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Original Article

AN ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN HYPERTENSIVE PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To an assessment of potential drug-drug interactions in hypertensive patients in a tertiary care hospital.

Methods: A prospective, observational study was conducted at a tertiary care hospital, Erode for a period of 8 mo. A sample of 480 patients was assessed for PDDIs using drug checker in Micromedex®-2.7.

Results: A total of 430 patients were analyzed and it was found to be 396 (82.50%) hypertensive patients had PDDIs, and a sum total of 1160 PDDIs were observed. Potential drug-drug interactions (PDDIs) higher in female hypertensive patients [255 (64.39%)] compared to males. Incidences of PDDIs were found to be higher in the age group of 60-70 y were [177 (44.69%)] and incidences of interactions based on the duration of (4-6 d) hospital stays were 272 (68.68%). Moreover, 49.24% of patients were found to be prescribed with more than 7 drugs, with higher incidences of PDDIs. Some of the most common drug interacting pair was between aspirin and clopidogrel combination observed in 325 PDDIs in the major, with pharmacodynamics in nature.

Conclusion: Clinical pharmacist ought to have the role of regular monitoring of drug therapy in identifying and preventing the medications that have the potential to cause drug-drug interactions, thereby minimizing the undesirable outcomes in drug medical care and improving the quality of care.

Keywords: Hypertensive patients, PDDIs, Aspirin and clopidogrel, Incidences, Pharmacodynamics

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INTRODUCTION

Hypertension, also known as high or raised blood pressure, is a global public health issue. It contributes to the burden of heart disease, stroke and kidney failure, and premature mortality and disability. It disproportionately affects populations in low and middle-income countries where health systems are weak [1]. Hypertension rarely causes symptoms in the early stages and many people go undiagnosed. Those who are diagnosed may not have access to treatment and may not be able to successfully control their illness over the long-term [1-3].

The globally cardiovascular disease (CVD) accounts for approximately 17 million deaths a year, nearly one-third of the total [4]. Of these, complications of hypertension account for 9.4 million deaths worldwide every year [5]. Hypertension is responsible for at least 45% of deaths due to heart disease (total ischemic heart disease mortality), and 51% of deaths due to stroke (total stroke mortality) [4]. In 2008, worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension; the number of people with the condition rose from 600 million in 1980 to1 billion in 2008 [6].

The prevalence of hypertension is highest in the African Region at 46% of adults aged 25 and above, while the lowest prevalence at 35% is found in the Americas. Overall, high-income countries have a lower prevalence of hypertension-35%-than other groups at 40% [7].

Drug prescription in HT is complex and many factors such as polypharmacy, comorbid conditions, pharmacokinetic and pharmacodynamic variability, and noncompliance make this group a high risk as far as drug safety is concerned [8-10]. To inform health care providers and to provide pragmatic clinical suggestions and recommendations, international, regional, and national hypertension guidelines have been developed by expert groups globally. Most major hypertension treatment guidelines currently suggest that clinicians should strive to treat adults to a blood pressure target of ≤140/90 mm Hg [3, 11].

MATERIALS AND METHODS

The Research work was conducted in a tertiary care hospital, the work was reviewed and approved by the Institute Ethics Committee (Human Studies), ethics number is PP/2018/05 and hospital approved number is EMC/M PHARM/0140T18. Erode for a period of 8 mo in the hospitalized hypertensive patients. 480 hypertensive cases were taken in for the study. Inclusion criteria patients of both genders, aged more than 18 y, prescriptions with or 2 more drugs prescribed throughout the hospitalization had been only decided on for the study. Exclusion criteria were outpatients, Prescription with much less than 2 drugs prescribed as well as patients less than 18 y old, and outpatients. The consent form was obtained from hospital authority and hospitalized patients. The data were collected from case sheets of hospitalized patients and direct patient interview from hypertensive patients. The demographic details consist of age, gender, the reason for admission, past medical records, medication records, co-morbidities and any records of hypersensitive reactions. All the collected data have been documented in the certainly designed data collection form designed as per the need of the study. The patient drug therapy was reviewed each day and assessed for drug interactions checker by way of the use of Micromedex®-2.7 software. The diagnosed potential drug-drug interactions had been categorized into 3 groups based on severity, namely, minor, moderate, major and types respectively.

RESULTS

A total of 430 patients were analyzed and it was found to be 396 (82.50%) hypertensive patients had PDDIs, and a sum total of 1160 PDDIs were observed. Potential drug-drug interactions (PDDIs) higher in female hypertensive patients [255 (64.39%)] compared to males. Incidences of PDDIs were found to be higher in the age group of 60-70 y were [177 (44.69%)] and incidences of interactions based on the duration of (4-6 d) hospital stays were 272 (68.68%). Moreover, 49.24% of patients were found to be prescribed with more than 7 drugs, with higher incidences of PDDIs.

