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Original Research Article

Adverse drug reaction monitoring in patients of hypertension at a tertiary care hospital, Aurangabad, Maharashtra, India

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ABSTRACT

Background: Hypertension is one of the highest prevailing diseases worldwide. Due to long term therapy antihypertensive drugs are commonly associated with adverse drug reactions (ADRs). Therefore, the study was conducted with the objective to examine the incidence of different types of ADRs in drug treated hypertensive patients.
Methods: Present study was a prospective cross sectional observational study carried out in the outpatient of department of medicine of MGM hospital, a tertiary care teaching hospital, in Aurangabad. 320 diagnosed hypertensive patients were studied. Questionnaire was asked and their prescription were analysed and follow up was done.
Results: Among 320 patient's 75 patients were reported ADR. Males accounted for higher percent of ADRs 46 (61%) than females 29 (38.6%). Most of the patients 147 (55.9%) were on mono therapy. Calcium channel blocker was the frequently used class of drug, showed maximum number of ADR (30.6%) followed by ACE inhibitor (28%) and ARB (21.3%). As per WHO-UMC scale, type of reactions and their percentage were as certain (9.3%), Probable/ Likely (64%), possible (22.6%), and unlikely (4%). According to Naranjo scale most of the reactions were possible (64%). severity assessment is done by Hartwig and Siegel scale. No lethal ADR were reported. 4% reactions were severe, 32% were of moderate category and 64% were mild reactions.
Conclusions: Such type of studies are helpful in selection of appropriate medicines for hypertensive patients, enhancing patient adherence with the therapy by selecting medicines of lesser ADR profile, reducing unnecessary economic burden to the patients due to unwanted effects of the therapy.

Keywords: Hypertension, ADR monitoring, Causality assessment

INTRODUCTION

Hypertension is a chronic disease which is considered to be one of the major public health problem and a significant cardiovascular risk factor, where the systolic blood pressure is more than 140 mmHg and diastolic blood pressure is more than 90 mmHg.[1] It is considered to be one of the major public health problems and a significant cardiovascular risk factor. According to WHO each year, at least 7.1 million people die as a result of increased blood pressure.[2] Hypertension is a global disease considered as the leading risk factor for cardiovascular diseases with significant health burden and accounts for 9.4 million deaths as well as 7.0% disability-adjusted life years (DALYs) of global DALYs in 2010.[3] In the year 2000, it was also found that the world was estimated to have 1 billion people with hypertension and predicted to increase to 1.56 billion by 2025.[4] Outcome benefits have been demonstrated for Thiazide diuretics, beta blockers, long acting calcium channel antagonists, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. ADRs are considered among one of the leading causes of mortality. It was estimated that 6% of hospital

admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience serious ADR. Antihypertensive medications are frequently associated with ADRs which may limit treatment options and reduce patient compliance, which may hinder blood pressure control. It was believed that different discontinuation rates for various classes of antihypertensive medications are probably related to their different rates of adverse symptoms.[1]

According to the WHO definition, ADR is a response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function.[5] ADRs are considered among the leading causes of morbidity and mortality. Around 6% of hospital admissions are estimated to be due to ADRs and about 6-15% of hospitalized patient's experience a serious ADR.[6] Monitoring of ADRs in India is in its infancy. A study conducted in the Indian capital reports that 22.3% of the patients experienced ADRs.[7,8] Another report on ADR monitoring in northern India mentions that 5.9% of all visits to the medical department are drug related and ADRs accounted for 45% of events.[9]

Hence, there is a need to monitor the safety profile of all the medications on continuous basis and to review their therapeutic rationale in the light of add on information emanating out of the adverse drug reaction monitoring activities. Monitoring of ADRs is even more important in case of chronic ailments such as hypertension. More often than not, hypertension is an asymptomatic disorder and requires long term therapy predisposing to adverse drug events.[10] ADR monitoring studies for monitoring ADRs related to antihypertensive agents have been previously conducted by many workers in different parts of the world.[7,11,12]

Therefore, the present study was conducted to evaluate the incidence and nature of ADRs in patients receiving anti-hypertensive drugs.

METHODS

Study design

A prospective cross sectional observational study was carried out in the outpatient of department of general medicine of MGM Hospital, a tertiary care teaching hospital, in Aurangabad. The study was started after approval from the institutional ethics committee and the hospital authorities.

