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A PROSPECTIVE STUDY ON POTENTIAL DRUG – DRUG INTERACTIONS IN A SECONDARY CARE HOSPITAL

Dona Maria Jetto[1*], Alphine Roy[2], An Maria Jose[3], Harsha Rajesh[4], Johns Zacharia[5]

Department of Pharmacy Practice, Nirmala College of Pharmacy, Muvattupuzha, Ernakulam, 686661 Kerala, India.

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ABSTRACT

An interaction is said to occur when the effects of one drug are altered by the co-administration of another drug, herbal, medicine, food, drink or other environmental chemical agents. The net effect of 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 alteration in effect. Drug – drug interactions are a particularly important type of adverse drug event because they are often predictable based on previous reports, clinical studies and an understanding of pharmacologic principles. Some adverse drug events have life threatening consequences and may prompt the removal of popular medications from the market place. The study was a prospective observational study, conducted in secondary healthcare center in Muvattupuzha. In this case study, a total of 150 cases were included and the study population consisted of the patients admitted to the general medicine department of Nirmala Medical Centre, Muvattupuzha during a period of 4 months. General medicine department of Nirmala Medical Centre, a private cooperate hospital in Muvattupuzha. Out of the analysed cases, 108 cases were found to have PDDIs with Major (30.601%), Moderate (31.694%) and Minor (37.705%) interactions. In our study, more number of drug interactions were identified in elderly patients of age group >60 years (53.703%). Of the total 108 patients, 43.518% of the study subjects were males and 56.482% were females. A total of 57 patients had one or more comorbidities. The most common comorbid conditions observed in our study patients include Hypertension (21.29%), Diabetes mellitus (18.51%), Migraine (3.70%),Hyperlipidemia (5.55%) and Coronary artery disease (3.70%). Majority of PDDIs were seen in patients receiving 4-5 drugs (32.407%).The lack of awareness regarding the management of PDDIs have affected the quality of life of the patients. DDIs, being an avoidable adverse event, prescriptions adhering to treatment guidelines and proper monitoring by health care professionals can decrease the rate of PDDIs to a great extent.

Key words: PDDI, Adverse Drug Event.

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INTRODUCTION

Drug interactions represent an important source of medication error and is responsible for hospital admissions [1-3]. Administration of two or more drugs may lead to interactions leading to alteration in therapeutic response. Pharmacist plays an important role in monitoring interactions and on advising on management of interactions [4-6]. Drug-Drug interactions contribute to increased rate of morbidity and mortality, which neccessitates the importance of monitoring interactions and thus patient safety can be achieved [7]. The potential Drug-Drug interaction concept refers to the possibility a drug has to alter the effects of another when both are simultaneously administration [8].

MATERIALS AND METHODS

Study design

The study was a prospective observational study,

Corresponding Author:- **Dona Maria Jetto** Email:- donamariajetto@gmail.com

conducted in a secondary healthcare center in Muvattupuzha. Health care center was selected and healthcare professionals were informed well in advance.

Study Site

General medicine department of a private cooperate hospital in muvattupuzha.

Study Period: 6 Months

Study Criteria

Inclusion criteria:

1. Patients admitted in general medicine department.
2. Patients receiving two or more than two medications.

Exclusion criteria:

1. Patients with insufficient data in their record.
2. Those who are not willing to cooperate.

METHOD

Obtained approval for study protocol from the institutional review board. The verbal consent was obtained from each subject before initiating the study. Afterwards identified patients with drug interaction based on the treatment chart. A structured performa was used to collect various clinical & demographic details of the patient such as age, gender, length of hospital stay, primary diagnosis & clinical data's. Treatment data including prescribed drug, dosages, frequency & route of administration was recorded. Treatment chart was analysed using software's such as Micromedex & Stockleys drug interaction book. Interactions were assessed & categorized as major, moderate & minor based on severity. Incidence rate was calculated and as part of the study, prescription pattern of drugs in general medicine department was analysed [9].

Data Analysis

All the data obtained were subjected to analysis by converting into percentage. The data thus compiled was used as the base for final result and discussion.

