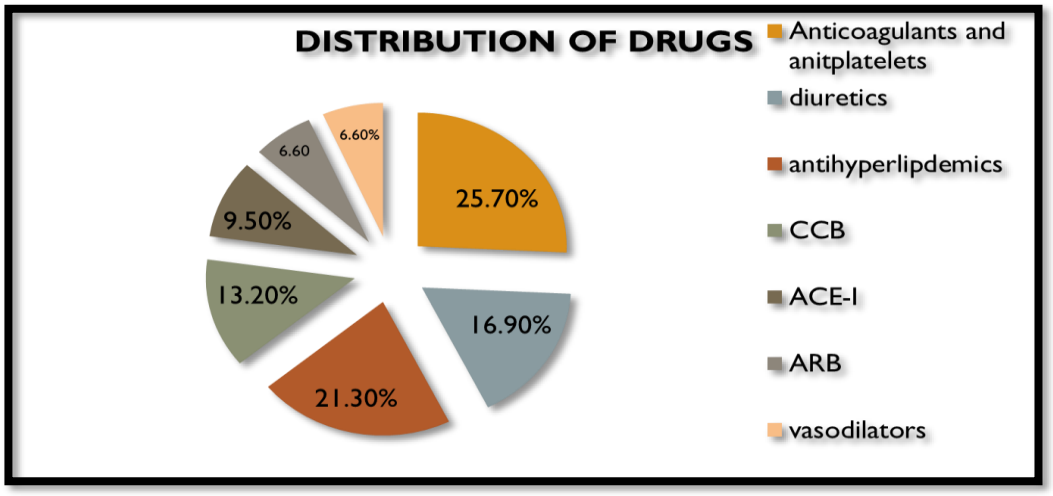

Table 3: Classification of drug-drug interactions based on severity

SEVERITY	NO. OF INTERACTIONS	PERCENTAGE
Major	9	12%
Moderate	27	36%
Minor	39	52%
Total	75	100%

Table 4: Distribution of number of interactions per patient

INTERACTION (per range)	No. of interactions per patient	percentage
0	7	9%
1-2	22	29%
3-4	18	24%
5-6	18	24%
7-8	10	14%
9-10	0	0%

Table 5: List of commonly occurring DDI's

INTERACTING PAIR	CONSEQUENCES
ENALAPRIL / FUROSEMIDE	RISK OF HYPOTENSION
DIGOXIN / FUROSEMIDE	INCREASED RISK OF DIGOXIN TOXICITY
ENALAPRIL / ASPIRIN	DECREASED EFFECTIVENESS OF ENALAPRIL
ASPIRIN / FUROSEMIDE	DECREASED DIURETIC EFFECTIVENESS
ASPIRIN / CLOPIDOGREL	INCREASED RISK OF BLEEDING
HEPARIN / ASPIRIN	INCREASED RISK OF BLEEDING
ENALAPRIL/ SPIRONOLACTONE	RISK OF HYPERKALEMIA
DIGOXIN/AMLODIPINE	RISK OF HEART BLOCK

Table 6: List of clinical consequences occurring due to drug-drug interactions

CLINICAL CONSEQUENCES	No. of DDI's	Percentage
Bleeding	23	30.66%
Furosemide effect↓	10	13.33%
Digoxin toxicity	6	8%
Increased B.P	10	13.33%
Decreased B.P	5	6.66%
Hyperkalemia	8	10.66%
Hypokalemia	9	12%
Q-T interval prolongation	4	5.33%

Table 7: Management options required for DDI's.