Table 1: Demographic profile of hypertensive patients

S. No.	Parameters	Total number of patients (n=396)	Percentage (%)
1.	Gender wise distribution		
	Male	141	35.60%
	Female	255	64.39%
2.	Age wise distribution		
	18-30	15	03.78%
	31-45	42	10.60%
	46-59	99	25.00%
	60-70	177	44.69%
	Above 70	63	15.90%
3.	Number of hospital stay (In days)		
	<3	85	21.46%
	4–6	272	68.68%
	>7	39	09.84%
4.	Number of prescribed drugs per day		
	<4	35	8.83%
	5-6	166	41.91%
	>7	195	49.24%

Table 2: Distribution of co-morbidities diseases in hypertensive patients

Co-morbidities disease	Total number of patients with PDDIs(n=396)	Percentage (%)
Hypertension	162	40.90%
Hypertension+Diabetes	68	17.17%
Hypertension+Cardiovascular disease	41	10.35%
Hypertension+Asthma	36	9.09%
Hypertension+kidney disease	12	3.03%
Pre-eclampsia	18	4.54%
Hypertension+Diabetes+cardiovascular disease	39	9.84%
Hypertension+Diabetes+Asthma	8	2.02%
pre-eclampsia+Diabetes	12	3.03%

On average, each patient had one or two coded diagnosis in which hypertension was the most common condition 162 (40.90%), followed by Hypertension with Diabetes mellitus 68 (17.17%) in hypertensive patients (table 2).

Table 3: Highest potential drug-drug interaction combinations in hypertensive patients

PDDIs combination	Types	Severity	Frequency (n=1160)	Percentage (%)
Aspirin+Clopidogrel	PD	Major	325	28.01
Amlodipine+Simvastatin	Unknown	Major	172	14.82
Digoxin+Bisoprolol	PD	Moderate	85	7.32
Captopril+Metformin	PD	Moderate	38	3.27
Hydrochlorothiazide+Captopril	PD	Moderate	41	3.53
Enalapril+Furosemide	PD	Moderate	67	5.77
Losartan+Captopril	PK	Major	47	4.05
Spironolactone+Potassium chloride	PK	Major	38	3.27
Atenolol+Metformin	PK	Moderate	66	5.68
Aspirin+Enalapril	PD	Moderate	39	3.36

Note: PD= Pharmacodynamics, PK= Pharmacokinetics

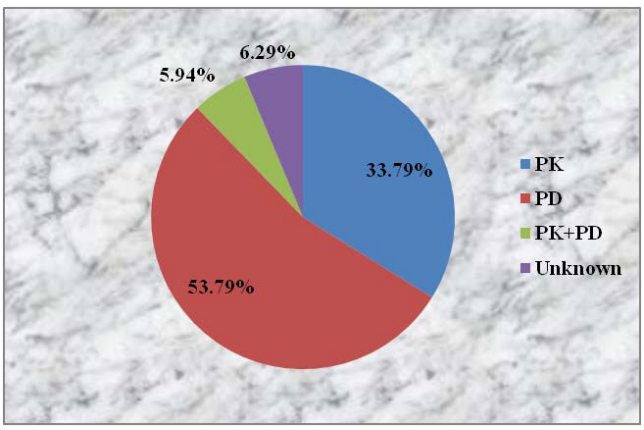

Fig. 1: Types of potential drug-drug interactions

Table 4: Anticipated effect, M. O. A, clinical management for common potential drug-drug interactions in hypertensive patients

PDDIs combination	Mechanism of action	Anticipated effects	Remedy
Aspirin+Clopidogrel	Additive Effect	Increased risk of bleeding.	Monitor for blood counts if co-administration is needed
Amlodipine+Simvastatin	Unknown	Increased simvastatin exposure and increased risk of myopathy, including rhabdomyolysis.	Dose adjustment required. Simvastatin should not exceed 20 mg/day
Digoxin+Bisoprolol	additive effects on AV node conduction	Increased risk of bradycardia and possible digitalis glycoside toxicity.	Monitor heart rate and PR interval
Captopril+Metformin	Unknown	Increased risk of hypoglycemia.	Monitor glucose level
Hydrochlorothiazide+Captopril	Vasodilation and relative intravascular volume depletion	Reduction of blood pressure	Decreasing or discontinuing the diuretic or increasing salt intake may minimize the risk of hypotensive effects.
Enalapril+Furosemide	Synergistic Effect	Result in postural hypotension	Discontinue the diuretic 2 or 3 d prior to ACEI
Losartan+Captopril	Dual blockade of the renin-angiotensin-aldosterone system	Increased risk of adverse events (ie, hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).	Monitor blood pressure, renal function, and electrolytes
Spironolactone+Potassium chloride	Decreased renal clearance	May result in hyperkalemia.	Discontinue potassium supplementations when spironolactone therapy is initiated. Monitor serum potassium closely.
Atenolol+Metformin	Altered glucose metabolism and beta-blockade	May result in hypoglycemia or hyperglycemia	Monitor for blood glucose level.
Aspirin+Enalapril	Antagonistic Effect	Decreased effectiveness of enalapril	Weigh benefit and risk.

