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EVALUATION OF DRUG-DRUG INTERACTION IN CHRONIC DISEASE PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: To assess the Drug-Drug interaction in a chronic disease condition in a tertiary care hospital. **Methods:** A hospital based Prospective Observational study was conducted for a period of 6 months, to assess the Drug-Drug interaction in a chronic disease condition in a tertiary care hospital. To study the effects and the type of drug interaction using www.drugs.com website. **Results:** A total of 110 patients were enrolled out of whom, 43 patients were female (39.1%) and 67 were male (60.9%), where 416 DDIs identified, 38 were major (9.13%), 321 were moderate (77.16%) and 57 (13.71%) were minor interactions. The number of potential DDI ranged from 1 to 16; 14 cases (12.7%) showed one potential DDI and 1 case (0.9%) showed 16 potential DDIs. The pharmacokinetic outcome was identified in 119 DDIs (27.05%) (Figure:5) and pharmacodynamics outcome was identified in 297 DDIs. Causality assessment was carried out using Drug Interaction Probability Scale (DIPS) to estimate the probability that an adverse reaction was caused by an interaction of the drugs in question; according to the total score of 10 questions the relationship is Doubtful (<2) (33.5%), Possible (2 to 4) (34.6%), Probable (5 to 8) (21.8%) and Highly probable (≥9) (2.7%). **Conclusion:** The study helps in understanding the possible drug interaction that can occur in patients with Chronic Obstructive Pulmonary Disease, hypertension, chronic kidney diseases and diabetes mellitus and avoid interactions in the future and provide a better health care to the patients.

KEYWORDS: Drug-drug interactions, pharmacodynamics, pharmacokinetic.

INTRODUCTION

Drug therapy becomes more complex with poly-pharmacy. Such prescriptions need to be evaluated thoroughly in order to avoid any chances of drug related problems (DRPs). Drug related problem lead to increase morbidity, mortality and increase health care expenses. The involvement of pharmacist in a health care system gives the opportunity to cater these demands and it gives the opportunity to involve greatly in the provision of drug related therapy which is not only effective but also free from any kind of toxicity. 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.

Drug-drug interactions can be classified in different ways. Pharmacokinetic and Pharmacodynamic interactions are important types of drug interactions classified on the basis of mechanism of action in clinical practice. In pharmacokinetic interactions, one drug affects the absorption, distribution, metabolism and excretion of other drug. While in pharmacodynamics interaction, two or more drugs may have additive or antagonistic effects.[1]

Based on the medications prescribed, the drug-drug interactions are identified and classified. According to severity, potential DDIs are classified as:

1) Major: The effects are potentially life threatening or capable of causing permanent damage.

2) Moderate: The effects may cause deterioration in patients' clinical status and additional treatment or extension of hospital stay.

3) Minor: The effects are usually mild.[2]Among the various professional services provided by the pharmacists, monitoring DRPs like DDIs is the most important one as it helps in improving patient safety in hospital settings. Since DDIs are an important cause for increase in morbidity and mortality rates in hospitalized

patients, it is imperative to assess the insight of DDIs in hospitalized patients.

The frequency with which therapeutic and other types of incompatibilities taking place can be drastically reduced if multiple drug therapy is always prescribed rationally and only when essential.

Clinical pharmacist occupies an important position in health care settings as it gets an opportunity to work in a team and utilize the professional skills, knowledge and expertise for better patient care.

The hazards resulting from the large number of drugs received over relatively short periods of time by many patients have been well documented. All the members of the health care team need to be alert to prevent therapeutically incompatible medications from reaching patients. It is utmost need not only to maintain complete and current patient medication records, but also to supervise and monitor drug therapy more closely by placing the pharmacist in clinical settings to detect and prevent DDI's.[1]

METHODOLOGY

Duration of study

- The study was conducted for a period of 6 months.

Site of study

- The study was conducted at Sapthagiri Institute of Medical Sciences & Research Centre, Bangalore. It is 300 bedded tertiary hospital having different specialties like medicine, surgery, orthopedics, pediatrics, obstetrics and gynecology. And ethical clearance was taken.

Study design

- A hospital based Prospective Observational study.

Sources of data and materials

- Patient case sheet.
- Laboratory data reports.
- Prescription of patient.
- Medical record department.
- www.drugs.com website

Patient consent forms

It contains demographic details of patients, purpose of study and brief detailed explanation of the study with local language and in English.

