A Pharmacovigilance Analysis of Antihypertensive Drugs in Essential Hypertension Patients in Tertiary Care Hospital

Ashok Singh Chouhan[1], Prof. (Dr.) Sangamesh B Puranik[2]

[1]Research Scholar, OPJS University, Churu, Rajasthan
[2]Professor, OPJS University, Churu, Rajasthan

Abstract

Hypertension is one of the high-prevalence diseases in primary care. Failure to achieve the target of blood pressure is affected by non-compliance due to the antihypertensive adverse reactions. This study aims to determine adverse drug reaction (ADR) of antihypertensive drugs in primary care settings. Prescriptions were screened for antihypertensives at the medicine outpatient department of a tertiary care teaching hospital. Medical records of the patients were scrutinized after which 286 prescriptions of patients suffering from hypertension were included. The collected data were sorted and analyzed on the basis of demographic characteristics and comorbidities. R Hypertension patients with antihypertensive drugs at least for a month were eligible in this study.

Keywords: *Hypertension; Drug Utilization Study; Antihypertensive, antihypertensives, pharmacoepidemiology.*

1. INTRODUCTION

Hypertension is the medical condition where the systolic blood pressure is more than 140 mm Hg and the diastolic blood pressure is more than 90 mm Hg. It is a chronic disease which is considered to be one of the major public health problems and a significant cardiovascular risk factor. According to the World Health Organization (WHO), each year, at least 7.1 million people die as a result of increased blood pressure.1 For the treatment of hypertension, a broad range of antihypertensive medications are currently available. Antihypertensive drugs are frequently associated with adverse drug reactions (ADRs) that may limit treatment options and reduce patient adherence, which may hinder blood pressure control. These drugs are believed to cause ADRs or symptoms that make patients feel worse than they did before beginning drug therapy for their "asymptomatic" disease. The study of adverse drug reactions (ADRs) is called Pharmacovigilance.1 The word Pharmacovigilance is come from Greek and Latin word, Greek Pharmakon means drug and Latin word vigilance means to alert, to keep watch on drugs/medicines.2 The care of patients is utmost important part of therapy and it is the responsibility on Health Care Professionals (HCPs) to fulfill with the rationale therapy. Pharmacovigilance is also the part of all phases especially in Phase IV trials i.e. also called as Post marketing Phase in which risks factors will evaluate in shortest possible time that will help to create the guidelines for future about the medicines. Drug utilization research also provides insight into the efficiency of drug use, i.e. whether a certain drug therapy provides value for money and the results of such research can be used to help to set priorities for the rational allocation of health care budgets.

2. LITERATURE REVIEW

Parminder Singh et.al (2020) Adverse Drug Reactions (ADRs) to treatment in patients having hypertension with comorbidities is common; however, information about their incidence, severity and is scanty. Such patients are generally prescribed with multiple medications representing different calls of antihypertensive agents to control the blood pressure. Joint National Committee (JNC 8) has published the guidelines on the basis of evidence-based literature for the management of high BP in adults. This study was planned to study the ADRs associated with the drug-treatments prescribed as per JNC-8 guidelines in such patients. This study was

conducted among patients prescribed with antihypertensive agents in medical OPD of SGRDIMS&R, Amritsar which is a tertiary care teaching hospital in Punjab. The study period was February 2019 - January 2020 i.e. for a period of one year. A total of 167 ADRs were detected, documented, assessed, and reported during the study period. Assessment of the ADRs revealed that diabetes mellitus is the most common association comorbidity in patients having hypertension and comorbidity. The most common type of ADR was seen in prescribed four drug combination followed by three drugs and one drug prescribed. Two drug combination was the most suitable for such patients and among these, CCB + ACEI and CCB + ARB were the most tolerated in such cases. Causality assessment revealed that 27.5% of ADRs were possibly drug-related and 70.6% were mild in nature. Preventability of ADRs was assessed and it revealed that 74% of ADRs was preventable. Drug combination of two drugs was best tolerated in such patients and such patients should be evaluated for comorbidities before prescribing drug treatment.

