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Prevalence of Adverse Drug Reactions of Anti-Hypertensive Drugs in a Tertiary Care Hospital, Bhairahawa, Nepal

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ABSTRACT

Introduction

Hypertension represents the common disease worldwide which mostly requires long-term therapy and combination of two or more antihypertensive drugs. These drugs are frequently linked to adverse drug reactions. The objective of the study was to determine the prevalence of adverse drug reactions in patients under anti-hypertensive drugs.

Methods

The study was a cross-sectional study conducted among 250 hypertensive patients under medications at the medicine department of Universal College of Medical Sciences- Teaching Hospital. Face-to-face interviews were used to gather the data, which was then recorded on an adverse medication reaction monitoring form. Naranjo algorithm scale was used to categorize the causality relationship of adverse drug reactions.

Results

Out of 250 hypertensive patients, a total of 73 ADR cases (29.2%) were observed. The most commonly linked drugs with ADRs were calcium channel blockers (65.8%) followed by ARBs (12.3%), Beta-blockers (9.6%) and Diuretics (6.8%). Amlodipine (62.9%) was found to be the most frequently linked drug to ADR. Most of the ADRs in the current study fell under category possible (38.3%) followed by definite (28.8%), probable (21.9%) and doubtful (11%) respectively.

Conclusions

Patients taking anti-hypertensive drugs commonly experience adverse drug reactions. The study recommends that ADR monitoring be conducted continually in hospital settings in order to identify and document any adverse effects brought on by various drugs so that it would be helpful for doctors to rationally prescribe.

Keywords: adverse drug reaction; anti-hypertensive drugs; calcium channel blockers.

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INTRODUCTION

Adverse drug reaction (ADR) is described as "a response to a drug that is unpleasant and undesired and occurs at levels commonly used in human for the prophylaxis, diagnosis, and treatment of disease, or for alteration of physiological function" by the World Health Organization (WHO).[1] One of the main factors contributing to morbidity and mortality is thought to be ADRs. According to estimates, ADRs account for around 6% of hospital admissions, and 6-15% of hospitalized patients have significant ADRs.[2]

Hypertension is regarded as the main risk factor for cardiovascular diseases with significant global health burden.[3] According to the STEP Wise Approach to Surveillance (STEPS) surveys, Nepal has shown an increase in hypertension from 21.5% in 2008 to 24.5% in 2019.[4] Antihypertensive medications are frequently linked to ADRs due to long-term therapy and use of two or more medications. Researchers in several nations have already carried out pharmacovigilance studies to track adverse drug reactions (ADRs) associated with antihypertensive medications.[5-7] A study conducted in Nepal reported that 17.54% of the patients experienced ADRs during anti-hypertensive therapy.[8] As the newer medications are entering the Nepalese market, the need for ADR monitoring is crucial and important to encourage healthcare professionals to recognize their responsibilities in the documentation, and reporting of ADRs for maximizing patient safety.

The primary objective of this study was to determine the prevalence of ADRs in patients receiving anti-hypertensive agents at Universal College of Medical Sciences- Teaching Hospital (UCMS-TH) and to compile a list of different side effects of first line antihypertensive drugs.

METHODS

A hospital-based cross-sectional study with duration of ten months from February 2022 to November 2022 was undertaken at the medical outpatient department of UCMS-TH, Bhairahawa to assess the prevalence of adverse drug reactions of first line antihypertensive drugs. The Institutional Review Board (IRB) of the UCMS-TH provided its ethical approval with IRC number UCMS/IRC/027/22.

Purposive sampling technique was used in the study. With a confidence level of 95% and an acceptable error of 5%, the sample size was determined using Cochran's method for prospective studies, which used the prevalence of ADRs associated with the use of antihypertensive medications as 17.54%.[8] Using this formula, we calculated sample size as follows:

Sample size (n) = z^2 p q/ d^2 where,

Prevalence of ADRs of antihypertensive drugs (p) = 17.54% = 0.1754

q = (1-p) = (1-0.1754) = 0.8246

Standard variate at the confidence interval level 95% (z) = 1.96

Acceptable error (d) = 5% = 0.05

n = z^2 p (1- q) /d^2

= 1.96^2 x 0.1754 x 0. 8246/ 0.0025

= 222.25

With a 10% non-response rate, the calculated sample size was approximately 244.47. A total of 250 patients were enrolled finally.

