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Adverse drug reactions of antihypertensive agents at tertiary care hospital in central Nepal

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ABSTRACT

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 Angiotensin-converting 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.

Key words: Adverse drug reactions; Antihypertensive agents; Naranjo Algorithm

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INTRODUCTION

Hypertension is defined conventionally as a sustained increase in blood pressure (BP) ≥140/90 mm Hg, a criterion that characterizes a group of patients whose risk of hypertension related cardiovascular disease is high enough to merit medical attention. Actually, the risk of both fatal and nonfatal cardiovascular disease in adults is lowest with systolic blood pressures (SBP) of <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg; these risks increase progressively with higher systolic and diastolic blood pressures.[1]

Worldwide prevalence estimates for hypertension may be as much as one billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension. The World Health Organization (WHO) reports that suboptimal BP (>115 mmHg SBP) is responsible for 62% of Cardiovascular disease (CVD) and 49% of ischemic heart disease (IHD), with little variation by sex. In addition, suboptimal BP is the number one attributable risk factor for death throughout the world.[2]

In addition to the distress of the patients actually suffering from one or several ADRs, the cost of ADRs has been estimated to be high due to prolongation of hospital visits.[3] Achieving BP goals usually requires two or more antihypertensive agents (AHAs); however; increasing the number of AHAs in a regimen may lead to even more adverse effects.[4]

An ADR is a harmful or unintended response. It is claimed to be the fourth leading cause of death,

higher than pulmonary disease, Acquired Immune Deficiency Syndrome (AIDS), accidents, and automobile deaths.[5]

The study was conducted with the objective to examine the incidence of different types of adverse drug reactions in drug treated hypertensive patients.

MATERIALS AND METHODS

The study was conducted at department of Cardiology of College of Medical Sciences-teaching hospital. The cardiology department was taken as the research area since it has sufficient number of patients on hypertension, is well staffed and organized, and has relatively good recording of the clinical events. The source population consisted of 382 hypertensive patients started on anti-hypertensive treatment at COMS- TH from July 2014 to September 2014. It is a cross sectional study. All newly diagnosed and old patients receiving antihypertensive medications irrespective of age and sex treated with at least one AHA will be included in the study.

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. The questionnaire also involved the examination findings of the patients involving the height, weight, BMI and vitals including temperature, pulse rate, respiratory rate (RR) and BP.

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 (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure. A "probable" reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawl but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state. A "possible" reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) 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.[6]

The data obtained was entered in Microsoft Excel and further analysis done by SPSS (Statistical package for the Social Sciences) Version 17.0. The tables, figures and graphs were used to present the findings in the study patients.

Statistical Package for Social Sciences (SPSS) was used to calculate Chi square test to test the significant differences of adverse reactions between the groups. The probability of significance was set at 5% and 95% confidence limit, so differences in which $P < 0.05$ was regarded as statistically significant. The associations between the independent and dependent variables were tested using OR. Ethical clearance was obtained from the Institutional Ethical Committee of CMS-TH.

RESULTS

As shown table 1 , among the 382 patients, 219 (57.30%) were males and 163(42.70%) females. The most vulnerable age group with hypertension under medication was 51 to 60 years (115 or 30.10%) years followed by 61 to 70 years (88 or 23.04%) and 41 to 50 years having 68 (17.80%) patients.

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%) and BAA (6 or 8.95%) as shown in table 2.

There were 254 patients taking concomitant medications and among these 46 (18.11%) were having ADRs as represented in table 3.

CVS (40 or 59.70%) was the most affected followed by CNS (16 or 23.88%) and respiratory and dermatological system each in 11 (16.42%) cases. The involvement of other organ systems is as picturized in figure 1.

As depicted in table 4, among a total of 40 CVS ADRs, postural hypotension was seen in 25 cases. Enalapril was the offending drug in seven cases, losartan in six, amlodipine in five, ramipril in four, and atenolol, metoprolol and telmisartan in one case each. Pedal edema was noted in 11 cases in which all the cases were attributed to amlodipine.