Selection criteria

The study population included all diagnosed hypertensive patients according to JNC 8 and aged >18 years of either sex. Follow up of at least 3 months was done.

Patients who did not receive antihypertensive treatment and patients below 18 years of age were excluded. Patients were diagnosed hypertensive if they had at least 2 visits with diagnosis of hypertension or they had prescription of antihypertensive drug with one recording of elevated BP or they had elevated BP on two visits. Elevated BP was defined as systolic BP (SBP) >140 mmHg and diastolic BP (DBP) >90 mmHg.[13]

Questionnaire was asked to the patients about their particulars, AHA received by the patient, dose and duration of treatment, any suspected ADR, onset and duration of ADR, system/s involved and any treatment received. The information was also sought from the patient's records wherever necessary. Data of antihypertensive drugs was recorded and grouped according to class of drug. Antihypertensive drugs were grouped in to seven groups: calcium channel blockers (CCB), beta blockers, diuretics, alfa blockers, angiotensin convertase enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), centrally acting drugs.

The probability that the adverse event was related to drug therapy was classified as definite, probable, possible, or doubtful. A definite reaction was one that followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues; followed a recognized response to the suspected drug and was confirmed by improvement on withdrawing the drug and reappeared on re-exposure. A probable reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug and could not be reasonably explained by the known characteristics of the patient's clinical state. A possible reaction followed a temporal sequence after a drug, possibly followed a recognized pattern to the suspected drug and could be explained by characteristics of the patient's disease. A reaction was defined as doubtful if it was likely related to factors other than a drug.[14]

The data obtained was entered in microsoft excel and further analysis done by SPSS (statistical package for the social sciences) version 25.0. The tables, figures and graphs were used to present the findings in the study patients.

RESULTS

In our study total 320 patients were included. Total number of ADR reported was 75.

Demographic distribution of patient

The mean age (mean±SD) of the patients was 56.12±11.84 years with range 18-80 years and the median age was 58

years (Table 1). Test of proportion showed most of the patients were significantly higher in the age group 41-60 years 147 (45.9%). A total of 42 ADRs (56%) were observed in the patient age group of 61-80 years, followed by 28 (37.3%) in 41-60 years, 5 (6.6%) in 18-40 years. Among 320 patients, 180 patients were male while 140 were females. 75 patients were reported ADR and males accounted for higher percent of ADRs 46 (61%) than females 29 (38.6%).

Duration of hypertension

Mean duration of hypertension (mean±SD) in the patients was 3.97±1.55 (Table 2). Test of proportion showed 163 (50.9%) patients were less than 3 years, followed by 138 (43.1%) patients were between 4-6 years and least were 19 (5.9%) were having history of >7 years. 39 patients among 163 of <3 years duration reports ADR which is highest in number.

Table 1: Distribution of age/gender group.

Age group (in years)	Number of patients		Total (%)	ADR reported (%)
	Male (n=180)	Female (n=140)		
18-40	21	12	34 (10.6)	5 (6.6)
41-60	83	65	147 (45.9)	28 (37.3)
61-80	76	63	139 (43.4)	42 (56)
ADR reported (%)	46 (61)	29 (38.6)		

Table 2: Duration of hypertension.

Duration (in years)	Number of patients	Percent	ADR reported (n=75)
<3	163	50.9	39
4-6	138	43.1	31
>7	19	5.9	5

Table 3: Utilization pattern of different antihypertensive drugs.

Treatments	Number of patients used antihypertensive drug	ADR reported (n=75)	Percent of ADR reported
Monotherapy (N=147)		(n=31)	
CCBs	65	11	14.6
ARB	29	5	6.6
ACEI	17	8	10.6
Beta blocker	19	4	5.3
Alpha blocker	8	2	2.6
Diuretics	9	1	1.3
Dual therapy (N=99)		(n=19)	
CCB+ARB	38	7	9.3
CCB+beta blocker	21	5	6.6
CCB+diuretic	15	4	5.3
ARB+diuretic	13	2	2.6
Others	12	1	1.3
Triple therapy (N=45)		(n=17)	
CCB+ARB+diuretic	27	8	10.6
CCB+beta blocker+diuretic	12	7	9.3
Others	8	2	2.6
Polytherapy (N=29)	29	8	10.6

Table 4: Adverse drug reactions.