In the study, outpatients over the age of 18 years who had been diagnosed with essential hypertension and had been on at least one first-line antihypertensive medication for at least three months were included. Verbal and written consent was taken from the respondent

before each interview and the objectives of the research were clarified to them.

The data was gathered using a semi-structured questionnaire that was based on an Adverse Drug Reaction Monitoring (ADRM) form created in accordance with WHO monitoring guidelines.

Questionnaire was prepared and translated into local Nepali language after reviewing similar studies conducted in Nepal. The questionnaire was used during a face-to-face interview. Naranjo algorithm scale was used to categorize the causality relationship of ADRs into possible, probable, definite and doubtful. [9]

The data were entered and analyzed using SPSS version 20, statistical software for the social sciences. Frequency, percentage, mean, and standard deviation (SD) were used to produce descriptive statistics. The significant difference of incidence of ADRs between the types of therapy was analyzed using chi-square test. P value was used to establish a statistical relationship between two variables, with a P value of 0.05 or less being regarded statistically significant.

RESULTS

The majority of the hypertensive patients (n=77) were in the age range of 61 to 70 years, with 134 (53.6%) males and 116 (46.4%) females. The patients' mean weight was 61.38 + 12.55 (Mean + SD) and their mean age was 56.79 + 14.10 (Mean + SD). A total of 73 ADR cases (29.2%) were observed, with 37 (14.8%) male patients and 36 (14.4%) female patients (Table 1).

Table 2. Group of anti-hypertensive drugs with incidence of ADRs.

Class of Anti-hypertensive drugs	ADR reported (% of total ADR cases)
Calcium channel blockers	48(65.8%)
Angiotensin receptor blockers	9(12.3%)
Beta-blockers	7(9.6%)
Diuretics	5(6.8%)
ACE- Inhibitors	4(5.5%)
Total	73(100%)

Calcium Channel blockers (CCBs) were the most often prescribed therapeutic class for the incidence of ADRs (n= 48), followed by angiotensin receptor blockers (n=9), β-blockers (n=7), diuretics (n=5), and angiotensin converting enzyme inhibitors (n=4) as shown in Table 2.

Table 1. Different age groups in ADR and non-ADR hypertensive patients.

Age groups (years)	Patients with ADRs (n=73)		Patients without ADRs (n=177)		Total
	Male	Female	Male	Female	
21-30	0	1	3	12	16(6.4%)
31-40	1	5	6	4	16(6.4%)
41-50	2	9	14	17	42(16.8%)
51-60	8	6	31	17	62(24.8%)
61-70	21	12	27	17	77(30.8%)
Above 71	5	3	16	13	37(14.8%)
Total	37(14.8%)	36(14.4%)	97(38.8%)	80(32%)	250(100%)

Table 3. Association of ADR incidence with types of therapy				
Types of therapy	ADR present	ADR absent	Total	P-value
Monotherapy	19 (14.7%)	110 (85.3%)	129 (100%)	<0.001*
Combinational therapy	54 (44.6%)	67 (55.4%)	121 (100%)	
Total	73 (29.2%)	177 (70.8%)	250 (100%)	

Chi-square test, * p<0.05 considered as statistically significant

ADRs were present in 54 (44.6%) of the 121 patients on combination antihypertensive medications, as indicated in Table 3. The incidence of ADR is significantly associated with types of therapy (p=<0.001).

The most frequent side effects of amlodipine use were: pedal edema, headache, hypotension, abdominal pain, and chest pain. The next medicine on the list of suspected drugs was losartan (ARB), which had 8 (or 11% of all ADRs),

Table 4. ADRs and the suspected anti-hypertensive groups		
Suspected drugs	ADRs experienced	No. of ADRs (% of total ADR cases)
Amlodipine	Pedal edema	27(37%)
	Headache	9(12.3%)
	Hypotension	5(6.8%)
	Abdominal pain	3(4.1%)
	Chest pain	2(2.7%)
	Total	46(62.9%)
Nifedipine	Palpitation	2(2.7%)
Losartan	Dizziness	3(4.1%)
	Hypotension	4(5.5%)
	Cough	1(1.4%)
	Total	8(11%)
Telmisartan	Dizziness	1(1.4%)
Enalapril	Dry cough	4(5.5%)
Metoprolol	Hypotension	1(1.4%)
Atenolol	Hypotension	4(5.5%)
	Headache	1(1.4%)
	Constipation	1(1.4%)
	Total	6(8.3%)
Hydrochlorothiazide	Dizziness	3(4.1%)
	Muscle cramp	2(2.7%)
	Total	5(6.8%)

Amlodipine was reported to be the most frequently linked drug to ADRs (n = 46), accounting for two thirds of all reported ADRs. with coughing, hypotension, and dizziness as the side effects. The most typical ADR associated with Enalapril in our study was dry cough (Table 4).