Among a total of 16 CNS ADRs reported, 12 of them were dizziness among which four were caused by amlodipine, two by enalapril, furosemide, and losartan each and one each by nifedipine and ramipril. (table 5)

The result of Naranjo Algorithm is represented by table 6. Only nine (13.4%) ADRs were definite, 16 (23.9%) probable, 39 (58.2%) possible and three (4.5%) cases were categorized as doubtful.

DISCUSSION

Diuretics, ARBs, CCBs, BAA and ACEIs are consistently the most frequently prescribed AHAs in both younger and older patients with hypertension as recommended by JNC 8. These are the commonly prescribed drugs in several other studies.[7, 8, 9, 10, 11-13.]

The percentage of polytherapy was highest in hypertensive patients in similar other studies.[7, 11, 14.] More so, many studies have demonstrated the benefits of use of antihypertensive combinations which is usually due to the co-morbidity nature of the diseases[15,16] and so, combination therapy seems to be a more rational approach to reduce cardiovascular risk factor in hypertension.[17]

The most common anti-hypertensive fixed dose combination therapy involved in the study was furosemide + hydrochlorothiazide (n=101) followed by amlodipine + losartan (38), telmisartan + hydrochlorothiazide (36), amlodipine + atenolol (18) and losartan + hydrochlorothiazide (15). Telmisartan+hydrochlorothiazide (15%) was the commonly used fixed dose combination as presented by Arshad et al.[11]

It was observed that furosemide (109) was the most commonly used diuretic, losartan (119) ARB, amlodipine (90) CCB, metoprolol (87) BAA and enalapril (60) ACEI.

As anticipated, multiple therapies (more than one drug) were associated with more number of ADR (n=49, 73.13%) as against monotherapy (n=18,

Table:1 Distribution of Age and Sex of the study population

Age Range (years)	Sex		Total	%
	Male	Female		
<30	1	0	1	0.26
31-40	9	23	32	8.38
41-50	34	34	68	17.80
51-60	50	65	115	30.10
61-70	52	36	88	23.04
71-80	57	5	62	16.23
>80	16	0	16	4.19
Total	**219**	**163**	**382**	**100.00**

Table 2 :Group of AHAs with incidence of ADR

Class of AHAs	Cases with ADR	%
CCB	22	32.84
ACEI	17	25.38
ARB	12	17.91
Diuretic	10	14.92
BAA	6	8.95
Total	67	100.00

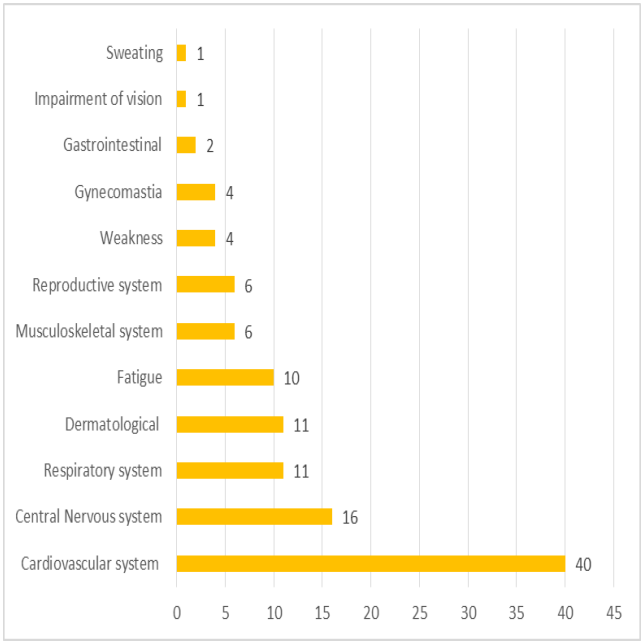

Figure 2: Frequency of category of ADRs

Table 3: Association of ADR with concomitant drugs

Concomitant drugs	ADR		Total (%)	P value
	Yes (%)	No %)		
Yes	46 (18.11)	46 (18.11)	46 (18.11)	0.679
No	21 (16.40)	107 (83.60)	128 (100.0)	
Total	**67 (17.54)**	**315 (82.46)**	**382(100.0)**	