Management	Number of DDI's	Percentage
Dose adjustment	14	18.66%
No management required	9	12%
Monitor for signs and symptoms	16	21.33%
Monitor for drug levels	18	24%
Avoid the combination or substitute	7	9.33%
Monitor for electrolytes levels	11	14.66%

DISCUSSION:

DDI is a major concern in the treatment of patients presenting with cardiovascular diseases as most of the cardiac patients present with comorbid conditions leading to prescription of multiple drugs. It has been observed that cardiac patients are more prone to drug interactions as compared to other patients Picazo J et al (2016). The severity of DDI may vary from non signi significant interactions to serious or life threatening interactions

The present study identified the pattern of DDI's in cardiac patients admitted to the tertiary care teaching hospital. The incidence rate of DDI was (89.3%). The value obtained in the present study is less compared to the study by Vijay Kulkarni et al (2013) and relatively more when compared with the study by Ghulam Murtaza et al (2016). in Morocco who reported an incidence rate of (68.11%). These differences might be because our study took into consideration all the drug interactions of moderate and minor severity and also the database used for

identifying drug interactions in contrast to others studies.

Total 75 drug-drug interactions were found in 75 patients. Among 75 Patients that were included, 51 patients were male which accounts for (68. %) and 24 patients were females which accounts for (32%). Therefore the predominance of males were slightly less when compared to the study by Netsanet Diksis et al.

Of the total DDI's identified, the interacting combination of minor severity (52%) constituted majority of DDI's. This finding is different from most of the DDI studies conducted worldwide. This was followed by interacting combinations of moderate severity (36%). The interactions of major severity were found to be least. Therefore, this trend of severity assessment of drug-drug interactions was found to be different when compared with the study of Muhammad Zeeshan Khan et al (2019).

The incidence of cardiovascular diseases (CVDs) has increased in recent decades they are considered as the primary cause of mortality in the world. In India, coronary artery disease is the largest contributor to CVD accounting for over all disease burden. Mozayani A et al (2004). Similarly, among the various cardiovascular diseases in our study Coronary Artery Diseases (CAD) (29%) was found to be predominant. This was subsequently followed by others (25%), Congestive heart failure (24%), and Myocardial infarction (22%).

The class of drugs most commonly involved in drug-drug interactions was found to be Anticoagulants & Antiplatelet (25.7%).This result differs from the results of another study Ajay D. Shanbhag et al (2016). The most common interacting pairs identified in our study were aspirin / clopidogrel, enalapril / furosemide, heparin/aspirin, digoxin / furosemide and enalapril / aspirin.

A significant positive relationship was found between the length of hospital stay and DDIs. Our finding well resembles to the finding by several studies which have also shown that increased incidence of DDI's corresponds with an increase in duration of hospital stay. The reason might be that the likelihood of getting the multiple drugs increases with the increased length of hospital stay which in turn will increase the likelihood of DDI's. Similar positive linear relationship was also found between the number of medicines prescribed and DDI's. The findings well correlate with the fact that polypharmacy increases the likelihood of DDIs to a great extent as shown by study of Sushmita Sharma et al (2014).

The National Patient Safety Agency risk assessment of anticoagulation therapy highlighted co-prescribing of NSAIDs and other interacting medicines in cardiac patients as one of the 15 key high risk prescribing practices. The potential consequence of such prescribing practice leads to an increase in the risk of bleeding complication therefore, the incidence of bleeding (30.66%) in our study was found to be highest.

Caution must be exercised by maintaining the normal range of activated partial thromboplastin time (aPTT) and INR value because even slight increase or decrease in plasma drug concentration can have profound clinical effects.The most common management plan found for most of the DDIs was monitoring drug levels (24%).This finding was different from another study reported in the literature where the dosage adjustment was most common. Melody Rose Vijay et al (2019). The suggested action to be taken in most cases was monitoring drug levels, signs and symptoms, electrolyte levels.

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CONCLUSION:

The present study shows that DDI's are frequent among hospitalized cardiac patients and highlights the need to screen prescriptions of cardiovascular patients for DDI's, as this helps in detection and prevention of possible adverse drug interactions. Thus, this study assists in understanding the factors associated with DDI's that can help in safe and effective use of drugs in future.

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