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ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN HOSPITALIZED PATIENTS IN INDIA

Pavan Kumar K.*, Srinivas Rao B.[1], Priyanka B.[1], Apoorva Dev M.[1] and Sai Krishna G.[2]

[1]Department of Pharmacy Practice, PES College of Pharmacy, Bangalore, India.

[2]Department of Pharmacy Practice, JSS College of Pharmacy, Mysore, India.

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***Corresponding Author**
Dr. Pavan Kumar K.
Department of Pharmacy Practice, PES College of Pharmacy, Bangalore, India.

ABSTRACT

Background: Now a day's drug therapy is becoming more complex. Nevertheless in clinical practice Drug-Drug Interactions (DDIs) may lead to an increased risk of hospitalization and higher health care costs. Although prescription of more drugs for one patient is common and a necessary practice, it shown that the incidence of potential DDIs (pDDIs) is close to 40% in patients taking 5 drugs and exceeds 80% in patients taking 7 or more medications. **Methodology:** A prospective observational study was conducted over a period of 6 months in hospitalized patients. The patient's information's was taken from the patient records, case sheets or drug charts. The medications of a patient were analyzed for possible interactions. Pearson correlation was used for estimating correlation between the hospital stay and drug interactions, number of drugs dispensed and the occurrence of drug interactions at 95% confidence level with p value < 0.05. **Results:** A total of 200 patients were enrolled in the study. 339 potential Drug Drug Interactions (pDDIs) were identified among 139 patients. The incidence 69.5% of pDDIs was identified. The most common interactions with anticoagulants (24%), antiplatelets (15%) and antibiotics (15%) followed by other medications. Majority of interactions were moderate, delayed onset and pharmacodynamic in nature. **Conclusion:** The present study identified and documented pDDIs in hospitalized patients. Factors which lead to drug interactions were identified. This study highlights the need for screening prescriptions of hospitalized patients for pDDIs and pro active monitoring of patients who have identified risk factors which helps in detection and prevention of possible ADRs.

KEYWORDS: Potential Drug-Drug Interactions, in-patients, and drug chart review.

INTRODUCTION

A drug interaction is a circumstance in which one drug affects the activity of another drug, when both are administered simultaneously. The net effect of the interaction may be, Synergism or additive effect, Antagonism or substractive effect and Idiosyncratic effect. Typically, interactions between drugs are known as drug-drug interaction. However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and medicinal plants or herbs (drug-plant interactions). Drug Interaction is an increasingly important cause of adverse drug reactions.[1]

TYPES OF DRUG INTERACTIONS

Depending on the type of the effect produced, drug interaction may be classified as follows:

1. **Inhibiting Drug Interaction:** An inhibiting interaction partially or completely prevents a drug from exerting its action thus diminishing its effect in the patient. Antagonism, a type of inhibiting interaction occurs when a drug with a given activity is blocked by a drug with a nullifying action.

Examples: Amphetamine and Barbiturates, Adrenaline and propanolol, Morphine and Nalaxone.

2. **Potentiating Drug Interaction:** A potentiating interaction enhances the toxic or therapeutic action of a drug in patients. Synergism, a type of potentiating interaction occurs when the combined effect of two or more drugs, acting simultaneously is greater than the sum of the individual effects produced when each drug is administered alone.

Examples: Isoniazid and Rifampicin, Levodopa and Carbidopa, Sulfonamide and trimethoprim.

MECHANISM OF DRUG INTERACTIONS[3]

Drug Interactions can be broadly divided into Pharmacokinetic and Pharmacodynamic drug interactions.

a) Pharmacokinetic Interactions: Pharmacokinetic Interactions are those which can affect the process by which drugs are absorbed, distributed, metabolised and excreted.

b) Pharmacodynamic Interactions: Pharmacodynamic Interactions occur due to modification of action of one drug at the target site by another drug, independent of a change in its concentration.

CAUSES OF DRUG INTERACTIONS[2]

1. Administration of two or more drugs simultaneously (Drug Explosion) - It is a common practice to prescribe more drugs at a time which is referred as "Therapeutic Jungle or Polypharmacy"
2. Patients consulting various doctors – Sometimes if a patient is not satisfied with one doctor, they may refer another doctor without revealing about their past medical history.
3. Use of non-prescribed or OTC drugs – A patient may take the over the counter drugs like analgesics, antacids, antipyretics etc which are available without physician's prescriptions.
4. Patient's non adherence – Sometimes patient doesn't comply with the instructions given by the physician and may consume foods that are been prohibited which can result in drug-food interactions.

