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PROSPECTIVE STUDY ON DRUG-DRUG INTERACTIONS OF NARROW THERAPEUTIC INDEX DRUGS

S. Priya Rajam Vivean*, M. Ashok Kumar and P. Shanmugasundaram

Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS) Pallavaram, Chennai - 600117, Tamil Nadu, India.

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Correspondence to Author:
S. Priya Rajam Vivean

Indira Grandeur-BFO1, E. B. road, Mogappair East, Chennai - 600037, Tamil Nadu, India.

E-mail: priyasagayaraj16@gmail.com

ABSTRACT: Drug interaction generally refers to a modification of the expected drug response in the patient as a result of exposure of the patient to another drug or substance. Some unintentional drug interactions produce adverse reactions in the patient, whereas some drug interactions may be intentional, to provide an improved therapeutic response or to decrease adverse drug effects. They are divided into three groups depending on the underlying mechanism of interaction: pharmaceutical, pharmacokinetic or pharmacodynamic interaction.

INTRODUCTION: Narrow therapeutic index drugs are drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and / or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening, possibly resulting in hospitalization, disability, or even death. Examples of Narrow Therapeutic Index drugs include digoxin, theophylline, carbamazepine, warfarin, lithium and phenytoin.

A Drug-drug interaction is defined as the pharmacological or clinical response to the administration or co-exposure of a drug with another drug that modifies the patient's response to the drug index [1].

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The effect of a drug-drug interaction might be apparent as decline in therapeutic effect of a drug, increased occurrence of ADRs and compromised treatment outcomes [2, 3]. Advanced age, poly-pharmacy and multiple prescribers have been identified as risk factors for occurrence of potential drug interactions [4]. DDIs are more likely to happen in the elderly because they tend to use multiple medications and have altered pharmacokinetics [5, 6]. When two or more drugs are administered, the activity of one or both the drugs may be altered, resulting in the formation of a new compound, before the administration of drug in the body is pharmaceutical interaction.

When the pharmacological effect of the drug is altered during its absorption, distribution, metabolism or elimination process, it is known as pharmacokinetic interaction. The synergism and antagonism effects among drugs occurring at the site of action are called pharmacodynamic interactions [7, 8]. A potential drug-drug interaction is an event that is likely to develop if pharmacists do not make any appropriate intervention. Drug-drug interactions pose significant challenge to health

care providers and may affect morbidity, mortality and a patient's quality of life.

The pharmacist, along with the prescriber must ensure that the patients are aware of the side effects caused by the drugs. The role of a pharmacist is to promote drug utilization evaluation to minimize the drug interactions. The nature and severity of all drug-drug interactions should be identified to educate the staff (physician, nurses, etc) [9, 10].

Objective:

- To evaluate the actual doses in which the drug interaction occurs.
- To evaluate the consequences of drug interactions.
- To study the nature and mechanism in which drug interactions occur.

MATERIALS AND METHODS:

Materials:

Study Site: Department of General medicine in a Tertiary care hospital.

Study Population: Patients from a Tertiary care hospital.

Sample size: 50

Study Period: 9 months.

Study design: Prospective study.

Inclusion Criteria:

i. Patient who receives narrow therapeutic index drugs.
ii. Both sexes above 18 years of age.

Exclusion Criteria:

i. Pregnant and nursing women.
ii. Patients who are on comatose.

Method: The prospective study was carried out for a period of nine months in a Tertiary care hospital. Ethical approval was obtained from the Research and Ethics committee, prior to study initiation. Prescriptions with narrow therapeutic index drugs prescribed were selected for the study.

All the necessary and relevant data were collected from inpatient case notes, treatment charts, and laboratory data reports were entered in the proforma. The patient and their case notes were followed till discharge. Drug interactions were identified using computerized drug-drug interaction data base systems such as drugs.com, medscape, upto date and micromedex. Then by using these computerized data bases, the drug-drug interactions were identified and classified according to databases. According to severity, Potential drug-drug interactions were classified as:

Major: Life threatening effects or permanent damage may be caused.

Moderate: Patient's clinical status may be diminished and hospital stay may be extended or additional treatment needed.

Minor: Mild effects.

Depending upon the mechanism of interaction, drug interactions are subdivided into three groups: pharmaceutical, pharmacokinetic and pharmaco-dynamic interactions.