Bikash Roy et.al (2019) Background: Every drug has the potentiality to cause an adverse drug reaction (ADR). ADRs are a major problem in drug therapy .The aim of this study was to assess the incidence and causality of ADRs to antihypertensive agents used for the essential hypertensive patients attending at the general medicine out patients departments of Hi-Tech Medical College and Hospital, Bhubaneswar Odisha, during the time period of November 2016 to October 2018.Methods: This prospective-observational study was carried out in general medicine outpatient department of Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha.Results: Out of 254 patients, 78 (30.71%) patients were developed ADRs to antihypertensive drugs. 51 (65.38%) were female and 27 (34.62%) were male. Calcium channel blockers were the commonest therapeutic class of antihypertensive drugs associated with ADRs (n = 50, 64.10%). According to WHO causality assessment scale most of the ADRs were "probable" 41 (52.56%), followed by "possible" 21 (26.92%), unclassifiable 13 (16.67%) and unlikely 3 (3.85%).Conclusions: The results of this study concluded that antihypertensive drugs able to induce the development of adverse drug reactions, which were significant cause of increase burden on health care system and decrease the quality of life, the health care professionals should take care about the rational use of antihypertensive agents. Thus, to minimize the incidence of adverse drug reaction and to increase the quality of life.

Harish Govind Naik et.al (2019) Among many public health challenges in the world, hypertension has a very important role to play and even more so in India. In India, hypertension prevalence ranges between 12 and 17% in rural and 20 and 40% among urban adults. For cardiovascular disease and stroke, hypertension is an important risk factor and it alone is responsible for about 50% of cardiovascular disease worldwide. Effective hypertensive treatment yields substantial benefit on these conditions. In achieving this, rational drug prescribing and drug utilization (DU) studies are vital. DU studies and prescription monitoring help in identifying associated problem, yield valuable feedback to the clinician, and thus help in bringing an awareness of the irrational prescribing and thus encouraging rational prescription. This study was fabricated to see the DU pattern of antihypertensive drugs in our teaching hospital. Case records diagnosed with hypertension were collected; the demographic information and prescription pattern were evaluated. The data collected were analyzed using Microsoft Excel software. Of 93 cases studied, 47 patients were male and 46 were female. The age of the patients in the study ranged from 32 to 87 years. In the study, calcium channel blockers (CCBs) and diuretics were the frontline antihypertensive agents. If the overall DU frequency was considered, then CCBs were the preferred drugs with 87.09% utilization followed by diuretics with 64.71%. The WHO indicators (defined daily doses [DDD], DDD/1000 inhabitant/day) were used. The DDD/1000 inhabitant/day of amlodipine was the highest (17.5). Mostly, generic medicines were prescribed, which are welcoming and frequent use of generic drugs has to be encouraged.

Amit Sharma et.al (2018) Hypertension is a common disease which is also known as elevated blood pressure above the normal i.e. systolic blood pressure above 130 mmHg and diastolic blood pressure above 90 mmHg. Hypertension is one of the highest prevailing diseases worldwide. Patients with hypertension are at higher risk of developing stroke, myocardial infarction renal failure as well as various vascular diseases. Near about 75 million of adults in the United States are diagnosed with hypertension according to American Heart Association. A Drug Utilization review on of hypertensive drugs was commenced to determine and evaluate the different classes of antihypertensive medications with respect to diagnosis and ADR's. Study was commenced in Guru Gobind Singh Medical College and Hospital, Faridkot. Study was conducted for period of 6 months commencing from October, 2015 to March, 2016 as per inclusion exclusion criteria. The inclusion criteria were set to patients suffering from hypertension. During the study period and as per inclusion criteria of the study, 150 patients were enrolled out of whom 83 (55.3%) were male and were 67 (44.7%) female irrespective to heredity. The age of patients ranged from 21-85 years with a higher number of the patients belonging to age group ranging between 51-60 years (38.7%). Most of the hypertensive patients were illiterate 83 (55.3%) and unemployed 140 (93.7%) and duration of the disease was less than 5 years in 51 (34%) patients. Among 150