FACTORS RESPONSIBLE FOR DRUG INTERACTIONS

1. Physiology of an individual: Factors such as age, gender, weight and genetic variations influences the occurrence of drug interactions.
2. Dietary factors: Constituents of an individual's diet may interact with certain drugs.
3. Disease conditions: Pathological conditions like liver disease, kidney disease, or altered enzyme systems may affect the handling of drugs by the body and thus leads to adverse drug interactions.
4. Lack of knowledge: Insufficient understanding of the pharmacokinetics and pharmacodynamics of the drug may lead to drug interactions.

CLINICAL MANAGEMANT OF DRUG-DRUG INTERACTIONS

a) Avoiding the combination entirely

For some drug interactions, the benefit always outweighs the risk, and the combination should be avoided. Because drug classes are usually heterogeneous with regard to drug interactions, one can often select a no interacting alternative for either the object drug or the precipitant drug.

b) 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.

c) 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 2 hours before or 4 hours after the precipitant drug. In this way, the object drug can be absorbed into the circulation before the precipitant drug appears.

d) 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 changes can be made, or the drugs discontinued if necessary.

e) 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.

f) Improve computerized screening systems

It is clear that computerized drug interaction screening systems have not been as successful as one hoped.

OBJECTIVES

a) To assess the potential DDIs in the drug chart of the hospitalized patients.

b) Assessing the risk factors (Moderate, major) and suggesting prescriber about the possible risk which can improve desired patients clinical outcome during hospital stay.

METHODOLOGY

A prospective observational non interventional study was conducted at BGS super speciality global hospitals, Bangalore for a period of 6 months.

Study criteria

INCLUSION CRITERIA

1. The patients admitted in the hospital of above 18 years in internal medicines
2. Patient who stayed for more than 48 hours was included in the study.
3. Patients who depended on the therapy were included in the study.
4. Patients on multiple drug therapy; with minimum of three drugs.
5. Patients of both sexes.

EXCLUSIVE CRITERIA

1. Patients below 18 years of age
2. Patients who were on the radio therapy was excluded from the study
3. Patients who discharged below 48 hours were excluded from the study.
4. Outpatient basis and self medication patients are excluded from the study
5. Patients on herbal medications.
6. Pregnant and lactating women.
7. Patients on non-prescription drugs or self-medication.
8. Pharmaceutical incompatibilities.
9. Drug-Alcohol interactions.
10. Patient under critical conditions and requiring critical stay.
11. Patients treated on outpatient basis

Drug Interaction Probability Scale (DIPS)

Patient data collection form was prepared and adopted for the collection of data. After diagnosing the medical condition and prescribing the drug therapy the medication chart was taken for the evaluation of the drug interactions. The Drug Interaction Probability Scale (DIPS) is designed to assess the probability of a causal relationship between a potential drug interaction and an event.[18]

Question	Yes	No	Unknown or Non Applicable
1. Are there previous *credible* reports of this interaction in humans?	+1	-1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
3. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	-1	0
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if there was no dechallenge, choose *Unknown or Non Applicable* and skip question 6)	+1	-2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	-1	0
7. Are there reasonable alternative causes for the event?[a]	-1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	-1	0

[a] Consider clinical conditions, other interacting drugs, lack of compliance, risk factors (e.g., age, inappropriate doses of object drug). A No answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score:

Highly Probable	**>8**
Probable	**5-8**
Possible	**2-4**
Doubtful	**<2**

Figure No. 1: Drug Interaction Probability Scale (DIPS)

Directions to use DIPS

- Circle the appropriate answer for each question, and add up the total score.

- Object drug = Drug affected by the interaction.

Precipitant drug = Drug that causes the interaction.

- Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (eg, no dechallenge; dose not changed, etc).

Explanation of Severity levels

Level 5 - Severe

The interaction between these medications may be life-threatening or may cause permanent damage. These medications are not usually used concurrently; medical intervention may be required.

Level 4 - Moderate

These medications may interact resulting in the potential deterioration of the patient's condition. The patient should be monitored for the possible manifestations of the interaction. Medical intervention or a change in therapy may be required.

Level 3 - Minor

Clinical effects of the interaction are limited and may be bothersome but would not usually require a major change to therapy. The patient should be monitored for the possible manifestations of the interaction.