RESULTS:

TABLE 1: AGE WISE DISTRIBUTION

Age in Years	No. of Patients (n = 50)	Percentage of Patients
20-30	6	12%
30-40	2	4%
40-50	12	24%
50-60	10	20%
60-70	10	20%
70-80	8	16%
80-90	2	4%

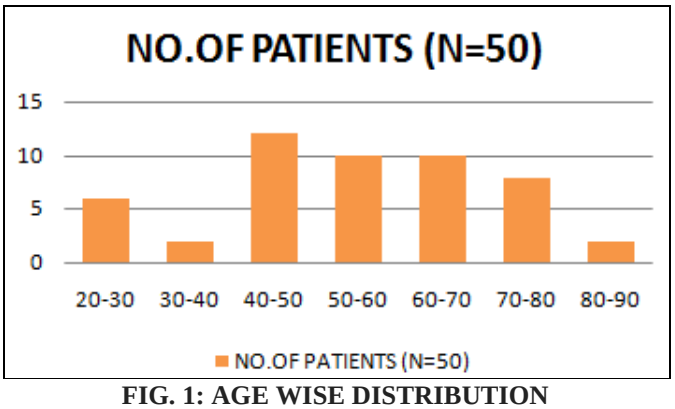

FIG. 1: AGE WISE DISTRIBUTION

Out of selected 50 patients, 6 patients (12%) were in the age group of 20-30 years, 2 patients (4%) were in the age group of 30-40 years, 12 patients (24%) were in the age group of 40-50 years, 10

patients (20%) in the age group of 50-60 years, 10 patients (20%) in the age group of 60-70 years, 8 patients (16%) in the age group of 70-80 years of age and 2 patients (4%) in the age group of 80-90 years of age.

TABLE 2: GENDER WISE DISTRIBUTION

Gender	No. of Patients (n = 50)	Percentage
Male	34	68%
Female	16	32%

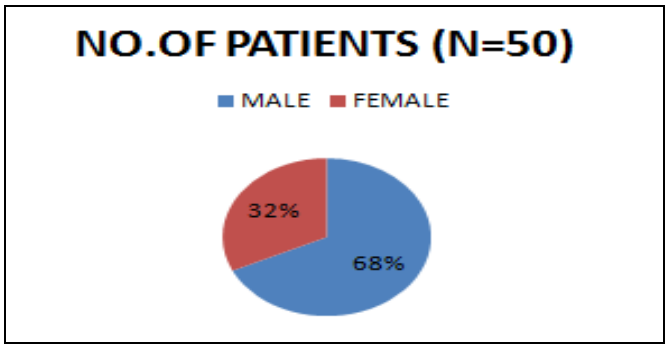

FIG. 2: GENDER WISE DISTRIBUTION

Out of selected 50 patients, 34 patients (68%) were male, and 16 patients (32%) were female.

TABLE 3: DISTRIBUTION BASED ON COMORBIDITIES

Comorbidities	No of Patients (n = 50)	Percentage
Diabetes Mellitus	9	18%
Hypertension	5	10%
Bronchial Asthma	8	16%
Lower Respiratory Tract Infection	6	12%
Copd	20	40%
Osteoarthritis	1	2%
No Comorbidities	1	2%

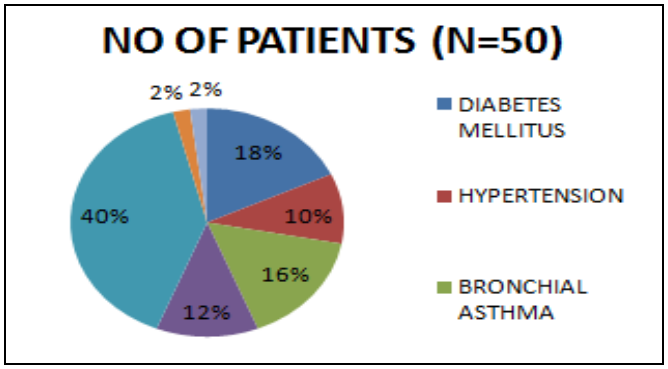

FIG. 3: DISTRIBUTION BASED ON COMORBIDITIES

Out of selected 50 patients, 9 patients (18%) were having Diabetes, 5 patients (10%) were having Hypertension, 8 patients (16%) were having Bronchial Asthma, 6 patients (12%) were having lower respiratory tract infection, 20 patients (40%) were having COPD, and 1 patient (2%) was having osteoarthritis.