Class of drugs	Adverse events experienced	Number of patients	%
CCB	Pedal edema, giddiness, headache, abdominal pain, bradycardia	23	30.6

Continued.

Class of drugs	Adverse events experienced	Number of patients	%
ACE Inhibitor	Dry cough, dizziness, headache, drowsiness, diarrhea, hypotension, weakness, cough, rash, metallic or salty taste.	21	28
ARB	Anxiety, nausea and vomiting, headache, abdominal pain, restlessness, itching and inflammatory swelling	16	21.3
Beta blocker	Constipation, nausea and vomiting, headache, hypoglycemia, postural hypotension	8	10.6
Diuretics	Hypotension, muscle cramps, headache vertigo, pain in legs, dysuria	4	5.3
Other	Skin reaction	3	4

Table 5: WHO causality assessment of ADRs.

Type of reactions	Number of patients reported ADR (n=75)	Percent
WHO causality assessment		
Certain	7	9.3
Probable/likely	48	64
Possible	17	22.6
Unlikely	3	4
Conditional/unclassified	-	-
Unassessable/unclassifiable	-	-
Causality assessment of ADRs by Naranjo scale		
Definite	7	9.3
Possible	17	22.6
Probable	48	64
Doubtful	3	4
Severity of reported ADRs by modified Hartwig and Siegel scale		
Lethal	-	-
Severe	3	4
Moderate	24	32
Mild	48	64

Utilization pattern of different antihypertensive drugs

Test of proportion showed most of the patients 147 (45.9%) were on mono therapy significantly higher than dual therapy, triple therapy and poly therapy, 99 (30.9%), 45 (14%), 29 (9%), respectively (Table 3).

Out of 147 patients on mono therapy CCBs was the frequently used class of drug for mono therapy (65) among which 11 patients reported ADR. 99 patients were on dual drug therapies. CCB+ARB were among the maximum utilized drugs. 45 patients were on triple drug therapy with CCB+ARB+diuretic. Polytherapy was seen in 29 patients.

ADRs and therapeutics class of suspected medication

Total 75 patients were reported ADR. 28% patients who were on ACEI and 30.6% patients receiving CCB reported side effect (Table 4).

ADRs WHO causality assessment

In the present study, causality assessment between the drug and suspected reaction was determined by using WHO-UMC scale and Naranjo scale (Table 5). Causality assessment of ADRs was done using WHO-UMC scale which categorizes ADRs as certain, probable, possible and unlikely. Table 5 shows that type of reactions and their percentage are as certain (9.3%), probable/likely (64%), possible (22.6%) and unlikely (4%). According to Naranjo criteria, the ADRs are analyzed on the basis of a questionnaire comprising 10 questions in which each question is given a score of +2, +1, 0 or -1 depending on the analysis. When totalled if the score is >9: labelled as definite ADR, if 5-8: probable ADR, if 1-4: possible ADR, if 0: doubtful ADR. According to Naranjo scale, type of reactions and their percentage are as definite (9.3%), possible (64%), probable (22.6%) and doubtful (4%). Severity assessment is done by Hartwig and Siegel scale. Reactions can be lethal, severe, moderate and mild. In our study no lethal ADR were reported. 4% reactions were

severe, 32% were of moderate category and 64% were mild reactions.

DISCUSSION

As per the study criteria total 320 cases of hypertensive patients (both sex) of different age group ranges from 18-80 years were collected. Maximum number of patients were from the age group of 41-60 (45.9%) years followed by 61-80 (43.4%) and least number in 18-40 (10.6%) years of age of patients are from this age group (Table 1). Plasma renin falls by 17% each decade which may be the possible reason of hypertension in older population.[15] Similar results were obtained by Sharma et al.[15] A total of 42 ADRs (56%) were observed in the patient age group of 61-80 years, followed by 28 (37.3%) in 41-60 years, 5 (6.6%) in 18-40 years. Kumar et al also observed that 35.3% patients who developed ADR were from age group 41-50 years. Least were from 20-30 years (2.9%).[2]

Total 320 patients were there, including 180 (56.2%) males and 140 (43.7%) females, showing a predominance of male population (Table 1). The hypothetical cause of higher number of male patients is elevated levels of androgen such as testosterone as they play a role in elevation of blood pressure.[16] A similar study was also conducted by Sharma et al in 2018 which is supporting our study.[15] In our study among 320 patients, 75 patients were reported ADR and males accounted for higher percent of ADRs (61%) than females (38.6%). Khurshid et al observed that females experienced more ADRs which is opposite to our result.[17]