Level 2 - Caution

The interaction may occur based on the mechanism of action of the co-administered medicines. Be alert for increased or decreased effect, depending on the combination of medicines.

Level 1 - Not clinically significant

The interaction may occur, but the outcome is not clinically significant.

Level 0 - Not established

The interaction may theoretically occur due to its pharmacokinetics and pharmacodynamics. There have not been any established reports of the interaction.

RESULTS AND DISCUSSION

A total of 200 patients were enrolled into the study based on the study criteria. Observational statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean + (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Pearson correlation was used to assess the correlation between the two data's generated. Out of total 200 patients, the majority of 57.5% patients were males followed by 42.5% females. Majority of study population belonged to the age group of 20-39 years (42.5%), followed by 40-59 years (31%) and ≥ 60 years (26.5%) respectively.

Table No. 1: Demographic details of the study population

DEMOGRAPHICS	CATEGORY	NO. OF SUBJECTS (N = 200)	PERCENTAGE (%)
AGE	20-39	85	42.5 %
	40-59	62	31 %
	≥ 60	53	26.5 %
GENDER	Male	115	57.5 %
	Female	85	42.5 %

After complete review of 200 patient's drug charts, it reveals that there are 139 potential drug interactions which account 69.5%.

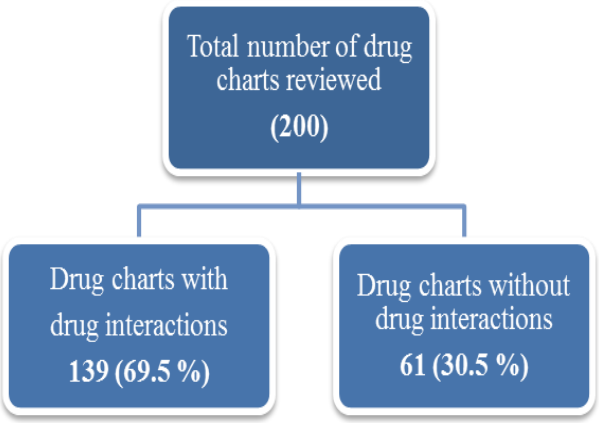

Figure No. 2: Occurrence of Drug Interactions among study population

Totally, 339 interactions had observed in 139 drug charts. Out of 339 interactions, 151(45%) interactions were found to be pharmacokinetic interactions and 188 (55%) were pharmacodynamic interactions respectively.

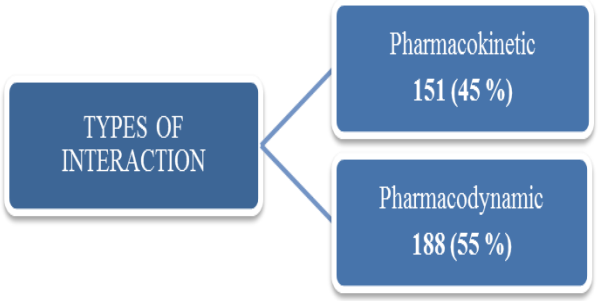

Figure No. 3: Types of Drug Interactions among study population

Among 339 drug interactions, 26(7%) interactions account as minor, 199(59%) as moderate, 111(33%) as major and 3(1%) as contraindicated interactions.

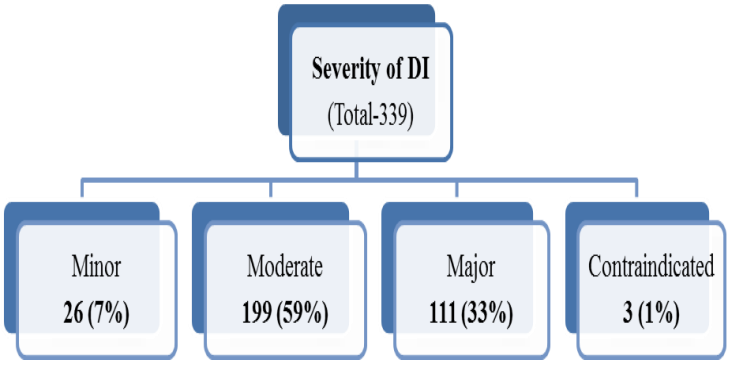

Figure No. 4: Severity of Drug Interactions among study population

Table No. 2 shows the relationship between the hospital stay and the occurrence of drug interactions. For accuracy, Pearson correlation was calculated and the value obtained was (r= 0.9439) with 95% confidence level p-value <0.05. The value obtained was p=0.01578 with two tailed test. So the relationship between hospital stay and drug interactions shown the significant linear correlation with 95% confidence level.

