

Adverse drug reaction profile and prescription pattern of antihypertensive drug monotherapy at tertiary care hospital Nepalgunj, Nepal

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ABSTRACT

Background: Hypertension is the leading cause of morbidity and mortality worldwide which requires long term therapy to prevent complication associated with it. As drugs are used for longer duration it is necessary to know potential undesirable effects for making the appropriate choice. Aim and objective of the study was to monitor the adverse drug reactions (ADRs) and to know prescribing pattern of antihypertensive monotherapy.

Methods: The present work was an open, non-comparative, observational study conducted on seventy-three (73) hypertensive patients who were prescribed single antihypertensive drug at medical OPD of Nepalgunj Medical college by conducting patient interviews, recording the data on ADR monitoring form.

Results: Calcium channel blockers were found to be the most frequently associated drugs with adverse drug reactions (n=12), followed by diuretics (n=6), Angiotensin converting enzyme inhibitors (n=3), β-blockers (n=2) and Angiotensin receptor blocker (n=1). Among individual drugs, amlodipine was found to be the commonest drug associated with adverse drug reactions (n = 10). On analysis of prescription pattern again amlodipine was most commonly prescribed antihypertensive monotherapy followed by hydrochlorothiazide.

Conclusions: Amlodipine was most commonly associated with ADRs and it was also most commonly prescribed antihypertensive drugs as monotherapy. The above findings would be useful for physicians in rational prescribing.

Keywords: Adverse drug reaction, Antihypertensive agents, Prescription pattern

INTRODUCTION

Hypertension is the clinical condition where the systolic blood pressure is more than 140mmHg and the diastolic blood pressure is more than 90mmHg.¹ It is the leading cause of morbidity and mortality worldwide. It is a potent risk factor for second major cardiovascular events, but the most for cerebrovascular accidents particularly in the elderly.² The Global Burden of Disease Study found that hypertension was the third most preventable cause of death worldwide and the second most common condition in Western countries.³ Hypertension is treated by a broad

range of antihypertensive medications which 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.⁴ Adverse drug reactions have been creating headlines over the last forty years since the thalidomide tragedy. International attention to patient safety has been growing significantly since the publication of the US Institute of Medicine report "To err is human:

building a safer health system”.⁵ Hypertension is usually asymptomatic yet requires long-term therapy, consideration of potential undesirable effects of drugs used for its treatment is important for making the appropriate choice. In this context, a precise understanding of the efficacy and typical adverse reaction profiles of the different drugs is essential. Even with a good knowledge of all of these aspects, however, no fixed plan for drug treatment of hypertension suitable for every patient can be established. A good control of blood pressure and avoidance of adverse drug reactions can, however, be achieved by appropriate drug selection and dosage, carried out after careful consideration of the known adverse reaction profiles as well as the known spectrum of pharmacological actions of the different compounds in reducing blood pressure.⁶

In medicine practice, there is growing concern regarding the irrational prescription pattern and use of antihypertensive drugs. A prescription-based survey is considered to be one of the most effective methods to assess and evaluate the prescribing attitude of physicians and dispensing practice of pharmacists. It is also important to consider the recommendations of international bodies on hypertension that help to improve prescribing practice of physicians and ultimately, the clinical standards.⁷

The adverse drug reaction and prescription pattern of different antihypertensive medication are also not well studied in Nepalese population despite of clearly mentioned in textbook and literature. The result on side effect profile and prescription pattern would provide the necessary information on side effect of different antihypertensive medications as well as some information on reasons of poor compliance of antihypertensive medication.

METHODS

The study was conducted between May 2016 to November 2016 by attending the medicine OPD on a daily basis. An informed consent was taken from the patients participating in the study. A total of seventy-three patients who had been taking antihypertensive as monotherapy or newly diagnosed hypertensive patients who were prescribed single antihypertensive drug were included in this study. The present work was an open, non-comparative, Prospective observational study to monitor ADRs associated with antihypertensive medicines and to know their prescription pattern. All newly diagnosed and old patients receiving only antihypertensive medications as monotherapy irrespective of age and sex were included in the study. All mentally compromised or unconscious patients, patients unable to respond to verbal questions, patient suffering from myocardial infarction, diabetes mellitus, CHF, COPD, Peripheral vascular disease, patients taking more than one antihypertensive drug and patients taking other medication, were excluded from the study. Preliminary questionnaire was prepared and filed tested for 1 week then it was modified as per requirement

