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Adverse Drug Reactions of Anti-hypertensives in Medicine Department of A Tertiary Care Hospital: A Twelve Month Observation

Sagar B Bhagat[1*], Abhijeet D Joshi[1], Ketaki C Patil[1], Rohini S Gambre[1] and Sadiq B Patel[1]

[1]Department of Pharmacology, Grant Government Medical College and Sir JJ Groups of Hospitals, Byculla, Mumbai, India.

Authors' contributions

Authors SBB, KCP, ADJ designed the study; authors SBB, RSG managed the literature search; authors SBB, ADJ, SBP analysis of the study; author SBB, KCP wrote the final draft of the manuscript. All authors read and approve the final manuscript.

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ABSTRACT

Background: Cardiovascular diseases are one of the leading causes of mortality and morbidity around the globe. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. As more and more anti-hypertensive drugs are coming in market it is necessary to keep a check on its various unknown ADRs due to wide ethnic variability of the population.
Methods: An observational, cross sectional study conducted in the Department of Pharmacology in collaboration with department of Medicine, at Grant Govt. Medical College & Sir JJ Group of Hospital, Mumbai among the hypertensive patients over a period of 12 months.
Results: A total of 853 hypertensive patients were observed in this study. Among them total of 166 ADRs were observed. Beta Blockers (BB) were associated with maximum number of ADRs. 48 (30%) ADRs were observed in age group of 51-60 years.114 (71.25%) ADRs were type A while 46

**Corresponding author: Email: sagarbhagat04@gmail.com;*

(28.75%) were type B. Severity assessment showed 102(63.75%) ADRs to be moderate. Causality assessment showed 117 (73.12%) ADRs in the probable category. Bronchospasm, pedal edema, cough, and hypotension were the most common ADR observed due to BB, calcium channel blockers, Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers, respectively. The maximum number of ADRs (16.25%) was reported for Atenolol. One hundred and five (65.6%) ADRs resolved without any interventions and thirteen ADRs resolved with interventions.

Conclusion: Among the antihypertensive drug, maximum ADRs (30%) were reported for beta blockers. Most ADRs of antihypertensive drugs were moderate in severity and the causality analysis revealed them as 'probable'.

Keywords: Adverse drug reaction; anti-hypertensive; medicine; pharmacovigilance.

1. INTRODUCTION

WHO defines an adverse drug reaction (ADR) as "*any noxious, unintended & undesired effect to a drug that is administered in standard doses by the proper route for the purpose of prophylaxis, diagnosis or treatment".* [1] This definition clearly includes all unintended reactions to a medication. However, ADRs that are not fatal or life threatening and those not leading to hospitalization or permanent disability are generally not identified or quantified to the same extent as compared to more serious reactions. ADRs are one of the important causes of mortality and morbidity in both hospitalized and ambulatory patients. [2] They play a substantial burden on limited healthcare resources and have considerable negative impact on both health and healthcare costs by affecting patient's recovery. [2,3] Several studies have shown that the proportion of patients admitted with ADRs ranges from approximately 2.0 to 21.4%, whereas between 1.7 and 25.1% of inpatients are reported to have developed an ADR during their hospital stay [4].

Cardiovascular diseases are one of the leading causes of mortality and morbidity around the globe. [5] High Blood pressure (BP) is a major risk factor and is associated with several types of cardiovascular disease. [6] Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. [7] Studies have shown that nearly two-fifths of the Indian adult population is hypertensive. [8] As more and more anti-hypertensive drugs are coming in market, it is necessary to keep a check on its various unknown ADRs due to wide ethnic variability of the population.

Therefore this study was planned with the objective to evaluate the incidence, nature and severity of ADRs in patients receiving anti-hypertensive agents and also to compare the nature of adverse drug reaction between various groups of anti-hypertensive drugs.

2. MATERIALS AND METHODS

This was an observational, cross sectional study conducted in the Department of Pharmacology in collaboration with Department of Medicine, at Grant Govt. Medical College & Sir JJ Group of Hospital, Mumbai over a period of 12 months from March 2013 to February 2014.The study commenced after approval of Institutional Ethics Committee(IEC). Confidentiality with respect to identity of participating patients was maintained at all levels. Patients of either sex or age diagnosed with hypertension by the consulting physicians of our tertiary care hospital after recording blood pressure for frequent time and at frequent intervals, taking atleast one anti-hypertensive drug and willing to participate in the study were included in the study while mentally compromised, unconscious patients and patients unable to respond to verbal questions were excluded from the study. A written inform consent was taken from every patient at the start of the study and the personal right to withdraw from study at any point was ensured. The patients were followed up regularly for 1 year All the doctors, residents, interns and nurses were encouraged to notify the ADRs either telephonically or directly reporting to the Dept. of Pharmacology by the study co-coordinators. Reporting was done according to 'CDSCO ADR REPORTING FORM' [9] which consists of details like drug history and information like onset and nature of reaction ,associated drug and past history of similar or other allergic reaction. The person attached with medical fraternity who first noticed ADR and reported the same to the clinician, filled the ADR form and same was verified by the clinician of our hospital. The patients who developed ADRs were actively

