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Prevalence of Drug-Drug Interactions in Hypertensive Patients in Secondary Care Teaching Hospital

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A B S T R A C T
A drug-drug interaction (DDI) occurs when two (or more) drugs are administered concomitantly and another one, with the result of either increasing or decreasing the effect of the object drug, or producing a new and unanticipated effect (1), alters the pharmacological effects of one drug. Drug-Drug Interactions are considered to be beneficial or harmful and depend on several factors related to the type of medication, the patient or the conditions under which the medication is used [(2)]. The harmful consequences of Drug-Drug Interactions range from minor morbidities to fatal consequences
Keywords: Drug-Drug interactions, hypertension, angiotensin converting enzymes, prescriptions, captopril

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Contents

1. Introduction

A drug-drug interaction (DDI) occurs when two (or more) drugs are administered concomitantly and another one, with the result of either increasing or decreasing the effect of the object drug, or producing a new and unanticipated effect (1), alters the pharmacological effects of one drug. Drug-Drug Interactions are considered to be beneficial or harmful and depend on several factors related to the type of medication, the patient or the conditions under which the medication is used [(2)]. The harmful consequences of Drug-Drug Interactions range from minor morbidities to fatal consequences. Hypertension is a common disease in which blood flows through blood vessels at higher than normal pressures. There are two types of hypertension. First is primary hypertension that is a common type that develops over the years as the person ages. The second type of hypertension is the secondary one, which is because of another medical condition or use of certain medicines. It usually resolves when the cause is treated or removed. Several classes of drugs are used in the pharmacological management of hypertension, including diuretics, adrenergic receptor antagonists, Angiotensin converting enzyme inhibitors (ACEIs), Angiotensin II receptor blockers (ARBs), Calcium channel blockers (CCBs), central acting agents and vasodilators. These classes of drugs are discussed in detail in Chapter Two. The management of hypertension quite often relies on a combination therapy, whereby two or more antihypertensive agents are used concurrently for the

optimal control of blood pressure in a patient. For this reason, hypertensive patients are at a high risk of experiencing Drug-Drug Interactions because of the different types and numbers of drugs that they receive [3].

Besides this, there are quite often drugs used concurrently for the management of co-morbid conditions such as diabetes mellitus, myocardial infarction, congestive cardiac failure and chronic kidney disease [3]. Some interactions between antihypertensive drugs may be beneficial and clinically relevant. For example, the interactions between enalapril and furosemide, and between enalapril and hydrochlorothiazide (HCTZ), are classified as moderate interactions and their effects may be additive on lowering blood pressure. They are therefore frequently combined together. On the other hand, some interactions between antihypertensive drugs may be harmful to the patient. For example, the interaction between enalapril and spironolactone, and between enalapril and digoxin, are major interactions known to cause hyperkalemia, which may be fatal, especially if the patients are dehydrated, diabetic, have kidney disease or heart failure. Interactions of this kind require very close monitoring, and dose adjustment. The combination of Beta-blockers (BBs) and digoxin can result in digitalis toxicity. Careful monitoring of signs like nausea, vomiting and arrhythmias would prevent the adverse outcome of digitalis toxicity [5].

Careful monitoring of drug combinations in hypertensive patients is thus recommended to avoid adverse drug reactions. Knowledge of the prevalence and types of prevailing Drug-Drug Interactions in hypertensive patients provides alerts on the negative outcomes that should be monitored and avoided. This study therefore sets out to identify the patterns of Drug-Drug Interactions in hypertensive patients and the resultant clinical outcomes. So there is a more chance of medication related problems in geriatric population who are considered as a special population. Many studies have reflected Poly pharmacy as one of the major risk factors in occurrence of PDrug-Drug Interactions. Patient populations at high risk include the elderly, critical care patients and patients with Co morbidities. The elderly populations are at increased risk because of decreased functioning of the physiological systems, presence of co-morbidities, which require multiple medications for proper treatment. Medication safety is an important issue for the physician, pharmacist and other health care professionals.[4, 5, 6]

Classification of Drug Interactions:

Drug-Drug Interactions may be classified as minor, moderate or major depending on the resulting clinical implications. Major interactions are defined as those that may be life threatening, cause intoxication or permanent damage [8]. Drug combinations with major interactions should be avoided and where not possible, very close monitoring and dose adjustment is required. Moderate interactions are defined as those that frequently cause therapeutic complications; the drug combination may be continued with careful monitoring of the patient and dose adjustment as appropriate [8]. Minor interactions are associated with an increase or a reduction of drug efficacy, especially in patients with risk factors [8]. These interactions are insignificant and unlikely hence monitoring or a dose adjustment is not needed [8]. Examples of these classes of interactions are presented in Table 1.