accordingly. Details necessary for evaluation regarding chief complaints of the patients, previous allergies, comorbidities, and others were collected from the patient's clinical records. Data from interview were collected by using questionnaire. The information collected includes patient information (initials, age, sex, height, weight), suspected adverse event (brief description of the reaction, onset date/stop date of occurrence of events, outcomes of events, treatment receive), suspected medication (name, indication, start date/stop date, dose, frequency, route of administration), Medical history (past/present), concomitant medication, relevant test /laboratory data, other relevant history including pre-existing medical conditions. Patients were asked about side effects which they felt after taking medication. This entire information gathered was entered in prepared questionnaire. All data collected were coded as per variables and entered in SPSS data sheet and analyzed using the statistical software SPSS 16.0 for windows.

The estimation of the probability that a drug caused an adverse clinical event is usually based on clinical judgment. For this study, the Naranjo’s scale which categorizes the causality relationship into definite, probable, possible or unlikely was used for the assessment of the exact nature of ADR.⁸

RESULTS

Table 1: Frequency of different age groups in ADR and non-ADR patients.

Age group (years)	No. of Patient with ADR		No. of patient without ADR		Total
	Male	Female	Male	Female	
20-29	-	-	1	-	1
30-39	2	-	-	-	2
40-49	2	2	5	5	14
50-59	7	5	14	8	34
60-69	3	2	9	4	18
70-79	1	-	-	1	2
80-89	-	-	1	1	2
Total	15	9	30	19	73

Among the 73- hypertensive patients 45 (61.6%) were males and 28 (38.4%) were females with mean age of 56.23±9.69 (Mean±SD), and mean BMI of 25.17±2.53 (Mean±SD). A total of 15 ADRs were observed in 24 out of 73 hypertensive patients. Among the 24 patients reported with ADRs 15 (62.5%) patients were male and 9 (37.5%) were female Most vulnerable age group was 50-59 years with respect to ADRs (n=12) followed by 60-69 years (n=5), and 40-49 years (n=4) respectively (Table 1).

On Naranjo’s Probability scale 63.7% of the reported ADRs were classified as “possible”, 28.7% as “probable” and 7.8% as “Definite” based on causality assessment scale for adverse drug reaction. Calcium Channel blockers (CCBs) was found to be commonest therapeutic class

associated with ADRs (n= 12), followed by diuretic (n=6), angiotensin converting enzyme inhibitors (n=3), β-blockers (n=2) and angiotensin receptor blocker (n=1) (Table 2 and Table 3).

Among individual drugs amlodipine was found to be the commonest drug associated with ADRs. The common complaints with the usage of amlodipine were ankle oedema, gastro-oesophageal reflux, gingival enlargement, headache, palpitation. Hydrochlorothiazide was the next drug on the list of suspect drugs with complaints of diarrhoea, impotence, joint pain, paranaesthesia, and thirst.

With usage of enalapril urticaria, and dry cough were ADR (Table 3).

Table 2: Group of antihypertensive drugs with incidence of ADR.

Class of AHA	Cases with ADR	Percentage
CCB	12	50
Diuretics	6	25
ACEI	3	12.5
Beta-Blocker	2	8.33
ARB	1	4.17
Total	24	100

Table 3: Adverse drug reactions and the suspected antihypertensive medicines.

Suspected drugs	ADRs experienced (No. of patients)	Total no. of patients with ADRs / No. of patients receiving drugs
Calcium channel blockers		
1. Amlodipine	Ankle Oedema-4, GERD-2, Gingival enlargement-1, Headache-2	10/41
2. Nifedipine	Palpitation-1, Palpitation-2	2/3
Total		12/44
Diuretics (Hydrochlorothiazide)	Diarrhoea-2, Impotence-1, Joint pain-1 Paresthesia-1, Thirst-1	6/12
ACE Inhibitors (Enalapril)	Urticaria-1, Cough-2	3/8
ARBs (Losartan)	Dizziness-1	1/5
Beta-blockers (Atenolol)	Tremor-1, Bradycardia-1	2/4

Drug prescribing pattern of different antihypertensive agents as monotherapy is shown in Table 4. Out of 73 patients prescription's 41 (56.16%) patients were prescribed amlodipine followed by hydrochlorothiazide 12 (16.43%). Amlodipine being most frequently prescribed drug as monotherapy (Table 4).