RESULT

In this research work, a total of 150 cases were included and the study population consisted of the patients admitted to the general medicine department of Nirmala Medical Centre, Muvattupuzha during a period of 6 months. Out of the analysedcases , 108 cases were found to have PDDIs with Major (30.601%), Moderate (31.694%) and Minor (37.705%) interactions. In our study, more number of drug interactions were identified in the elderly patients of age group >60 years (53.703%). Of the total patients, 43.518% of the study subjects were males and 56.482% were females. A total of 57 patients had one or more comorbidities. The most common comorbid conditions observed in the study patients includes Hypertension, Diabetes mellitus, Asthma , Hyperlipidemia and Coronary artery diseases. Majority of PDDIs were seen in patients receiving 4-5 drugs (32.407%). Majority of the study patients received multiple medications due to their multiple conditions. It is obvious that the patients with multiple disorders require several medications in treating their disease conditions [10].

Incidence of potential drug-drug interactions

Out of 150 patients reviewed, 108 patients were found to have had at least one potential drug – drug interaction giving the incidence rate of 72% . A total of 183 potential DDIs were identified from 108 patients. The patients admitted to the general medicine department are at risk for the development of PDDIs, as their condition is complicated by disease severity, which can alter the pharmacologic response to medications. The number of prescribed drugs is another important risk factor for the occurrence of PDDIs which was seen in our study population.

In a study conducted by Olga Morales - Rios et al. (2018) on the potential drug- drug interactions in the emergency department , out of 915 patients that were included in the analysis , the incidence rate of PDDIs was found to be 61% [11-14].

Age Wise Distribution of Patients With Potential DDIS

In our study, more number of drug interactions were identified in the elderly patients of age group >60 years (53.703%). In this age group, PDDIs were identified in 58 patients. The patients belonging to the age group of >60 years have an average of 3 PDDIs per patient. Most of the patients in this age group were having multiple co – morbid conditions, higher level of disease warranting the use of multiple drug therapy to treat such conditions. The age wise distribution of patients with PDDIs is shown in Fig No 1.

Table 1. Co-morbid Conditions In Patients With Potential Drug Drug Interactions

	Comorbid diseases	Number of times of occurrence	Percentage (%)
Comorbid Conditions	Nil	51	47.222
	Hypertension	23	21.296
	Diabetes	20	18.519
	Migraine	4	3.704 3.704

	Hyperlipidemia	6	5.555 5.55
	Coronary artery disease	4	3.704

Table 2.Polypharmacy in patients with potential drug – drug interactions

Range of number of drugs in individual cases	Number of cases	Percentage
2-3	1	0.925
4 – 5	35	32.407
6 – 10	34	31.482
11 – 15	26	24.075
≥16	12	11.110

Table 3. Severity of Potential Drug Drug Interactions

Severity	Major	Moderate	Minor
Number	56	58	69
Percentage	30.601	31.694	37.705

Table 4. Mechanism of major drug – drug interactions

S.No	Interacting drugs	Mechanism
1.	Aspirin + Torsemide	Pharmacokinetic
2.	Prochlorperazine +Ondansetron	Pharmacodynamic
3.	Clopidogrel + Aspirin	Pharmacodynamic
4.	Ivabradine + Levofloxacin	Pharmacodynamic
5.	Amiodarone + Norfloxacin	Pharmacodynamic
6.	Budesonide + Norfloxacin	Pharmacodynamic
7.	Ivabradine + Ondansetron	Pharmacodynamic
8.	Ivabradine + Amiodarone	Pharmacodynamic
9.	Clopidogrel + Diltiazem	Pharmacokinetic
10.	Metronidazole + Ondansetron	Pharmacodynamic
11.	Ciprofloxacin + Escitalopram	Pharmacodynamic
12.	Ivabradine + Norfloxacin	Pharmacodynamic
13.	Clopidogrel + Heparin	Pharmacodynamic
14.	Ciprofloxacin + Tolvaptan	Pharmacokinetic
15.	Ofloxacin + Budesonide	Pharmacodynamic
16.	Ciprofloxacin + Ondansetron	Pharmacodynamic
17.	Dexamethasone + Tramadol	Pharmacokinetic
18.	Ciprofloxacin + Metronidazole	Pharmacodynamic
19.	Diazepam + Tramadol	Pharmacodynamic
20.	Theophylline + Levofloxacin	Pharmacokinetic
21.	Clopidogrel + Tramadol	Pharmacokinetic
22.	Alprazolam + Hydrocodone	Pharmacodynamic
23.	Ondansetron + Hydrocodone	Pharmacodynamic
24.	Tramadol + Alprazolam	Pharmacodynamic
25.	Aspirin + Glimepiride	Pharmacodynamic
26.	Tolvaptan + Furosemide	Pharmacokinetic
27.	Glimiperide + Pioglytazone	Pharmacodynamic
28.	Mefenamic acid + Diclofenac sodium	Pharmacodynamic
29.	Domperidone + Ondansetron	Pharmacodynamic
30.	Heparin + Aspirin	Pharmacodynamic

Table 5. List of top ten drug interactions implicated in Potential Drug – Drug Interactions

Sl No.	Drug combinations	Severity of interaction	Effect
1	Clopidogrel + Heparin	Major	Additive effect.