Patient profile forms

It contains patient demographic details like name, age, sex, weight, IP.NO., date of admission, date of discharge, complaints on admission, medical history, medication history, social history, family history, previous allergies and it includes physical examination, provisional diagnosis, routine biochemical investigations, final diagnosis, drug treatment chart, progress chart and discharge medications.

Drug interaction documentation form

No. of interactions, types of interaction (drug-drug interaction), pharmacokinetic drug interactions (absorption, distribution, metabolism, elimination), pharmacodynamic drug interactions (additive, antagonistic effect, synergistic effect), severity (major, moderate, minor), mechanism of drug interaction, management of drug interaction, description of drug interaction.

RESULTS AND DISCUSSION

During the study period, a total of 110 patients were enrolled out of whom, 43 patients were female (39.1%) and 67 were male (60.9%) (Figure1). In this study, majority of the population were males which was similar to a study conducted by **Ahmed et al.**[1] The age of patients ranged from 1 to 96 years and majority of the patients were in the age group of 55-75 years. The average age of patients was found to be 54.26 years. We considered 4 different diseases during the study period i.e. Diabetes mellitus (22 Cases), Hypertension (28 Cases), Chronic kidney disease (32 Cases), COPD (28 Cases) (Figure: 2)

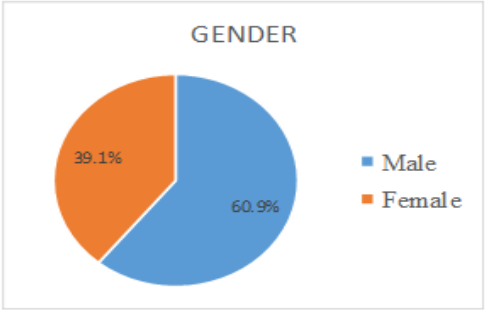

Figure1: Gender distribution.

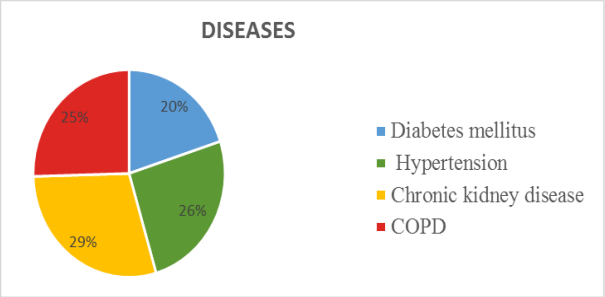

Figure 2: Disease distribution.

From among the 416 DDIs identified, 38 were major (9.13%), 321 were moderate (77.16%) and 57 (13.71%) were minor interactions (Table 1) (Figure 3). which can be compared with the results obtained by **Jacqueline M et al**[15] where the major, moderate and minor DDIs were 17%, 56% and 27% respectively whereas the result of the research done by **Virendra K.P et al** [16] denotes that the Interactions with major severity accounted for 126 (32.5%) followed by moderate and minor severity that accounted for 234 (60.3%) and 28 (7.20%).

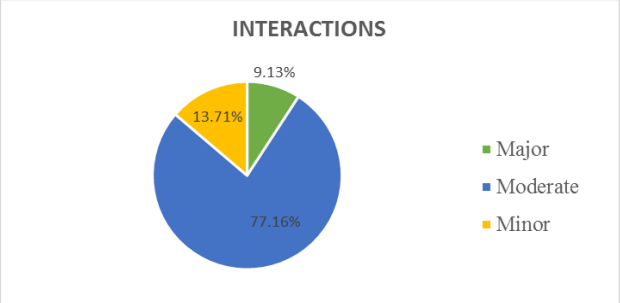

Figure 3: Drug interaction.

Table 1: Distribution of DDIs according to the degree of severity.

Severity of DDIs	No. of DDIs	Percentage of DDIs
Major	38	9.13
Moderate	321	77.16
Minor	57	13.71
Total No: of DDIs	416	100

The number of potential DDI ranged from 1 to 16; 14 cases (12.7%) showed one potential DDI and 1 case (0.9%) showed 16 potential DDIs (Table 2). At least 1 DDI was seen in 14 cases (12.7%) which is similar to the study by Namrata Bajracharya et al that is out of 411 cases, 118 (45.7%) had 1 DDI; whereas according to the study by **Jeannette E F et al**[17] out of 21277 cases, 5909 (27.8%) encountered at least one DDI which is contrary to the present study.