Table No. 2: Relationship between duration of hospital stay and interactions occurred among the study population

Sl.No	DURATION OF HOSPITAL STAY (Days)	NO. OF PATIENTS	INTERACTIONS OCCURRED	PERCENTAGE OF DRUG INTERACTIONS
1	1-3	90	46	45%
2	4-6	53	52	26.5%
3	7-9	33	54	16.5%
4	10-12	15	87	7.5%
5	≥13	9	100	4.5%
		Total= 200	**Total= 339**	**Total= 100%**

The below table No. 3 depicts the relationship between number of drugs prescribed and the drug interactions occurred. The Pearson correlation was calculated between no. of drugs prescribed and the drug interactions occurred. The Pearson correlation value was obtained as (r=0.8482 at 95% confidence level) and the p value was less than 0.05. The value obtained was p=0.01578 with two tailed test. So the relationship between no. of drugs prescribed and drug interactions shown the significant linear correlation with 95% confidence level.

Table No. 3: Relationship between no. of drugs prescribed and interactions occurred among the study population

Sl.No	NO. OF DRUGS PRESCRIBED	INTERACTIONS OCCURRED	PERCENTAGE OF DRUG INTERACTIONS
1	1-5	74	26.2%
2	6-10	80	23.5%
3	11-15	88	24.7%
4	16-20	97	25.6%
		Total= 339	**Total= 100 %**

As the major interactions are more serious, this study concentrated on the drug classes which engaged with major interactions. The below figure No. 4 gives the information regarding the drug classes which are involved in the major interactions. From the following data, anticoagulants/antiplatelets are at higher frequency (24%) in causing major drug interactions followed by the antibiotics (15%) and so on as shown in the below figure.

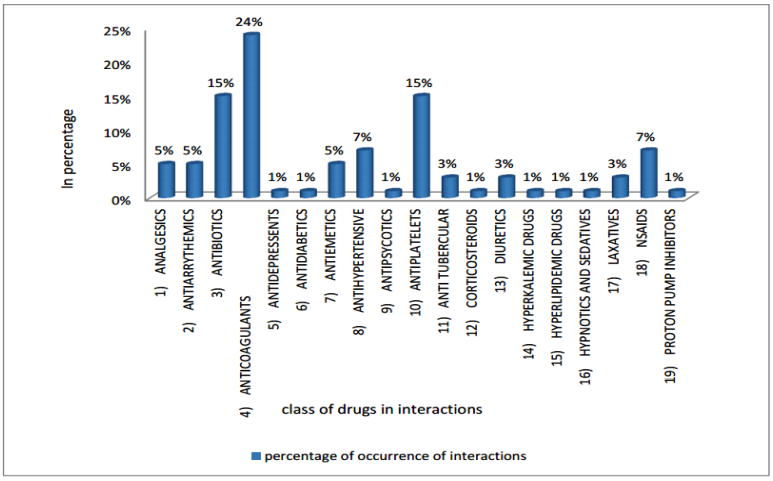

Figure No. 5: Drug classes which Involved in occurrence of major interactions among study population

Figure No. 5 depicts the list of drugs involved in the major drug interactions among the study population. From the observation we found that, Aspirin (17), heparin (10), enoxaparin (7), clopidogrel (9) and ciprofloxacin (8) were having higher rate of interactions with other drugs.

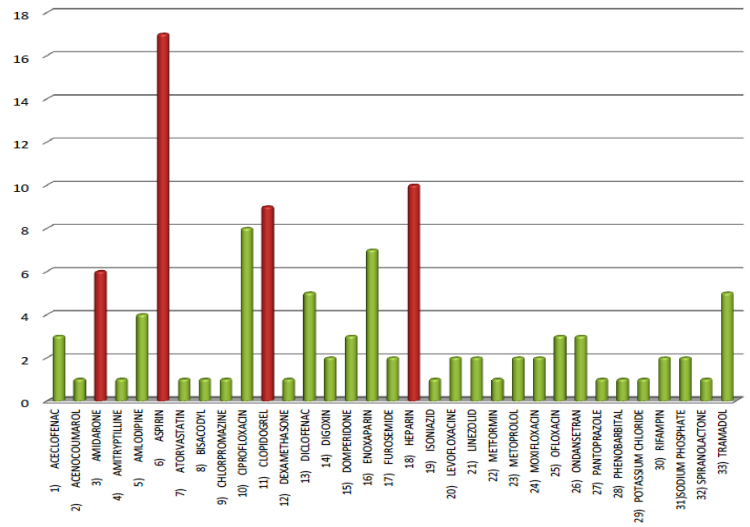

Figure No. 6: List of drugs involved in major interactions among study population