2	Ondansetron + Ciprofloxacin	Major	Both drugs increases QT interval and arrythmia.
3	Aspirin + Torsemide	Major	Both drugs increase toxicity by decreased renal prostaglandin synthesis.
4	Ciprofloxacin + Metronidazole	Major	Additive QT Interval prolongation.
5	Clopidogrel + Diltiazem	Major	Inhibition of CYP3A4 mediated Clopidogrel activation by Diltiazem.
6	Theophylline + Diazepam	Moderate	Decreased Benzodiazepine effectiveness
7	Phenytoin + Atorvastatin	Moderate	Inhibition of CYP3A4 mediated Atorvastatin metabolism by Phenytoin
8	Amiodarone + Atorvastatin	Moderate	Inhibition of CYP3A4 mediated Atorvastatin metabolism .
9	Valproic acid + Diclofenac	Minor	Valproic acid will increase the level of Diclofenac by affecting hepatic enzyme CYP2C9/10 Metabolism
10	Terbutaline + Theophylline	Minor	Increases theophylline metabolism.

Table 6. Management of Potential DDIs

S. No	Management Options	No. of Interactions
1	Monitor ECG Levels	11
2	Avoid Drug Use	6
3	Dose Reduction	5
4	Monitor Blood Loss	3
5	Monitor Glucose Level	1
6	Monitor Renal Function	1
7	Monitor Blood Count	1
8	Spacing Of Drugs	1
9	Use Of Alternatives	1