Another classification of Drug-Drug Interactions is A, B, C, D and X, whereby Drug-Drug Interactions are categorized based on an assigned risk rating as follows: A means that there is no interaction, B means that there is no action needed, C means monitor therapy, D means modify the regimen and the X means avoid combination [9]. 6 Drug-Drug Interactions can also be classified as Pharmacodynamics or pharmacokinetic drug interactions based on the mechanism of the interaction [10]. Pharmacodynamics Drug-Drug Interactions are interactions in which the drugs influence each other's effect directly. They can be synergistic (e.g. Amiloride and ACEIs) or antagonistic (e.g. Nonsteroidal anti-inflammatory drugs (NSAIDS) and ACEIs which reduces antihypertensive effects).

On the other hand, pharmacokinetic interactions occur in the absorption, distribution and metabolism or elimination level. One such example at the absorption level is between digoxin and verapamil, which increases the bioavailability of verapamil following oral administration. At the metabolism level, verapamil increases the bioavailability of loperamide by inhibition of P-glycoprotein.

Hypertension

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure, putting them under increased stress [9]. Each time the heart beats; it pumps blood into the vessels, which carry the blood throughout the body. The force of blood pushing against the walls of blood vessels (arteries) as the heart pumps it creates blood pressure. The higher the pressure, the harder the heart has to pump [20]. When systolic blood pressure is equal to or above 140 mmHg and/or a diastolic blood pressure equal to or above 90 mm Hg the blood pressure is considered to be raised or high. In a survey carried out in Sub Saharan Africa in two urban and two rural settings, the prevalence of hypertension was reported as 19.3, 21.4, 23.7 and 30.8% [10].

2. Materials and Methods

Study Center:

Government General Hospital, Anantapur, Anantapuramu District.

Study Duration: 6 Months.

Incluscion Criteria:

Patients who were diagnosis as Hypertension were included in to the study with age group of 21-60.

Exclusion Criteria:

- Patients who are having other complications were excluded.
- Patients who fails in age criteria.

Data Collections: Hypertensive patients were interviewed & their prescriptions were collected and evaluated for drug

interactions prescriptions which have drug interactions were in turn evaluated and classified into three types,

- Serious (life threatening)
- Moderate
- Minor drug interactions

Data analysis

- Patient Characteristics
- All the enrolled patients were grouped according to their age, gender, number of drugs prescribed and presence of co morbidities.
- Potential Drug-Drug Interactions
- Patients who experienced potential drug-drug interactions were categorized and analyzed separately.
- Prevalence of PDrug-Drug Interactions was calculated by using the following equation.

Severity of potential drug-drug interactions was assessed by using Micromedex software and was categorized as minor, moderate and major interactions, which were analyzed. The distribution of potential drug-drug interactions per patient was evaluated.

Predictors of Potential Drug-Drug Interactions

Patients with potential drug drug Interactions and patients without potential drug-drug Interactions were grouped and compared according to their age, gender, number of drugs and presence of co morbidities. Continuous variables like age and number of drugs were presented as mean +/- Standard Deviation. Categorical variables like gender and presence of chronic diseases with or without co morbidities were presented as number with percentage.

