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A study of adverse drug reactions due to antihypertensive drugs in a tertiary care teaching hospital**V. Raghu Kumar, V. Raghu Ram, B. Guru Prasad*, G. P Mohanta and P.K Manna**

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Abstract

Adverse drug reactions (ADRs) present a serious public health problem that can affect patients, caregivers, pharmaceutical companies, and the health care system as a whole. The objective of the present study was to evaluate Adverse Drug Reactions associated with antihypertensive drugs. The present study was an open, non-comparative, observational study was done to monitor ADRs associated with antihypertensive medicines in a university teaching hospital. A total of 34 adverse drug reactions were observed in 250 hypertensive patients during the four month study. A high percentage of adverse drug reactions occurred in middle aged and female patients. Of the 34 adverse drug reactions, 18 (52.9%) were mild, 14 (41.2%) moderate and only 2 (5.8%) were classified as severe. Combination therapy was associated with significantly high occurrence ($P < 0.05$) of adverse drug reactions, with a total of 21 (61.8%) as compared to monotherapy ($n=13$, 38.2%). Cardiovascular adverse drug reactions constituted a major component, followed by gastrointestinal and respiratory complaints. Finally our study presents the adverse drug reaction profile of antihypertensive medicines prescribed in our University Teaching Hospital. Beta-blockers were the drug category associated with majority of adverse drug reactions, followed by angiotensin-converting enzyme inhibitors and calcium channel blockers.

Key-Words: Adverse Drug Reaction, Hypertension, Beta-blockers, Angiotensin-converting enzyme inhibitors, Calcium channel blockers.

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.^[1] 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.

It is thought that different discontinuation rates for various classes of antihypertensive agents are probably related to their different rates of adverse symptoms.²⁻⁵ Aggressive treatment of hypertension and treating to goal blood pressure can reduce cardiovascular events.⁶⁻⁷ Achieving blood pressure goals usually requires two or more antihypertensive drugs;⁸ however; increasing the number of antihypertensive drugs in a regimen may lead to even more adverse effects.

It is estimated that the prevalence of hypertension in India is about 25% among urban adults and 10% in the rural areas.⁹ The lifetime risk of developing hypertension is estimated to be 90%.¹⁰

According to the World Health Organization (WHO) definition, an adverse drug reaction (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.'¹¹ ADR can also be defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or

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specific treatment, or alteration of the dosage regimen, or withdrawal of the product.¹² Adverse drug reactions (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 patients experience a serious ADR.¹¹⁶ When the Food and Drug Administration (FDA) approves a new drug for marketing, its complete adverse events profile may not be known because of the limitation of pre-approval clinical trials. Typically, clinical trials for new drugs are of short duration and are conducted in populations that number up to 5000, therefore, the most common dose related ADRs are usually detected in the pre-marketing phase while ADRs which are rare and those detected on long term use are not. A case in point is the development of brownish blue pigmentation of nails of a patient on atenolol for 3 years. Another patient on amlodipine for 8 years developed Schamberg's like purpuric pigmentation.¹³

Since most trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medication suspected of interaction with the study drug, the study population may not be true representative of the real world where the drug is eventually used.¹⁴ 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.^[21] Adverse drug reaction monitoring studies for monitoring ADRs related to antihypertensive agents have been previously conducted by many workers in different parts of the world.¹⁵⁻¹⁷

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.¹⁸⁻¹⁹ 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.²⁰ The objective of the study is to evaluate the incidence of ADRs in patients receiving anti-hypertensive drugs.

Material and Methods

The study protocol was approved by Annamali University Institutional Review Board. The study was conducted between July 2010 to December 2010 by pharmacist attending the medicine OPD on a daily basis. An informed consent form was taken from the patients participating in the study. The present work was an open, non-comparative, observational study to

monitor ADRs associated with antihypertensive medicines in a university teaching hospital. All newly diagnosed and old patients receiving antihypertensive medications irrespective of age and sex were included in the study. All mentally compromised or unconscious patients and patients unable to respond to verbal questions were excluded from the study. All drug-related adverse events were evaluated according to the "WHO Probability Assessment Scale. (Table 1)"²¹ In calculating the ADRs associated with a specific drug category, a minimum of 6 prescriptions were considered for significant result. Student's *t* test was used for statistical analysis at $P < 0.05$ using Graph Pad Instat software Version 3.06.