Table 4: Cardiovascular side effects

ADR	Amlodipine	Atenolol	Enalapril	Losartan	Metoprolol	Ramipril	Telmisartan	Total
Postural hypotension	5	1	7	6	1	4	1	25
Pedal edema	11	0	0	0	0	0	0	11
Perspiration	2	0	0	0	0	0	0	2
Flushing	1	0	0	0	0	0	0	1
Chest pain	1	0	0	0	0	0	0	1
Total	18	1	7	6	1	4	1	40

Table 5: CNS side effects

ADR	Amlodipine	Enalapril	Furosemide	Losartan	Metoprolol	Nifedipine	Ramipril	Total
Dizziness	4	2	2	2	0	1	1	12
Headache	0	0	0	1	0	0	0	1
Insomnia	1	0	0	1	1	0	0	3
Total	5	2	2	4	1	1	1	16

Table 6: Classification of result of Naranjo Algorithm

Category	No of cases	%
Definite	9	13.4
Doubtful	3	4.5
Possible	39	58.2
Probable	16	23.9
Total	67	100.0

26.86%). Many epidemiological studies on risk factors for ADRs had shown that patients on multiple therapies were more likely to develop ADRs as compared to patients on monotherapy.7,

Out of 242 (63.35%) patients receiving polytherapy, 49 (20.25%) were having ADRs. The ADR risk increases with the number of medications taken as there is the increased ADR in patients taking combination therapy. Similar findings were observed by other researchers.[7,18-20]

CCBs (32.84%) were the drug class with highest number of ADRs followed by ACEI (25.38%), ARB (17.91%), diuretic (14.92%) and BAA (8.95%).

The most common CVS complaints are postural hypotension (n=25) and pedal edema (n=11). Others are perspiration, flushing and chest pain.

The pedal edema is the reason for discontinuation of medication (amlodipine) though postural hypotension is the commonest complaint. This finding is supported by the study of Ibn et al.[9]

The commonest CNS complaint was dizziness. Others are headache and insomnia.

Among individual drugs amlodipine was found to be the commonest drug associated with ADRs (31.34%) with one third of total number of reported ADRs.[7,13] The most common systems associated with ADRs in our study were the CVS followed by CNS, respiratory and dermatological system. Similar finding was observed by Kumar et al[21] and Ahmad et al.[22]

The common complaints with the usage of amlodipine were: pedal oedema, postural hypotension dizziness, perspiration, fatigue, flushing and constipation. Oedema has been reported as the most common problem with amlodipine by Ramesh et al.[23] and also in other study conducted on 57 patients in Belgium by Biston et al.[24,25] 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.[26]

The side effects experienced by enalapril and

ramipril were postural hypotension, dry cough, dizziness, angioedema, rash, fatigue, numbness and paresthesia in limbs. 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.

The users of beta-blockers had a higher incidence of effect in the reproductive system. The impotence was seen in four cases of metoprolol users and one case of propanolol. The incidence of sexual dysfunction in men with hypertension who are treated with β receptor antagonists is not clearly defined.

Dizziness, fatigue, paresthesia in limbs, peripheral numbness had been reported as common side effects associated with diuretic furosemide. These side effects could be related to the fluid or electrolytes imbalance caused by these medicines, due to sodium ions depletion.[7, 27] Gynecomastia (three cases) and fatigue were observed with spironolactone. Spironolactone enhances the peripheral metabolism of testosterone resulting in increase in the ratio of conversion of testosterone to estradiol and by displacing estradiol from sex hormone binding globulin, increases both total and free estrogen levels .[28-30]

On Naranjo's probability scale more than half (58.2%) of the reported ADRs were classified as possible, 23.9% as probable, 13.4% definite and 4.5% as doubtful. This result is similar to studies done by Khurshid et al.[7] and Rende et al.[31]

CONCLUSION

In this pharmacovigilance study, CCBs were found to be the most frequently associated drugs with ADRs followed by ACEI, ARB, diuretics and BAA. Among individual drugs amlodipine was found to be the commonest drug associated with ADRs. On Naranjo's probability scale, more than half of the reported ADRs were classified as possible. This study is helpful in selection of appropriate medicines for hypertensive patients, enhancing patient adherence with the therapy by selecting medicines of lesser ADRs profile, reducing unnecessary economic burden to the patients due to unwanted effects of the therapy.

Declaration

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