CONCLUSION

The present study identified pDDIs and also documented interactions in hospitalized patients which may lead to adverse drug reactions (ADRs). The males 80(59%) are having higher hospitalization than the females 58(41%) and major were the pharmacodynamic interactions and delayed in nature. The study highlights the need for screening prescriptions of

hospitalized patients for pDDIs and proactive monitoring of patients who have identified risk factors, this helps in detection and prevention of possible ADRs.

LIMITATIONS OF THE STUDY

a) The study was conducted in a small population for a limited period of time.
b) The study did not involve the special population.

FUTURE DIRECTIONS

a) To ensure the clinical pharmacist to take a vital role in identification, assessment, minimizations of potential DDIs and help for the better patient care.
b) To ensure the clinician about the possible drug interactions before prescribing the medications to the patient.

REFERENCES

1. Tripathi KD. Essentials of Medical Pharmacology. 6th edition, jaypee Brothers, Medical Publishers (P) Ltd., Page.no: 889-896.
2. Scott R. Penzak, Pharm.D. Director, Clinical Pharmacokinetics Research Laboratory Clinical Centre Pharmacy Department National Institutes of Health, December, 2010.
3. Mark HB, Michele S, Genell L. Incidence and risk of potential adverse drug interaction in the emergency room. Ann Intern Med. 2001 June; 49(3): 283-8.
4. Jiansong Yang, Maria Kjellsson1et al: The effects of dose staggering on metabolic drug–drug interactions; European Journal of Pharmaceutical Sciences, 2003; 20: 223–232.
5. Becker ML, Kallewaard M, Caspers PW, Schalekamp T, Stricker BH. Potential determinants of drug-drug interaction associated dispensing in community pharmacies. Drug Saf. 2005; 28: 371-378.
6. Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. J Am Pharm Assoc. 2001; 41: 200–4.
7. Doucet J, Chassagne P, Trivalle C, Landrin I, Pauty MD, Kadri N, et al. Drug-drug interactions related to hospital admissions in older adults: A prospective study of 1000 patients. J Am Geriatr Soc. 1996; 44: 944–8.
8. Chrischilles EA, Fulda TR, Byrns PJ, Winckler SC, Rupp MT, Chui MA. The role of pharmacy computer systems in preventing medication errors. J Am Pharm Assoc (Wash) 2002; 42: 439–48.
9. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clin Pharmacokinetic. 2002; 41: 343–70.

10. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol. 2002; 40: 567–72.
11. Frank G.A. Jansman, pharm D et.al. Consensus-Based Evaluation of Clinical Significance and Management of Anticancer Drug Interactions. Clinical Therapeutics, 2011; 33(3): 305-314.
12. Camelia Bucsa et al: How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? European Journal of Internal Medicine. 2013; 24: 27-33.
13. Verendra K Patel, Leelavathi D Acharya et al: Potential drug-drug interactions in patients admitted to cardiology wards of a South Indian teaching hospital. Australian Medical Journal AMJ. 2001; 4(1): 9-14.
14. Priska Vonbanch et al: prevalence of potential drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. European Journal of Internal Medicine. 2008; 19: 413-420.
15. Yunn-Fang Ho et al: Detecting Drug–Drug Interactions In Medication Profiles of Psychiatric Inpatients: A Two-Stage Approach, J Formos Med Assoc. 2002; 101: 294–297.
16. Ana L.Hincape, M.S, Lisa e. Hines, pharm.D. et al: Impact of a drug-drug interaction intervention on pharmacy and medical students‟ knowledge and attitudes: A 1-year follow-up; Research in Social and Administrative Pharmacy; 2012; 8: 472–477.
17. Churi et.al; Assesment of drug drug interactions in hospitalized patients in India; Asian J Pharma Clin Res, 2011; 4(Suppl 1): 62-65.
18. Horn JR, et al. 2007. Proposal for a New Tool to Evaluate Drug Interaction Cases. Ann Pharmacother. 41(4): 674.