Table 2: Distribution of cases with number of DDIs.

No. of DDIs	No. of cases	Percentage of Cases
1	14	12.7
2	16	14.5
3	24	21.8
4	12	10.9
5	16	14.5
6	5	4.5
7	7	6.4
9	1	0.9
10	3	2.7
11	1	0.9
12	1	0.9
13	1	0.9
16		0.9

The DDIs could be classified as pharmacokinetic and pharmacodynamics outcomes (Figure: 4). The pharmacokinetic outcome was identified in 119 DDIs (27.05%) (Figure:5) and pharmacodynamics outcome was identified in 297 DDIs (67.5%) (Figure:6), 24 DDIs (5.45%) has both pharmacokinetic and Pharmacodynamics outcomes which is similar to the study conducted by Virendra K.P et al[16] conveys that out of 388 pDDIs, [251 (64.69%)] were pharmacodynamic drug interactions, [78 (20.1%)] were pharmacokinetic and [59 (15.2%)] were unknown, whereas according to Ramya Balaprabha G et al[9] studies shows 102(36.5%) and 177(53.4%) are pharmacokinetic and pharmacodynamic drug interaction respectively is lower than the present study. Which on considering the disease view the Pharmacodynamics and Pharmacokinetics outcomes are mentioned. (Table 3)

Table 3: Distribution of cases with Interactions.

SI.No	Diseases	No: of Cases	Pharmacodynamics	Pharmacokinetics
1	COPD	28	94	15
2	Hypertension	28	56	26
3	Chronic Kidney Disease	32	98	77
4	Diabetes mellitus	22	61	13

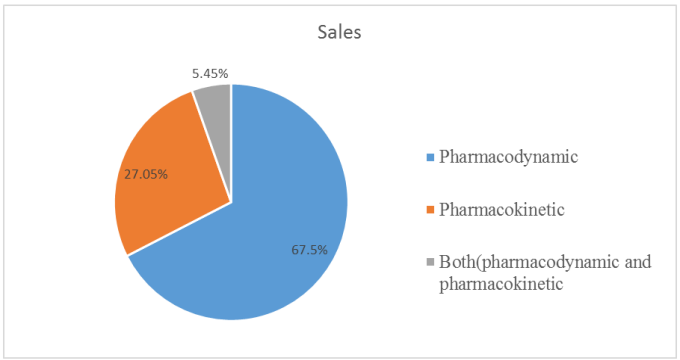

Figure 4: Mechanism of the drug interactions.

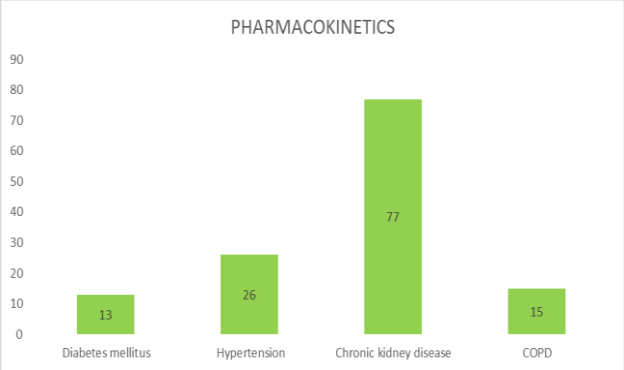

Figure 5: Pharmacokinetics.

Table 4: Most prevalent drug-drug interactions.