Fig 1. Age wise distribution of patients with Potential Drug – Drug Interactions

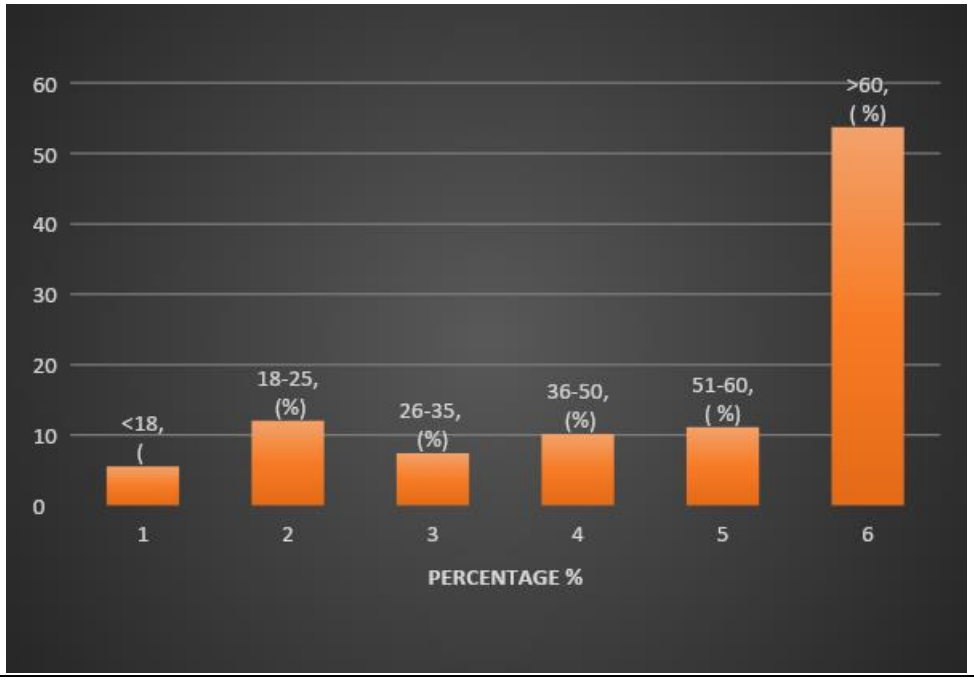
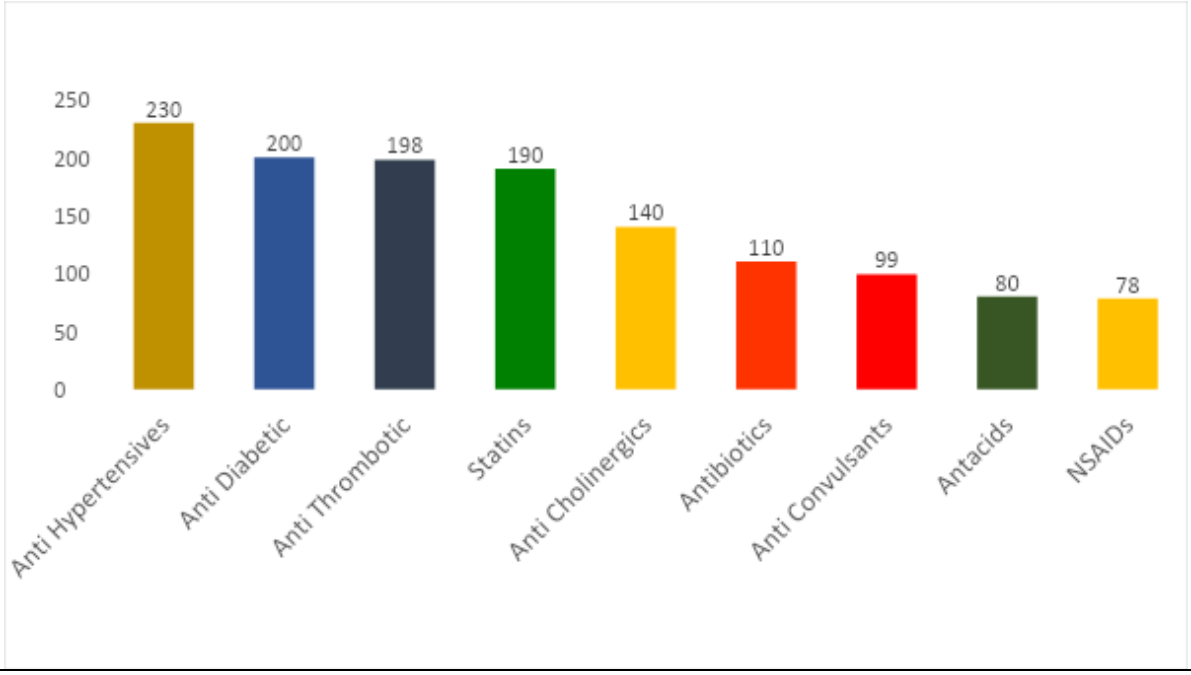


Fig 2. Commonly implicated drug classes in Potential DDIs



Gender wise distribution of patients with potential drug – drug interactions

Out of 108 patients with PDDIs, 47 were males and 61 were females. The incidence of PDDIs in male and female patients was found to be 43.518% and 56.428% respectively. Females are found to have an increased incidence of PDDIs than males. This can be attributed to the clinical conditions of female patients admitted to general ward, such as coronary artery disease, hypertension or diabetes, diabetes with renal dysfunction and any digestive disorder. The risk factors that play a key role are the post menopausal effects, sedentary lifestyle and diet. In contrast another study conducted by Kayshap M et al, it reported that incidence of PDDIs in males were higher (72%) in contrast to females (28%) which was due to their comorbid clinical conditions [15-18].

Number of co-morbidities in patients with PDDIS

In the patients with PDDIs, majority (52.77%) of patients presented with one or more comorbid conditions. The number of comorbidities in patients with PDDIs is presented in the Table 1. The commonly seen multiple comorbid conditions were hypertension, diabetes mellitus, migraine, hyperlipidemia, asthma and coronary artery disease. Presence of such comorbid conditions are the main reason for prescribing multiple drug therapy leading to occurrence of potential drug-drug interactions [19].

Polypharmacy in patients with PDDIS –

The number of PDDIs were high (32.407 %) in patients receiving more than 4-5 drugs and it was found to be less (0.925%) in patients receiving 2-3 drugs. The details of polypharmacy in patients with PDDIs are depicted in Table No.2. It was observed that all the patients admitted to the general medicine ward were prescribed with more than two drugs. ***In a study conducted by Almeida SM, the average number of medications prescribed to patients was found to be 9.15 ± 0.03 and 77% of the patients were prescribed more than 5 drug [20].