observed by regular visits by the study co-ordinator. On the basis of data collected, incidence of ADRs was calculated and classified according to age and gender. Furthermore the reported ADRs were classified by drug group responsible. Causality assessment was done according to Naranjo scale [10] and the severity was analysed according to modified Hartwig and Siegel's scale. [11] The ADRs were classified into types 'A' and 'B' according to Rawlins and Thompson classification of ADRs. [12]

3. RESULTS

During the study period of 12 months, a total of 853 hypertensive patients visited medicine department, of which 561 were male and 292 were female patients. Out of total 853 patients, a total of 166 ADRs were observed, but 6 patients did not participate in the study and were left out, so, 160 ADRs were analysed. Of the 160 ADRs, 96 (60%) were reported in male and 64(40%) were in females. Beta Blockers (BB) were associated with maximum number of ADRs in both male and females (Table 1). Majority of the ADRs were reported among the middle age and elderly patients, where, total of 48 ADRs (30%) were observed in age group of 51-60 years followed by 41 (25.62%) in 41-50 years (Table 2). Amongst the ADRs observed 114 ADRs (71.25%) belongs to type A while 46 ADRs (28.75%) belongs to type B (Table 3). Severity assessment by modified Hartwig and Siegel's scale showed 102 ADRs (63.75%) to be moderately severe followed by 45(28.12%) ADRs to be mild and 13(8.12%) ADRs were severe as 4 patients develop sever Bronchospasm, 3 had syncopal attack, 4 developed hypotension, 1 patients develop angioedema and 1 patient was admitted due to sever giddiness (Table 4). Causality assessment by Naranjo scale showed 117 ADRs (73.12%) in the probable category, 22 (13.75%) in definite category (Table 5). When individual classes of drugs were analysed Beta blockers was associated with maximum number of observed ADRs i.e. 51(31.87%) followed by 35ADRs (21.87%) by Angiotensin Converting Enzyme Inhibitors (ACEI) (Table 6). Bronchospasm was the most common ADR observed due to BB (Table 7). While pedal edema due to calcium channel blocker (CCB) (Table 8), Cough due to ACEI (Table 9), Hypotension due to Angiotensin Receptor Blockers (ARBs) (Table 10) were the most common ADR observed with the respective classes of drugs. Twenty three ADRs (14.37%) were observed with other drugs apart from the conventional anti-hypertensive drugs (Table11). Atenolol was the drug with maximum of ADRs reported i.e. 26 (16.25%), followed by Enalapril i.e. 25 (15.62%) (Table12). The most common systems associated with ADRs in our study was the Respiratory system with 40 ADRs (25%) followed by Musculo-skeletal system with 36 (22.5%) (Table13). As far as treatment and outcomes were consider, 105 ADRs (65.62%) resolved without any interventions, in 22 ADRs (13.75%) dose was reduced, in 20 ADRs drugs was substituted and 13 ADRs resolved with interventions. No fatality was recorded in our study.

Table 1. Gender wise distribution of ADRs

Classes of drugs	No. of ADRs (%)	
	Male	Female
Beta Blockers(BB)	32 (33.33)	19 (29.68)
Calcium channel blockers(CCB)	19 (19.79)	13 (20.31)
Angiotensin converting enzyme inhibitor (ACEI)	19 (19.79)	16 (25)
Angiotensin receptor blockers (ARBs)	11 (11.45)	8 (12.5)
Miscellaneous	15 (15.62)	8 (12.5)
Total	96 (100)	64 (100)

Table 2. Age wise distribution of ADRs

Age (years)	No. of ADRs (%)	Class of drugs (No of ADRs)				
		BB	CCB	ACEI	ARBs	Miscellenous
31-40	14 (8.75)	3	5	3	2	1
41-50	41 (25.62)	11	8	11	3	8
51-60	48 (30)	16	9	8	7	8
61-70	40 (25)	12	8	8	6	6
>70	17 (10.62)	9	2	5	1	0
TOTAL	160 (100)	51	32	35	19	23