TABLE 4: INCIDENCE OF POLYPHARMACY

Number of drugs	Number of prescription (n=50)	Percentage (%)
6	10	20
9	2	4
10	8	16
11	4	8
12	4	8
13	8	16
17	2	4
19	12	24

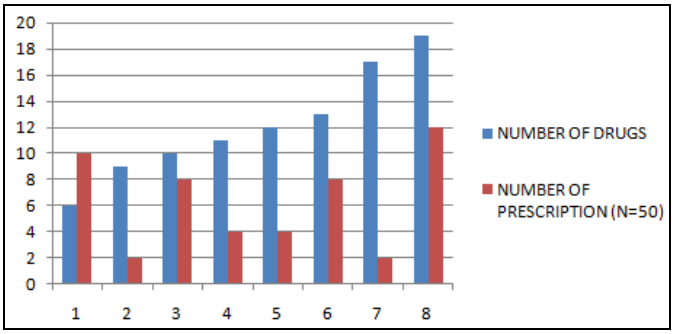

FIG. 4: INCIDENCE OF POLYPHARMACY

The number of drugs per prescription is shown in **Table 4**. The average number of drugs per prescription was 12.2. All prescriptions contained more than 5 drugs, 40% of prescriptions contain 6 to 10 drugs, and 32% of prescriptions contain 11 to 13 drugs and 28% of prescriptions contain 17 to 19 drugs. In research studies, it is stated that poly-pharmacy is defined as the concomitant use of five or more drugs.

TABLE 5: DISTRIBUTION BASED ON TYPES OF DRUG-DRUG INTERACTIONS

Types of drug interactions	No. of drug-drug interactions
Pharmaceutical Interaction	0
Pharmacokinetic Interaction	54
Pharmacodynamic Interaction	12

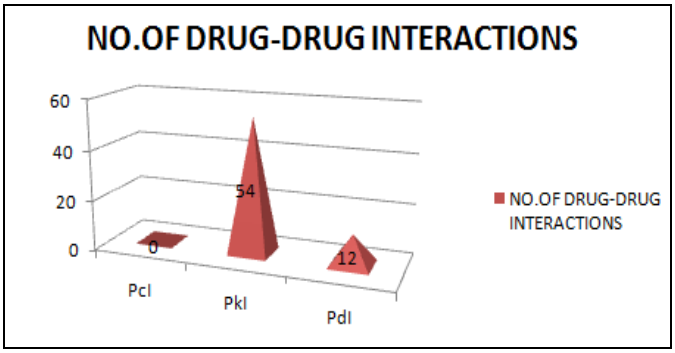

FIG. 5: DISTRIBUTION BASED ON TYPES OF DRUG-DRUG INTERACTIONS

TABLE 6: SEVERITY OF DRUG-DRUG INTERACTIONS

Severity of drug -drug interactions	No. of drug-drug interactions
Minor	12
Moderate	52
Severe	2

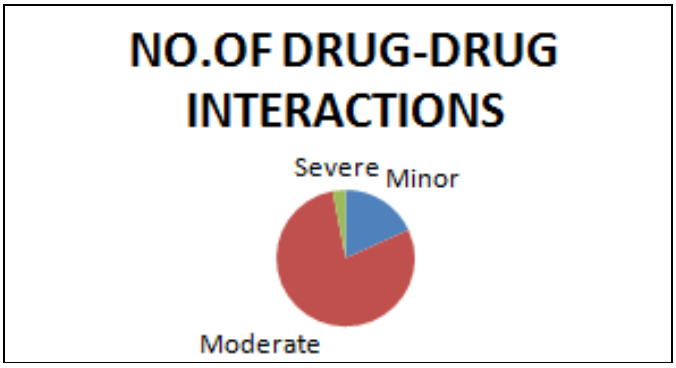

FIG. 6: SEVERITY OF DRUG-DRUG INTERACTIONS

TABLE 7: COMMONLY FOUND POTENTIAL DRUG-DRUG INTERACTIONS

Severity level	Interacting drugs	No. of patients
Major	Ciprofloxacin + Theophylline	2
Moderate	Omeprazole + Phenytoin	2
	Metronidazole + Theophylline	2
	Hydrocortisone + Theophylline	2
	Atenolol + Theophylline	12
	Dexamethasone + Theophylline	28
	Prednisolone + Theophylline	6
Minor	Omeprazole + Theophylline	12