Table 4: Prescription pattern of anti-Hypertensive drug monotherapy.

Anti-hypertensive monotherapy drugs	Number and percentage
Amlodipine	41(56.17%)
Nefidipine	3(4.1%)
Hydrochlorothiazide	12(16.43%)
Enalapril	8(10.96%)
Losatran	5(6.85%)
Atenolol	4(5.49%)
Total	73 (100%)

DISCUSSION

In present study, the male hypertensive population was found to be more susceptible to ADRs than the female one which is similar to finding of Paudel et al.⁹

This could be because of more number of male hypertensive patients attending to medical OPD. Incidence of ADRs was found to be higher in older patients i.e., more than 40 years as compared to younger ones i.e., less than 40 years. Compromised organ functions, decreased BMR (basal metabolic rate), concomitant disease conditions might be assigned as likely reasons for higher incidence of ADRs in older patients.¹⁰

Calcium channel blockers were the most frequently associated drugs with ADRs followed by diuretics. This is consistent with the findings of the common complaints with the usage of amlodipine were: ankle oedema, Gastro oesophageal reflux disease (GERD), headache, gingival enlargement, palpitation.^{5,9,11} Ankle edema has been reported as the most common problem with amlodipine by Ramesh et al and also in other study conducted on 57 patients in Belgium by Biston et al.¹²⁻¹⁴

Ankle edema occurs with amlodipine 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.¹⁰

Diarrhoea, impotence, joint pain, paraesthesia in limbs, thirst had been reported as common side effects associated with diuretic hydrochlorothiazide. These side effects could be related to the fluid or electrolytes imbalance caused by these medicines, due to sodium ions depletion.⁵

The side effects experienced by enalapril users were dry cough and urticaria. The cough is typically irritating, dry and non-productive and is not dose related. Dry cough and urticaria is mediated by the accumulation of bradykinin, substance P, and/or prostaglandins in the lungs and skin.⁹

With the use of atenolol patient were complaining of tremor and bradycardia. Tremor could be because of unblocked beta-2 receptor on skeletal muscle as atenolol is beta-1 selective blocker.¹⁵

Calcium channel blockers, diuretics, angiotensin receptor blockers, beta-adrenergic blockers, and angiotensin converting enzyme inhibitors were consistently the most frequently prescribed antihypertensive monotherapy drugs in both younger and older patients with hypertension as recommended by JNC 8. Among all amlodipine was most commonly prescribed drug. These findings were similar to the study of Kumar et al, Khursid et al, Paudel et al, and Madhwar et al.^{4,5,9,16}

In present study side effect gastro oesophageal reflux disease (GERD) was seen in 2 patients among amlodipine user. It is uncommon side effect noticed. It could be because calcium channel blockers are known to decrease the lower oesophageal sphincter (LOS) pressure in a dose-dependent manner, and impair oesophageal clearance.¹⁷ Further extensive research is required on larger population to elaborate this side effect.

The limitations of the present study include smaller sample size. The lack of awareness, motivation, and the socioeconomic and geographic background of our patient population attributes to a high rate of loss to follow-up. These have led to the smaller sample size and influenced present study design.

CONCLUSION

Attention must be paid to side-effects that can cause patient to drop out of treatment and might lead to failure to control hypertension. During this pharmacovigilance study, calcium channel blockers were found to be the most frequently associated drugs with ADRs followed by diuretics, ACE inhibitors, β -blockers, and ARBs. 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. On analysis of prescribing pattern again amlodipine was most commonly prescribed monotherapy agent for management of hypertension. As the present study is related to ADR profile of antihypertensive agents, it may be helpful in selection of appropriate medicines for hypertensive patients, enhancing

patient compliance with the therapy by selecting medicines of lesser ADRs profile, reducing unnecessary economic burden to the patients due to unwanted effects of the therapy. The present data suggest that the ADR monitoring needs to be done in hospital settings continuously so that untoward effect caused by different medicines can be identified and documented.

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