In our study, most of the patients 147 (45.9%) were on mono therapy which is significantly higher than dual therapy, triple therapy and poly therapy, 99 (30.9%), 45 (14%), 29 (9%) respectively (Table 3). Sharma et al observed that among 150 patients, 142 (94.7%) patients were on poly therapy significantly higher than mono therapy, double therapy and triple therapy (0.7%), 0(0%), 7 (4.7%) respectively of all the collected cases.[15]

Out of 65 patients received CCB among monotherapy 11 14.6% patients reported ADR which is maximum. Among dual therapy patients receiving CCB and ARB reported ADR in 7 patients, 9.3% while 8 patients (10.6%) reported ADR among 27 patients who received triple therapy of CCB, ARB and diuretic (Table 3). Also, CCB was the frequently used drug for monotherapy. In a study by Mohd et al the most commonly prescribed antihypertensive among elderly patients was amlodipine.[18] This is also in consonance with the recommendations of the JNC on prevention, detection, evaluation and treatment of high blood pressure guidelines which state that low dose of different classes of antihypertensive drugs is more beneficial than a high dose of one.[19]

Among the total 75 ADR cases, CCBs contributed the most to 23 (30.6%) ADRs followed by ACEI in 21 (28%), ARB (16 or 21.3%), beta blocker (10.8%) and diuretic (4 or 5.3%) as shown in Table 4. Similar results were obtained by a study conducted by Paudel et al where they observed among the total 67 ADR cases, CCBs contributed to 22 (32.84%) ADRs followed by ACEI in 17 (25.38%), ARB (12 or 17.91%), diuretic (10 or 14.92%).[20]

The common side effect seen with ACEI were dry cough, dizziness, headache, diarrhea, hypotension, weakness, cough, rash, metallic or salty taste. The cough is typically irritating, dry and nonproductive and is not dose related. Dry cough is mediated by the accumulation in the lungs of bradykinin, substance P, and/or prostaglandins.[20] The common complaints with the usage of CCB were pedal edema, giddiness, headache, abdominal pain, bradycardia (Table 4). Oedema has been reported as the most common problem with amlodipine by Ramesh et al.[21] Edema occurs with CCBs because of vasodilation in the distal arterioles, thereby leading to increased intravascular capillary pressures and increased venous pressures, at least in the lower extremities and eventually leakage of fluid into the extracellular space.[22]

According to WHO-UMC scale maximum number of ADRs in probable class (64%) followed by possible (22.6%), unlikely (9.3%) and certain class (4%) (Table 5). Sharma et al observed that that type of reactions and their percentage are as certain (5.6%), possible (62.9%), probable/likely (19.5%) and unlikely (12.0%).[15] In our study, the result of Naranjo algorithm is represented by Table 5. Most of the ADR fall under probable category (64%) follower by possible (22.6%), definite (9.3%) and doubtful (4%) respectively. Paudel et al also observed the similar results. According to Sharma et al Naranjo scale showed certain (56 %), probable (24 %), possible (13%) and unlikely (08%). Khurshid et al also observed similar results.[15,20]

Moreover, as per the modified Hartwig and Siegel's scale maximum number of ADRs was mild category (64%) and lowest in severe type (4%) of reaction (Table 5). No ADRs were found in lethal type of reaction. These findings were consistent with the literature reported by Ganachari et al and Singh et al.[23,24]

CONCLUSION

In this pharmacovigilance study, CCBs were found to be the most frequently associated drugs with ADRs followed by ACEI, ARB, beta blocker and diuretics. On Naranjo's probability scale, more than half of the reported ADRs were classified as possible. Such type of studies are helpful in selection of appropriate medicines for hypertensive patients, enhancing patient adherence with the therapy by selecting medicines of lesser ADR profile, reducing unnecessary economic burden to the patients due to unwanted effects of the therapy. It is important to remember that most ADR's would subside once the offending agent is discontinued or dosage reduced. Therefore, monitoring of adverse effects due to antihypertensive medications, particularly of serious nature is mandatory. Hence, physicians, clinical pharmacists and

other health care professionals should report life threatening complications, hospitalizations (initial or prolonged) associated with anti-hypertensive drugs. The overall goal of treating hypertension is to reduce hypertension associated morbidity and mortality.

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