hypertensive patients, most common symptom was found to be breathlessness in 22 (14.7%) patients. Among the hypertensive class, it was found that diuretics were most prescribed drug followed by CCB's, ACE Inhibitors, β-Blockers,α-β adrenergic antagonist and Angiotensin II receptor antagonists.

Sabita Paudel et.al (2017) Background & Objectives: Acute Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. The study was conducted with the objective to examine the incidence of different types of adverse drug reactions in drug treated hypertensive patients. Materials & Methods: Patients (n=382) who received antihypertensive agents were selected and interviewed using a standardized questionnaire. The Naranjo Algorithm, which categorizes the causality relationship into definite, probable, possible and doubtful, was used for the assessment of the exact nature of Adverse drug reaction (ADR). Results: Calcium channel blockers (CCBs) were the drug class with highest number (22 or 32.84%) of ADRs followed by Angiotensinconverting enzyme Inhibitors (ACEI) in 17 (25.38%), Angiotensin Receptor Blockers (ARB) in 12 (17.91%), diuretics in 10 (14.92%) and beta adrenergic antagonist in six (8.95%). Cardiovascular system (40 or 59.70%) was the most affected followed by central nervous system (16 or 23.88%) and respiratory and dermatological system each in 11 (16.42%) cases. On Naranjo's probability scale, nine (13.4%) of the ADRs were definite, 39 (58.2%) possible, 16 (23.9%) probable and three (4.5%) doubtful. Conclusion: Calcium channel blockers were mostly associated with ADRs while Cardiovascular system was the most frequently affected.

3. METHODOLOGY

As the first step, the study proposal was presented to the Institutional Ethical Committee of Karwar Institute of Medical Sciences, Karwar. The present study was started once the permission was granted by the Ethical Committee. The present study included patients who were diagnosed of hypertension and admitted to the hospital. The retrospective analysis of case records of the hypertensive patients admitted to the Karwar Government Hospital during the period from July 1, 2017, to December 31, 2017, was carried out. Diagnosis along with the drugs prescribed was recorded for each patient.

Patients' characteristic were analyzed descriptively by explaining the characteristics of each variable. The ADR of each drugs in every prescription calculated to total events of ADR drugs. The total cases of all drugs were calculated from total cases of drug used by patients (one prescription was one case).

4. DATA ANALYSIS

Demography

A total of 286 hypertensive patients were included in the study. Table 1 gives an overview of the characteristics of the patients and prescriptions. Hypertension was observed to be more common in males (63.6%) than in females (36.4%). The mean age of males was 56.5 ± 15.9 as compared to 53.03 ± 19.3 in females. A total of 68.5% of the patients were in the 18–64 years age range whereas 31.5% were 65 years and above.

Utilization of antihypertensive drugs

A total of 511 antihypertensive drugs were prescribed during the study (1.78/prescription). Amlodipine was the single most prescribed antihypertensive agent (55.6%), followed by

Table 1: Characteristics of hypertensive patients and prescriptions

Variable	Value
Total number of prescriptions	286
Total number of antihypertensives prescribed	511
Gender	
Males	182 (63.6)
Females	104 (36.4)
Age (years)	
Males (mean±SD)	56.5±15.9
Females (mean±SD)	53.03±19.3
18-64	196 (68.5)
≥65	90 (31.5)
Number of drugs per prescription (mean±SD)	
Total	1.78±0.94
Gender	
Males	1.8±0.97
Females	1.7±0.89
Age (years)	
18-64	1.8±0.06
≥65	1.74±0.1