Table 5: Types of the prevalence of PDDIs

S. No.	Severity of PDDIs	Frequency (n=1160)	Percentage (%)
1.	Major	381	32.84%
2.	Moderate	496	42.75%
3.	Minor	283	24.39%

Out of 396 hypertensive patients, there was 96 interacting pair was identified during the study. Among 1160 PDDIs, 392 (33.79%) were pharmacokinetic interactions, 626 (53.96%) were pharmacodynamic interactions, 69 (05.94%) showing both mechanisms and 73 (06.29%) were an unknown mechanism. Among 392 pharmacokinetic drug interactions, 51 (13.01%) were due to absorption, 79 (20.15%) were due to distribution, 198 (50.51%) were due to metabolism and 64 (16.32%) were due to excretion. Among 626 (53.96%) pharmacodynamics interactions, 68 (10.86%) were synergistic, 185 (29.55%) were antagonistic, 324 (51.75%) were additive and 49 (7.82%) with both additive and antagonistic effects.

DISCUSSION

Drug interactions are a major area of challenge in recent times for the effective management of patient contamination. It is able to create a great health hazard to the patients when the risk-benefit ratio of combining interacting drugs is not as it should be envisioned. It has already been approximated that the impact of drug interactions can range from any minor morbidity to fatal effects. The study of drug-drug, interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is expected to improve drug protection and could allow individualized drug therapy.

In our study identified a total of 480 hypertensive patients were admitted to the hospital during the study period. Among these, 480 hypertensive patients, 396 (82.50%) had found to be PDDIs, 1160 PDDIs were found in 396 hypertensive patients (fig. 1). Out of which 255 (64.39%) female patients found to be higher PDDIs, compared to males 141 (35.60%), which are similar to the study conducted by Puspitasari *et al.,* [12] (table 1). Wherein it was also reported that the prevalence of hypertension is higher in female patients than in male patients [2]. Female patients are more prone to hypertension than male patients based on their etiology and pathophysiology. As an example, hypertension due to renal artery stenosis is more common in females than males. Other factors that cause hypertension in females are the use of oral contraceptives, pre-eclampsia, and vasculitis (inflammation of blood vessels) [3].

Our studies revealed that majority of the patients were found to be age group of 60-70 y, 177 (44.69%) (table 1). A study conducted by Kameswaran R *et al.* (2018) [13], reported that incidences of PDDIs were found to be higher in the age group of 60-70 y in cardiac [159 (44.16%)] patients. Another study conducted by Santi Purna Sari *et al.* (2018) [17] ACE inhibitor was more frequently used in females (59.15%), patients aged 6 0 y (38.03%), and those with no impairments of liver or kidney function (36.62%). Polypharmacy was identified in 67 prescriptions, and most cases received 5–6 drugs (50.75%). Older people were at high risk of developing an ADR due to pDDIs for several reasons. They are likely to have higher comorbidities and thus take several prescriptions and over the counter drugs.

The study revealed that 272 (68.68%) of cases reported that a number of hospital stay was between 4-6 d. (table 4) Kameswaran R et al. (2018) [13] conducted a study which showed that the majority of the cases, the number of hospital stay were between 4-6 d. The likelihood of getting the multiple drugs increases with the increased length of hospital stay which in turn will increase the likelihood of PDDIs.

In our study shows that 195 (49.24%) hypertensive patients were prescribed with more than 7 drugs (table 5). The study conducted by Puspitasari *et al.* (2015) [12] which have shown 57.14% of cases have been reported as the prescribing greater than 4. Types and combinations of prescribed antihypertension and the most prescribed drug for single prescriptions was amlodipine at Sukmajaya Community Health Center. Amlodipine has been shown to be a well-tolerated antihypertensive drug, especially in elderly patients. Amlodipine tolerability has also been shown to be good or excellent in most patients. This is because amlodipine is slowly absorbed, and the side effects of vasodilation tend to be smaller than other CCB-group drugs. Amlodipine also has a low rate of metabolism in the liver and a longer half-life than other drugs, allowing effective blood pressure control with once-daily dosing [5].