Statistical Analysis Applied for Potential Drug-Drug Interactions:

The predictors associated with the potential drug-drug interactions were identified at a p value of <0.05. Software used to perform these statistical was Graphpad Instat P

Ethical considerations:

Permission from the Institutional review board (IRB), Balaji college of Pharmacy, Ananthapuramu was taken before the study was started with reference number IRB/BCP-PP-08/16.remaining 42 prescriptions were found to be moderate drug-drug interactions, which requires continuous monitoring and some are some alteration are require in dosing intervals. In remaining prescriptions, 18 were found to be minor drug-drug interactions, which affect the patient's quality of life. Some alterations are required in dosing intervals. Of the total prescriptions, 26 prescriptions did not have any drug -drug Interactions

3. Results and Discussion

Out of 100 hypertensive patients 37 peoples are suffering from diabetes mellitus and 28 peoples are suffering from chronic kidney disease and 100 out of hypertensive patients 31 peoples are suffering suffering from congestive cardiac failure and 40 peoples are suffer from stoke where different age group peoples suffer from dyslipidemia and 100 out of 15 peoples where suffering from others. A total number of 100 prescription were collected from various hypertensive patients of different age groups out of which 14 prescriptions were found to be major drug-drug interactions which affects the patients quality of life severely &it may also needs hospitalizing in certain cases. In remaining 42 prescriptions were found to be moderate drug-drug interactions, which requires continuous monitoring and some are some alteration are require in dosing intervals.

Discussion:

There were more Males than females. Males were 52 whereas females were 48. This is consistent with other studies among hypertensive patients that have been done in the Eastern African regions, which showed that males were more likely to be hypertensive and therefore be on antihypertensive medication than females [(6)]. In our present study, the mean age of study subjects was found to be 49.82 years, which is not similar to other studies done in other settings, which reported a mean age of 55.2, 55.8 and 56.16 years respectively (6,36,37). The prevalence of potential drug interactions was 74 %, which is much higher than that found by Kothari [(3)].

This difference could be attributed to the use of different techniques to identify drug interactions, the differences in the inclusion criteria for the study as well as a different study setting. In the present study, enalapril + furosemide was the most common interacting drug pair. In the study by Kothari, the most common interacting drug pair reported was atenolol + amlodipine, but less common was enalapril + furosemide [(3)]. The implication of this finding is that although these drugs are commonly combined, patients must still be monitored for any signs of hypotension, decreased diuretic and antihypertensive effect and also hypokalemia. Another study had a combination of a loop diuretic + ACE inhibitor and Loop diuretic + NSAID as the most frequently occurring interacting drug pairs involving antihypertensive drugs [(12)].

Digoxin + furosemide was reported to be the predominant drug interaction in another study[(11)]. The present study reported a drug combination between Salbutamol + carvedilol in 4 (1.3%) patients. This finding was similar to that by Bertoli *et al* that reported a combination of Salbutamol + carvedilol in 2 patients, which was considered A major interaction with a potential outcome of bronchospasms (17). Kumara *et al* reported that females had 53.27% of the drug interactions in comparison to their Male counterparts at 43.67%. Females were utilizing more medications for physical ailments and comorbidities which made them more prone to poly pharmacy than males (38). Our study did not find statistically significant association between age and the number of drugs prescribed (p=0.301). This can be explained partly by the few elderly in this study and thus the effect of advancing age was not observed. The present study reported a statistically significant relationship between hospitalization status and the number of drugs prescribed, whereby an inpatient was more prone to poly pharmacy than an outpatient (p<0.001). An increase in the number of drugs used by patients is a predictive factor for drug interactions. Nonetheless, this finding has not been reported by other studies.

The present study also found a statistically significant positive relationship between length of hospital stay and the

number of drugs, which ultimately increased the occurrence of potential drug interactions. This finding resembled the study by Patel *et al* that reported a significant linear relationship ($p<0.0173$) between length of hospital stay and the occurrence of potential drug interactions (39). Diabetes mellitus was the predominant comorbidity in the present study with a prevalence of 42%. This is similar to another study among hypertensive patients in Kenya (36). This is also similar to findings reported in a previous study of hypertensive patients where the prevalence of diabetes was 41.8% (33). The present study reported a prevalence of 35% of cardiovascular diseases. These findings were similar to previous studies done which were reported as 20 % of the patients suffering from cardiovascular problems (41).