atenolol (17.1%) and enalapril (13.2%). As a class, CCBs were prescribed the most (72.3%) followed by the ACE-I/ARBs (34.9%) and the beta blockers (31.1%) [Table 2]. In terms of total number of antihypertensives prescribed (n = 511), the drug share of CCBs (40.5%) far exceeded that of ACE-I/ARBs (19.6%) and the beta blockers (17.4%). The thiazide diuretics comprised 35% of all the diuretics prescribed and had an overall utilization of 9%. Adherence to the NLEM was the most with the CCBs (98%), followed by the beta blockers (74.4%). Adherence to the NLEM was least with the diuretics (23%). Methyldopa is the only agent from the NLEM that has not been used. Overall adherence to the NLEM was 65%. Figure 1 shows the use of antihypertensive class of drugs on the basis of total number of drugs prescribed (n = 511).

Based on table 2 NSAID was the most commonly prescribed which is used to treat arthritis or muscle pain in hypertensive patients. Acetaminophen is a less-effective class of NSAID for dealing with pain if compared to other NSAIDs. However, paracetamol is more safe to use by those with cardiovascular disease than NSAIDs. Some respondents are known to get prescription for aspirin. This is because aspirin is a standard antiplatelet therapy for heart and blood vessel disease. The mechanism of aspirin, as an antiplatelet effect, is acetylation of cyclooxygenase in platelets which obstructs the permanent platelet formation Antiplatelet dose of Aspirin is 75-325 mg/ day.

Table 2 Distribution of Other Drug-Usage in hypertension Patients

Class of Therapy	Drugs	Number of Prescription (N=142)	Percentage
NSAID	Diclofenac Sodium	14	37.3%
	Acetaminophen	22	
	Mefenamic acid	13	
Corticosteroids	Aspirin	4	1.4%
	Dexamethasone	2	
Vitamin	Vitamin B12	16	26.1%
	Vitamin B6	6	
	Vitamin B1	6	
Supplement	Complex Vitamin B	9	11.3%
	Calcium Lactate	16	
Antigout	Allopurinol	5	3.6%
Antihistamines	Ranitidin	1	5.6%
	Chlorpheniramine (CTM)	7	
Antidiabetic	Glimepiride	8	8.4%
	Metformin	4	
Anticholesterol	Simvasatin	4	2.8%
Antacids	Antacids	4	2.8%
Antiangina	ISDN	1	0.7%

ADR of Captopril: dry cough and mouth

The ADR of dry cough and mouth occur in a respondent with a definite scale. In this study, respondent reported had dry cough after taking captopril and getting better after stop it. According to the literature, dry cough is the most-commonly occurred ADR of using captopril (about 5-20%). Dry cough can happens immediately within hours after first intake of the dose or delayed in weeks or months later. This ADR correlates to an increase in bradykinin and P-substance that are reversible if the drug is stopped.

The dry cough occurs due to an increase in cough sensitivity, namely formation of bradykinin and prostaglandin. Meanwhile, the dry mouth (rash) is caused by the the sulfhydryl (SH) group on captopril that is not possessed by other ACE-inhibitors. The dry mouth can be reversed when the drug is stopped or antihistmain is given. This ADR is experienced by 10% of the patients who get captopril therapy. Some effects may also disappear even though the patients continue to consume the drugs.

5. CONCLUSION

The use of antihypertensives in this tertiary care hospital largely conforms to the recommended treatment guidelines. ADR of captopril were dry cough and dry mouth (14.3%) with a definite scale, and abdominal pain (14.3%) with a probable scale. The ADRs associated with CVS were found to be most frequent in our study followed by gastrointestinal ADRs (abdominal pain, constipation and diarrhoea). This is supported by previous studies which report gastrointestinal ADRs among the top three ADRs. The shortcomings of this study are the absence of a control group to which we could have related the incidence of ADRs. Also the sample size was small and special groups like pregnant women, mentally challenged patients and drug addicts were not included in the study.

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