Results and Conclusion

A total of 34 ADRs were observed in 250 hypertensive patients (106 male and 144 female) during the four month of study with a mean age of 51.52 ± 12.1 ; mean BMI of 41.52 ± 13.9 kg/m². A higher percentage of ADRs occurred in females 20 (58.8%) than males 14 (41.2%). A total of 12 ADRs (35.3%) were observed in the patient age group of 41-50 y, followed by 9 (26.5%) in 51-60 y, 5 (14.7%) in 61-70 y, 4 in 31-40 y, 3 ADRs in >70 y and only 1 (2.9%) ADR in 20-30 y age group. Of the 34 ADRs, 18 (52.9%) were mild, 14 (41.2%) moderate and only 2 (5.8%) was classified as severe (one patient developed severe bronchospasm, syncope and generalized weakness with metoprolol (100 mg) and another developed severe hypotension (B.P. 90/59 mmHg) with atenolol (50 mg). Combination therapy was associated with significantly high occurrence ($P < 0.05$) of ADRs, with a total of 21 (61.8%) as compared to monotherapy ($n=13$, 38.2%). Among the organ systems affected, cardiovascular ADRs constituted a major component (35.3%), followed by gastrointestinal complaints (20.6%) and respiratory complaints (11.8). On the causality scale of WHO, 16 (47.1%) ADRs were classified possible, 12 (35.5%) probable, 4 (11.8%) unlikely, 1 (2.9%) certain, and 1 (2.9%) could not be categorized (unclassifiable). Among the 250 patients, 131 patients were treated with beta-blockers including atenolol ($n=68$), nebivolol ($n=32$) and metoprolol ($n=31$). Of these 11 (8.4%) patients experienced ADRs viz., hypotension (2.9%), giddiness (2.9%), headache (1.4%) and bradycardia (1.4%) with atenolol; impotence (3.2%), bronchospasm (6.4%) and irritation over whole body (3.2%) with metoprolol; and pedal edema (3.1%) with nebivolol. A total of 69 patients received treatment with ACE inhibitors comprising of ramipril ($n=61$) and enalapril ($n=8$). Among these a total of 5 (7.2%) patients experienced ADRs. Dry cough was the only ADR observed with ACE inhibitors with 12.5% and 6.5% of complaints due to enalapril and ramipril, respectively.

Calcium channel blockers (CCBs) were administered to 138 patients. Among these 9 (6.5%) patients experienced ADRs, including pedal oedema (2.3%), headache (1.5%), swelling of the face (0.8%), general oedema (0.8%), and giddiness (0.8%) with amlodipine and bradycardia (16.1%) with nifedipine.

In our study, the female hypertensive population was found to be more susceptible to ADRs than the male one. Most of the ADRs were mild or moderate only a couple of cases of ADRs were severe as the patients suffered from severe hypotension and needed to be hospitalized. The result confirms previous reports that the occurrence of ADRs is on the higher side in females.²²⁻²⁴ Though according to a recent survey, the overall tolerability of low to moderate dose antihypertensive medicines is likely to be similar in men and women.²⁵⁻²⁷ As expected, combination therapy was associated with higher number of ADRs as compared to monotherapy. Amlodipine and atenolol combination therapy leads to greater risk of ADRs than the monotherapy as reported earlier.²⁸⁻³⁰ In this study we found that CCBs were the commonest group of drugs prescribed, though beta-blockers and ACE inhibitors were associated with higher incidences of ADRs. Our findings corroborate the results of previous studies which mention beta-blockers as the drug category most often implicated with ADRs.³¹⁻³² Hence, there is a need to review the status of beta-blockers in management of hypertension. Recent prescribing patterns also suggest preferential use of CCBs (31.7%), over beta blockers (7.5%).

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.

To sum up, Beta-blockers were most frequently associated with ADRs, followed by angiotensin-converting enzyme inhibitors and calcium channel blockers. The results of the above study would be useful for the physicians in rational selection of drug therapy for treatment of hypertensive patients. 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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Table 1: WHO probability assessment (causality assessment) scale for adverse drug reactions

S/No.	CATEGORY	DESCRIPTION
1.	Certain	A clinical event, including laboratory test abnormality, that occurs in a plausible time in relation to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure, if necessary.
2.	Probable	A clinical event, including a laboratory test abnormality with a reasonable time relation to administration of drug, unlikely to be attributed to concurrent disease or other drug or chemical and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
3.	Probable	A clinical event, including laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drug or chemicals
4.	Unlikely	A clinical event including a laboratory test abnormality, which makes a causal relation improbable, and in which other drugs, chemical or underlying diseases provide plausible explanations.
5.	Conditional/unclassified	A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment, or the additional data are being examined.
6.	Inaccessible/unclassifiable	A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.

Table 2: Demographic characteristics of hypertensive patients

S/No	Patient characteristics	Mean±standard deviation
1.	Age (years)	51.52±12.10
2.	Weight (kg)	67.78±12.45
3.	Height (cm)	157.86±11.18
4.	Body mass index (kg/m ²)	41.52±13.90

Demographic characteristics of study patients; out of the total 250, males were 106 and females were 144.

Table 3: Adverse drug reactions and therapeutics class of suspected medication

S/No.	Drugs	Adverse events experienced	Total No of patients with ADRs/No of Patients receiving drugs	% ADRs
1.	CALCIUM CHANNEL BLOCKERS a. Amlodipine	Pedal edema -3, Oedema - 1 Giddiness -1, Headache and abdominal pain - 3	8/132	6.1%
	b. Nifedipine	Bradycardia -1	1/6	16.7%

	Total		9/138	6.5%
2.	BETA-BLOCKERS			
	a. Atenolol	Hypotension – 2 Giddiness -2 Headache -1 Bradycardia -1	6/68	8.8%
	b. Metoprolol	Impotence -1 Bronchospasm -2 Irritation over whole body -1	4/31	12.9%
	c. Nebivolol	Pedal edema - 1	1/32	3.1%
	Total		11/131	8.4%
3.	ACE INHIBITORS			
	a. Ramipril	Dry cough -4	4/61	6.5%
	b. Enalapril	Dry cough -1	1/8	12.5%
	Total		5/69	7.2%
4.	OTHERS			
	a. Telmisartan	Dry cough -1	1/10	10%
	b. Frusemide	Hypotension -1 Bradycardia -1	2/28	7.14%
	c. Hydrochloro- thiazide	Muscle cramps-1, Headache-1 Vertigo -1 Pain in legs -1	4/18	22.22%
	d. Prazosin	Headache-1 Postural hypotension -1	2/6	33.33%
	Total		9/62	14.5%