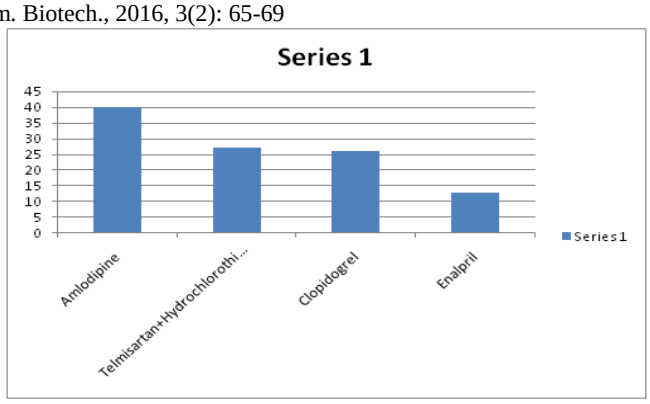

Figure 2: Graph Representation of table 2

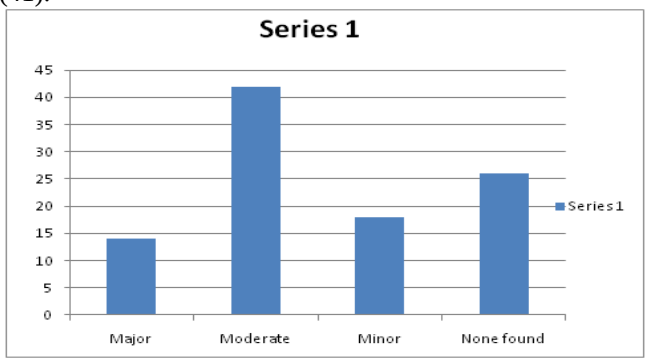

Figure 1: Graph Representation of table 1

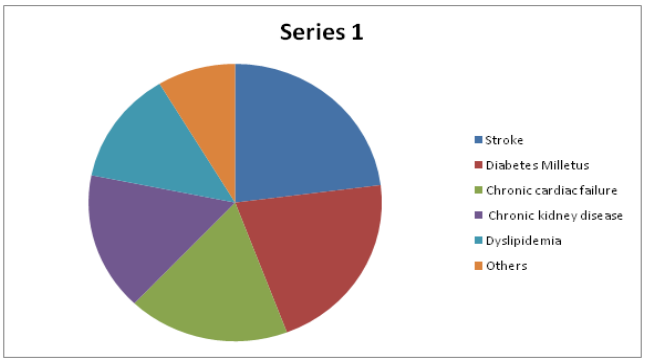

Figure 3: Prevalence of co morbidities in hypertensive patients

Table 1: Classification of Drug-Drug Interactions

Class	Drug pair	Result
Major	Lovastatin+Erythomycin Captopril +Spironolactone	Increased Risk of Rhabdomyolsis /myopathy/ Hyperkalemia
Moderate	Digoxin+Furosemide HCTZ+Diclofenac	Hypokalemia Decreased dieresis &Decreased antihypertensive efficacy
Minor	Furosemide+Aspirin	Decreased diuresis

Table 2: Socio demographic characteristics

Variables	No. of subjects	Percentage
24-34	11	11%
35-45	27	27%
46-36	28	28%
57-68	30	30%
>69	04	04%
Total	=100	100%

Table 3: Prevalence of co morbidities in hypertensive patients

Variables	Frequency	Percentage
DM	37	37%
CKD	28	28%
Congestive cardiac failure	31	31%
Stroke	40	40%
Dyslipidemia	23	23%
Others	15	15%

4. Conclusion

The community pharmacist is in a good position to create more awareness about drug drug interactions by conducting educational workshops our results shows that there is a significant difference between both the clinical relevant and economical outcomes ex: Enalapril, Hydrochlorothiazide. For this reason hypertensive, patients are at a high risk of

experience in drug drug interactions (Drug-Drug Interactions), because of the different types and number of drugs that they receive. The study was conducted to assess the drug interactions in prescriptions for chronic disease. The result of the study shows a prevalence of prescriptions with potential drug-drug interactions (Pdrug-Drug Interactions) among the 100 prescriptions receive. Anti-hypertensive and anti-diabetic drugs were commonly observed drug classes in potential drug interactions. Interactions between beta-adrenergic blockers and Glimepiride + Metformin was most commonly observed interaction in our study. Each prescription dispensed in community pharmacies and hospitals should be screened for potential drug interactions, awareness should be created by all health care professionals regarding drug interactions in order to avoid the effects of drug interactions by organizing continuous professional development programs and workshops.

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