SI. No	Drug Combinations		No.of cases	Severity	Consequences of DDI
1	Albuterol	Budesonide	13	Minor	Additive hypokalemia
2	Pantoprazole	Furosemide	10	Moderate	Increase risk of hypomagnesemia
3	Azithromycin	Albuterol	8	Moderate	Increase risk of irregular heart rate
4	Aspirin	Pantoprazole	7	Moderate	Increase risk of hypoglycemia
5	Albuterol	Ondansetron	6	Moderate	Increase risk of irregular heart rate
6	Insulin	Furosemide	6	Moderate	Interfere with blood glucose control and reduce the effectiveness of insulin
7	Aspirin	Telmisartan	5	Moderate	Reduce the effects of Telmisartan in lowering blood pressure
8	Ceftriaxone	Furosemide	5	Moderate	Cause kidney problems
9	Pantoprazole	Atorvastatin	4	Moderate	Increase the blood levels and effects of atorvastatin
10	Aspirin	Clopidogrel	4	Moderate	Cause unusual bleeding, severe abdominal pain, weakness, and the appearance of black, tarry stools
11	Insulin Aspirin	Glimepiride Insulin	4 4	Moderate Moderate	Increase risk of hypoglycemia Increase the risk of hypoglycemia, or low blood sugar.
12	Insulin	Albuterol	4	Moderate	Interfere with blood glucose control and reduce the effectiveness of insulin
13	Theophylline	Albuterol	4	Moderate	Increase cardiovascular side effects such as heart palpitations, increased heart and pulse rates, and blood pressure elevations.
14	Metformin	Glimepiride	3	Moderate	Increase the risk of hypoglycemia, or low blood sugar
15	Aspirin	Ramipril	2	Moderate	Aspirin, Ramipril. Pharmacodynamic antagonism. decrease in renal function
16	Ondansetron	Tramadol	4	Major	Increase the risk of serotonin syndrome and an irregular heart rhythm
17	Fluconazole	Clopidogrel	2	Major	Fluconazole may interfere with the effects of Clopidogrel

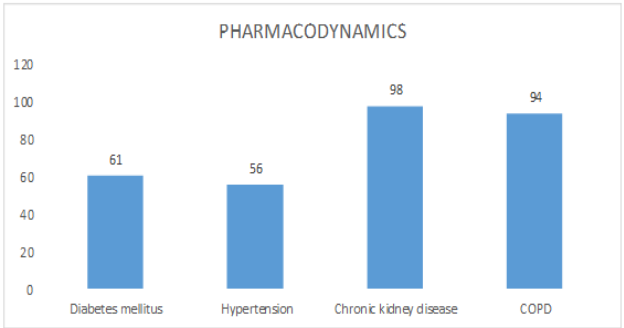

Figure 6: Pharmacodynamics.

The most common interactions reported were with Albuterol and Budesonide,[13] followed by Pantoprazole and Furosemide,[10] Azithromycin and Albuterol,[8] Aspirin and Pantoprazole[7] Albuterol and Ondansetron, [6] The effects reported were additive hypokalemia, increased risk of hypomagnesemia, increased risk of irregular heart rate, Increase risk of hypoglycemia. (Table 4)

Ondansetron and tramadol

These are major, pharmacokinetic and pharmacokinetic drug interactions. Combining these medications can increase the risk of serotonin syndrome and an irregular heart rhythm, both rare but potentially life-threatening effects of these drugs. Serotonin syndrome may include symptoms such as confusion, hallucination, seizure, extreme changes in blood pressure, increased heart rate, fever, excessive sweating, shivering or shaking, blurred vision, muscle spasm or stiffness, tremor, incoordination, stomach cramp, nausea, vomiting, and diarrhea. Severe cases may result in coma and even death. You should seek immediate medical attention if you experience these symptoms while taking the medications. You may be more susceptible to the irregular heart rhythm if you have a heart condition called congenital long QT syndrome, other cardiac diseases, conduction abnormalities, or electrolyte disturbances (for example, magnesium or potassium loss due to severe or prolonged diarrhea or vomiting). In addition, ondansetron may reduce the effects of tramadol in some patients. Co-administration of 5-HT3 receptor antagonists with tramadol should generally be avoided. Patients should be closely monitored for symptoms of the serotonin syndrome during treatment. Particular caution is warranted when initiating or increasing the dosages of these agents. In addition, the potential risk for serotonin syndrome should be considered.

even when administering serotonergic agents sequentially, as some agents may demonstrate a prolonged elimination half-life. If serotonin syndrome develops or is suspected during the course of therapy, all serotonergic agents should be discontinued immediately and supportive care rendered as necessary.[17]

Pantoprazole and furosemide

These are moderate, Pharmacodynamics and Pharmacokinetic drug interaction. Chronic use of proton pump inhibitors (PPIs) which is pantoprazole may induce hypomagnesemia and the risk may be increased during concomitant use of diuretics (Furosemide) or other agents that can cause magnesium loss. The mechanism via which hypomagnesemia may occur during long-term PPI use is unknown, although changes in intestinal absorption of magnesium may be involved. Serious adverse events include tetany, seizures, tremor, carpopedal spasm, atrial fibrillation, supraventricular tachycardia, and abnormal QT interval; however, patients do not always exhibit these symptoms. Monitoring of serum magnesium levels is recommended prior to initiation of therapy and periodically thereafter if prolonged treatment with a proton pump inhibitor is anticipated or when combined with other agents that can cause hypomagnesemia such as diuretics, aminoglycosides, cation exchange resins, amphotericin B, cetuximab, cisplatin, cyclosporine, foscarnet, pentamidine, and tacrolimus. Patients should be advised to seek immediate medical attention if they develop potential signs and symptoms of hypomagnesemia such as palpitations, arrhythmia, muscle spasm, tremor, or convulsions. In children, abnormal heart rates may cause fatigue, upset stomach, dizziness, and light headedness. Magnesium replacement as well as discontinuation of the PPI may be required in some patients.[18]