Severity of potential DDIS

Out of 108 potential drug - drug interactions observed in the present study, 56 (30.601 %), 58 (31.694%) and 69 (37.705%) potential DDIs were belonged to " major", " moderate" and "mild" in the severity category respectively. The level of severity of PDDIs is presented in Table No.3. The drugs which contributed to cause the major interactions were Ondansetron, Ciprofloxacin, Aspirin, Hydrocodon and Clopidogrel. Some of drugs that were involved in causing moderate interactions included Levodopa, Atorvastatin and Furosemide. Drugs like Valproic acid, Diclofenac ,Terbutaline and Theophylline accounted for the minor DIs [21].

Mechanism of major potential drug – drug interactions

The mechanism of potential drug drug interactions was assessed and classified as pharmacodyanamic and pharmacokinetic interactions. The number of Phamacokinetic DIs observed were 7 (23.334%) and the number of Pharmacodynamic DIs observed were

23 (76.666%). Among the total number of PDDIs, incidence of pharmacodynamic mechanism was high (76.666 %).

***A similar finding reported in a study conducted by Leelavadhi DA et al wherein among 388 PDDIs, (64.69%) were pharmacodynamic drug interactions and (20.1%) were pharmacokinetic drug interactions. The details of the mechanisms of potential DDIs are presented in Table No.4. The most commonly observed pharmacodynamic interaction was between Aspirin plus Clopidogrel which causes increased bleeding when administered together. Similarly is the use of Salbutamol plus Furosemide, due to synergism these drugs can alter the serum potassium levels in the patients resulting in hypokalemia [22].

Drug classes implicated in potential drug – drug interaction

In the present study, the drug classes commonly implicated in causing potential DDIs were anti platelet [n = 27] followed by anti biotics agents [n = 26] and bronchodilaters [n = 20] while least implicated drug classes were anti epileptics [n = 5] and corticosteroids [n = 3]. Most of the patients admitted to general medicine ward were suffering from diseases like hypertension, dyspnea, urinary tract infection, seizures and cardiovascular diseases. In a study conducted by Madhu P et al, antibiotics (48.9 %) and NSAIDs (27.6 %) were reported to be the commonly implicated drug classes. The drug classes commonly implicated in PDDIs are summarized in Fig No 2.

Drug interactions implicated in potential drug drug interactions

The drug combinations that were involved in causing PDDIs include co-administration of Ondansetron + Ciprofloxacin where both the drugs increases QT interval and arrythmia. Another PDDIs was between Aspirin + Torsemide wherein both drugs increases toxicity by decreased renal prostaglandin synthesis. Among the top ten drug combinations, the least implicated combination in causing PDDIs was Theophylline + Torsemide where, co-administration of these drugs caused increase in Theophylline metabolism [23].

**In a study conducted by Kashyap M reported that the top most identified interacting drugs were aspirin or combination of Aspirin &Clopidogrel along with anticoagulant and the second top most identified interacting drugs were combination of Clopidogrel and proton pump inhibitors. A list of top ten drug combinations implicated in PDDIs is presented in Table No.5.

Management of major potential drug – drug interactions

Management of potential DDIs is the crucial part of patient care. In the present study the main line of management of PDDIs was the monitoring for effects such as ECG Variation (n= 11) , Avoid Drug Use (n= 6) , Dose Reduction (n= 5) were observed. The details of management of Major potential DDIs are summarized in Table No.6. In rest of our PDDIs, management was done by methords like monitoring glucose level , monitoring renal function, monitoring blood count and by use of alternatives [24].

CONCLUSION

The present study was carried out in order to understand the prescribing patterns of drugs in patients admitted to the general medicine department of a secondary care hospital and to evaluate the potential drug – drug interactions. The severities of interactions were analyzed using Micromedex. One hundred and fifty cases were evaluated in the present study. Of these 150 cases, 108 cases were found to have atleast one potential drug – drug interactions. The major interactions were seen with drugs such as Clopidogrel, Ondansetron and Aspirin. Drug – Drug interactions are preventable medication errors associated with potentially serious adverse events and death. Therefore awareness of the most prevalent potential DDIs can help the healthcare professionals to prevent concomitant use of these dangerous medication combinations.

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Nil

CONFLICT OF INTEREST

No interest.

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