The study revealed that the highest number of diseases and co-morbid conditions were hypertension alone were 162 (40.90%),

hypertension+diabetes were 68 (17.17%), and Hypertension+ Cardiovascular diseases were 41 (10.35%), the most co-morbidities disease in hypertensive patients, and also the most of the female patients had found to be hypertensive and shown PDDIs (table 6), a similar study conducted by Romday *et al.* (2016) [14] reported that Diabetes mellitus (9.36%, males; 8.96%, females), other cardiovascular diseases (14.05%, males; 13.43%, females), acid peptic disease (7.69%, males; 7.46%, females) and dyslipidemia (11.70%, males; 13.43%, females) are the most common co-morbidities in hypertension patients.

The study shows that the highest monotherapy drugs prescribed were amlodipine 175, followed by telmisartan 65 patients, and olmesartan 58 patients. Combination of 2 drugs therapy were aspirin+clopidogrel 325 patients, followed by amlodipine+ simvastatin 172 patients, and Digoxin+bisoprolol 85 patients, whereas in a combination of 3 drugs therapy were telmisartan+ hydrochlorothiazide+metoprolol 4 patients, followed by furosemide+amlodipine+atenolol 3 patients.

The highest most common interacting pair in hypertensive patients had found to be between aspirin and clopidogrel; causing major pharmacodynamics interaction, with a frequency of 325 (28.01%), followed by amlodipine and simvastatin; causing major severity, with a frequency of 172 (14.82%) (table 10). The similar to the study conducted by Kameswaran R *et al.* (2018) [13] in which some of the most common drug interacting pair was aspirin and clopidogrel; causing major, pharmacodynamics interaction, with a frequency of 245.

The prevalence among 1160 PDDIs was 42.75% moderate in severity, 32.84% major severity and 24.39% minor severity (table 12). A similar study was performed by Puspitasari *et al.* (2015) [12]showed an overall 61.70% were in moderate severity, 29.79% were in major severity and 8.51% were in minor severity among the study conducted in hypertensive patients. Another author conducted study (2018) [16] Among the DDIs, there were 324 (81.81%) moderate DDIs followed by 42 (10.61%) major DDIs and 30 (7.58%) minor DDIs.

Out of 396 hypertensive patients, there was 96 interacting pair identified during the study. Among 1160 PDDIs, 392 (33.79%) were pharmacokinetic interactions, 626 (53.96%) were pharmacodynamic interactions, 69 (05.94%) showing both mechanisms and 73 (06.29%) were an unknown mechanism (table 13). Among 392 pharmacokinetic drug interactions, 51 (13.01%) were due to absorption, 79 (20.15%) were due to distribution, 198 (50.51%) were due to metabolism and 64 (16.32%) were due to excretion (table 14). Among 626 (53.96%) pharmacodynamic interactions, 68 (10.86%) were synergistic, 185 (29.55%) were antagonistic, 324 (51.75%) were additive and 49 (7.82%) with both additive and antagonistic effects (table 15). According to Nitin Kothari *et al.* (2014) [15], DDIs was affecting serum potassium level (32.24%). DDIs having unknown mechanism were 71 (7.73%) and pharmacokinetic DDIs were only 44 (4.79%). Out of 507 pharmacodynamic DDIs, 366 were synergistic type while 141 were of an antagonistic type. Majority of synergistic pharmacodynamic DDIs, the software found, were between beta-blocker-calcium channel blocker (CCB) drug pair and beta blocker-angiotensin receptor blocker (ARB) drug pair. Beta-blocker and CCB both increase anti-hypertensive property of each other.

Limitation

The study was carried out in a hypothetical way of approach to find the prevalence of drug interactions. The active possibilities of DIs respect to the time of drug administration, the half-life of drugs, elimination time were not assessed. The study also could not assess the outcomes of DIs in the selected patients.

CONCLUSION

Clinical pharmacist ought to have the role of regular monitoring of drug therapy in identifying and preventing the medications that have the potential to cause drug-drug interactions thereby minimizing the undesirable outcomes in drug medical care and improving the quality of care. Use of electronic database systems as decision support tools, automated prescription alerts to doctors, conducting educational programs and watchful towards drug choice will decrease the negative outcomes of pDDIs. Therefore a daily review of the drug therapy by a clinical pharmacist during a multidisciplinary team might help to identify and prevent potential drug-drug interactions particularly in patients with chronic disease receiving multiple associated with their co-morbid conditions. These can successively help to optimize drug therapy, improve the quality of care and condense the undesirable outcomes within patient drug therapy.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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