Azithromycin and albuterol

These are moderate, pharmacokinetic and preventable drug interaction. Using albuterol together with azithromycin can increase the risk of an irregular heart rhythm and potentially life-threatening.Beta-2 adrenergic agonists can cause dose-related prolongation of the QT interval and potassium loss. Theoretically, co-administration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. You may be more susceptible if you have a heart condition called.

congenital long QT syndrome, other cardiac diseases, conduction abnormalities, or electrolyte disturbances (for example, magnesium or potassium loss due to severe or prolonged diarrhea or vomiting). The risk may exist even when albuterol or similar medications are given by oral inhalation directly into the lungs, and more so if these products are overused. Caution is recommended if beta-2 agonists are used in combination with other drugs that can prolong the QT interval. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.[19]

Albuterol and ondansetron

These are moderate, Pharmacokinetic and preventable drug interaction. Using albuterol together with Ondansetron can increase the risk of an irregular heart rhythm that may be serious and potentially life-threatening, although it is a rare side effect. You may be more susceptible if you have a heart condition called congenital long QT syndrome, other cardiac diseases, conduction abnormalities, or electrolyte disturbances (for example, magnesium or potassium loss due to severe or prolonged diarrhea or vomiting). Co-administration with beta-2 adrenergic agonists may potentiate the hypokalemic effects of potassium-wasting diuretics. Beta-2 agonists can cause clinically significant but usually transient decreases in serum potassium concentrations. Since QT prolongation is a possible side effect of beta-2 agonists, exacerbation of hypokalemia may increase the risk of torsade de pointes and other serious arrhythmias. The interaction may be more likely with systemic or nebulized formulations of beta-2 agonists, high dosages of inhaled beta-2 agonists, or concomitant theophylline or corticosteroid therapy. Caution is advised when beta-2 agonists are used with potassium-wasting diuretics. Serum potassium level and cardiovascular status should be monitored, especially if

the beta-2 agonist is administered systemically or by nebulizer. Patients should be advised to notify their physician if they experience potential signs and symptoms of hypokalemia such as fatigue, weakness, myalgia, muscle cramps, numbness, tingling, abdominal pain, constipation, palpitation, and irregular heartbeat.[20] Causality assessment was carried out using Drug Interaction Probability Scale (DIPS) to estimate.

the probability that an adverse reaction was caused by an interaction of the drugs in question; according to the total score of 10 questions the relationship is Doubtful (<2) (33.5%), Possible (2 to 4) (34.6%), Probable (5 to 8) (21.8%) and Highly probable (≥9)(2.7%) (Table 5) Whereas according to study conducted by **Muhammad Zeeshan Khan et al** out of 155 cases which shows Doubtful (15.2%), Possible (51.89%), Probable 149 (17.69%), Highly probable (15.9%) which is contrary to the present study.[21]

Table:5 Dips scale.

DIPS SCALE		Score	Frequency	Percent
Valid	Doubtful	-4	3	2.7
	Doubtful	-3	1	.9
	Doubtful	-2	4	3.6
	Doubtful	-1	3	2.7
	Doubtful	0	14	12.7
	Doubtful	1	12	10.9
	Possible	2	18	16.4
	Possible	3	8	7.3
	Possible	4	12	10.9
	Probable	5	9	8.2
	Probable	6	5	4.5
	Probable	7	4	3.6
	Probable	8	6	5.5
	Highly probable	9	2	1.8
	Highly probable	15	1	.9
	Total		102	92.7
Missing	No interaction		8	7.3
Total			110	100.0

CONCLUSION

The study helped in understanding the possible drug interaction that can occur in patients with Chronic Obstructive Pulmonary, Disease, hypertension, chronic kidney diseases and diabetes mellitus and avoid interactions in the future and provide a better health care to the patients.

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