TABLE 8: FREQUENCY OF DRUG-DRUG INTERACTIONS

Frequency of DDIs	Number of patients (n = 50)	Percentage
1	42	84%
2	4	8%
3	4	8%

TABLE 9: LIST OF POTENTIAL DRUG-DRUG INTERACTIONS

Drugs	No. of patients	Potential effect
Omeprazole + Theophylline	12	Omeprazole will decrease the level or effect of theophylline by affecting hepatic enzyme CYP1A2 metabolism.
Omeprazole + phenytoin	2	Omeprazole will decrease the level or effect of phenytoin by affecting hepatic enzyme CYP2C9/10 metabolism.
Metronidazole + Theophylline	2	Metronidazole will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Hydrocortisone + Theophylline	2	Hydrocortisone will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Atenolol + Theophylline	12	Beta blockers antagonize theophylline effects, while at the same time increasing theophylline levels and toxicity.
Dexamethasone + Theophylline	28	Dexamethasone will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Prednisolone + Theophylline	6	Prednisolone will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Ciprofloxacin + Theophylline	2	Ciprofloxacin will increase the level or effect of theophylline by affecting hepatic enzyme CYP1A2 metabolism.

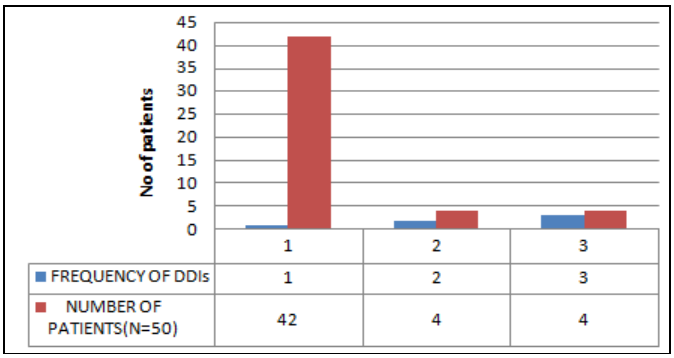

FIG. 7: FREQUENCY OF DDIs

DISCUSSION: Drug-drug interactions can lead to alteration of therapeutic response or increase untoward effects of many drugs (Baxter and Stockley, 2010). Special attention and thorough monitoring is definitely required for the patients who are at the most risk of developing potential drug-drug interactions (Rana *et al*., 2014). During 9 months of study, 50 prescriptions were analyzed out of which 34 (68%) were male and 16 (32%) were female. Among them 2 prescriptions were with major interactions, 52 prescriptions with moderate and 12 prescriptions with minor interactions. Majority of the patients were in the age group of 55-60 years, which was similar to the study conducted by Doubova *et al*., 2007. Of the potential drug-drug interactions, majority were of pharmacokinetic in nature followed by pharmacodynamic interactions. These findings were similar to the study conducted by Vonbach and Aparsu, who reported 76% of pharmacokinetic and 22% of pharmacodynamic interactions [11, 12].

Average number of drugs per prescription (12.55) indicates the incidence of polypharmacy, and in most cases it was unavoidable. The mean age of the patients was 55.4 years. These potential drug-drug interactions were reported to the consulting physician and the patients prescribed with these drugs were monitored. The best way to identify and treat drug interactions is the use of computer programs. Detection and reporting of Drug-drug interactions should be done by all health professionals to ensure patient's safety.

CONCLUSION: The present study revealed majority of potential drug interactions were pharmacokinetic in nature hence periodic auditing of prescriptions is vital for promotion of rational use of drugs, increasing the therapeutic efficacy, cost effectiveness and minimizing drug interactions. The use of computer assisted drug interaction software before prescribing drugs can serve as an important tool in identifying these potential drug-drug interactions which can help us to detect and prevent drug interactions. Hence pharmacist participation can improve the treatment to hospitalized patients and promote drug safety.

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