Table 5. Causality assessment of ADRs of anti-hypertensive drugs by Naranjo Scale

Type of reactions	Number of patients reported ADR (n=73)
Definite	21(28.8%)
Possible	28(38.3%)
Probable	16(21.9%)
Doubtful	8(11%)

The Naranjo scale classified the different types of adverse drug reactions into four categories: definite (28.8%), potential (38.3%), probable (21.9%), and questionable (11%) as shown in (Table 5).

DISCUSSION

The present study was conducted among 250 hypertensive patients to determine the adverse effect profile of first line antihypertensive drugs in tertiary care hospital in the outpatient department of medicine at the UCMS-TH in Bhairahawa, Nepal. Out of 250 patients, there were 134 (53.6%) males and 116 (46.4%) females, showing a predominance of male population. Increased levels of androgen, such as testosterone, which is linked to increase blood pressure, is the speculative cause of the higher proportion of male patients.[10]

Of the 73 patients who reported ADR, 37 (14.8%) were men and 36 (14.4%) women in our study. The study by Montastruc JL et al.[11] also indicated that the men and women are likely to tolerate low to moderate dose antihypertensive medicines similarly. But the studies conducted by Paudel et al.[8] and Neupane et al.[7] observed that males experienced more ADRs. This could be due to the fact that there were more male hypertensive patients who visited the medical OPD.

The anti-hypertensive drugs most frequently linked to ADRs were calcium channel blockers (65.8%), followed by ARBs (12.3%), beta-blockers (9.6%), and diuretics (6.8%). Similar findings were revealed by the studies conducted by Paudel et al.[8], Khursid F et al.[12], Basak SC et al.[13]

Compared to monotherapy (14.7%), combinational therapy (using more than one medicine) was linked to a higher proportion of adverse drug reactions (44.6%). It is abundantly obvious from this that the types of therapy are strongly linked with the incidence of ADRs (p=<0.001). Numerous epidemiological research on the risk factors for ADRs have revealed that patients receiving combinational medications have a higher probability of developing an ADR than those receiving monotherapy.[14,15] Combinational therapy must be discouraged since they increase the risk of ADRs brought on by drug-drug interactions. For the treatment of hypertension, it is advised to only prescribe medications that are absolutely necessary.

Amlodipine (62.9%) was reported as the most common drug linked to ADRs, accounting for two thirds of all reported ADRs. The most frequent side effects of amlodipine use were: pedal edema, headache, hypotension, abdominal pain and chest pain. Due to precapillary dilatation and reflex postcapillary constriction, amlodipine most likely increases the hydrostatic pressure in the lower extremities, which leads to pedal edema.[16] According to a study by Biston P et al. that involved 57 patients in Belgium, oedema has also been identified as the most typical side effect of amlodipine.[17]

Dry cough was a side effect of enalapril users in our study, which is consistent with the findings of investigations done by Woo KS et al.[18] and Basak Sc et al.[13] The cough is mediated by accumulation of bradykinin, substance P, and/or prostaglandins in the lungs.

Diuretics have been known to produce fluid

or electrolyte imbalances, which may be the cause of common side effects like dizziness and muscle cramps.[19] Most of the ADRs in the current study fell under category possible (38.3%) followed by definite (28.8%), probable (21.9%) and doubtful (11%) respectively. This result is similar to the studies done by Khursid F et al.[12] and Paudel S et al.[8]

CONCLUSIONS

Calcium channel blockers were reported to be the most common group associated with ADRs followed by ARBs, β-blockers, diuretics, and ACE inhibitors. More over one-third of the reported ADRs were categorized as possible on Naranjo's probability scale. The current study recommends that ADR monitoring be conducted continually in hospital settings in order to identify and document any adverse effects brought on by various medications.

The study had some limitations, including a small sample size, a short study period, and exclusively focused to the UCMS-TH.

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