Table 3. Type of ADRs

Type	No. of ADRs (%)	Class of drugs (No of ADRs)				
		BB	CCB	ACEI	ARBs	Miscellenous
A	114 (71.25)	38	19	26	14	17
B	46 (28.75)	13	13	9	5	6
Total	160 (100)	51	32	35	19	23

Table 4. Severity of ADRs by modified Hartwig and Siegel's scale

Severity of ADR	No. of ADRs (%)	Class of drugs (No of ADRs)				
		BB	CCB	ACEI	ARBs	Miscellenous
Mild	45 (28.12)	16	6	6	10	7
Moderate	102 (63.75)	27	26	24	9	16
Severe	13 (8.12)	8	0	5	0	0
Total	160 (100)	51	32	35	19	23

Table 5. Causality assessment by Naranjo scale

Causality of ADR	No. of ADRs (%)	Class of drugs (No of ADRs)				
		BB	CCB	ACEI	ARBs	Miscellenous
Definite	22 (13.75)	6	5	5	3	3
Probable	117 (73.12)	39	24	25	11	18
Possible	21 (13.12)	6	3	5	5	2
Doubtful	0 (0)	0	0	0	0	0
Total	160 (100)	51	32	35	19	23

Table 6. Classes of drugs and the observed ADRs

Classes of drugs	ADRs observed	Percentage (%)
BB	51	31.87
CCB	32	20
ACEI	35	21.87
ARBs	19	11.87
MISCELLENOUS	23	14.37
Total	160	100

Table 7. Beta blockers and the ADRs observed

ADRs	No of ADRs (%)	Drugs	Individual no.
Bronchospasm	18 (35.29)	Atenolol	8
		Metoprolol	6
		Propranolol	4
Bradycardia	8 (15.68)	Atenolol	6
		Metoprolol	2
Fatique	6 (11.76)	Atenolol	2
		Metoprolol	3
		Nebivelol	1
Nausea	6 (11.76)	Atenolol	1
		Metoprolol	3
		Nebivelol	2
Erectile dysfunction	3 (5.88)	Atenolol	3
Dry cough	3 (5.88)	Atenolol	3
Altered lipid profile	2 (3.92)	Atenolol	2
Insomnia	2 (3.92)	Metoprolol	2
Night mare	2 (3.92)	Metoprolol	2
Diarrhea	1 (1.96)	Atenolol	1
Total	51 (100)		51

Table 8. Calcium channel blockers and the ADRs observed

ADR	No of ADR (%)	Drugs	Individual No
Pedal edema	14 (43.75)	Amlodipine	9
		Nifedipine	5
Fatique	7 (21.87)	Amlodipine	5
		Nifedipine	2
Palpitations	6 (18.75)	Amlodipine	3
		Nifedipine	3
Headache	3 (9.37)	Nifedipine	3
Gum hypertrophy	2 (6.25)	Amlodipine	2
Total	32 (100)		32

Table 9. Angiotensin converting enzyme inhibitors and the ADRs observed

ADRs	No of ADR (%)	Drug	Individual no
Cough	14 (40)	Enalapril	8
		Ramipril	3
		Lisinipril	2
		Perindopril	1
Hypotension	6 (17.14)	Enalapril	3
		Ramipril	2
		Lisinipril	1
Nausea	3 (8.57)	Enalapril	3
Rashes	3 (8.57)	Enalapril	2
		Ramipril	1
Headache	2 (5.77)	Enalapril	2
Dizziness	2 (5.77)	Enalapril	2
Dysguesia	2 (5.77)	Enalapril	2
Angioedema	2 (5.77)	Enalapril	2
ARF	1 (2.85)	Enalapril	1
Total	35 (100)		35

Table 10. Angiotensin receptor blockers and the ADRs observed

ADRs	No of ADR (%)	Drug	Individual no
Hypotension	7 (36.84)	Losartan	3
		Telmisartan	2
		Olmesartan	2
Dry cough	3 (15.78)	Losartan	3
Weakness	3 (15.78)	Losartan	2
		Telmisartan	1
Hyperkalemia	2 (10.52)	Losartan	2
Myalgia	2 (10.52)	Losartan	2
Headache	2 (10.52)	Losartan	2
Total	19 (100)		19

4. DISCUSSION

The present study was conducted for a period of twelve month during which 853 hypertensive patients visited medicine department, among them total of 166 ADRs were reported, of which, 160 ADRs were analysed. Of the 160 ADRs, the demographic details showed 96 (60%) ADRs were reported in male and 64(40%) in females. This showed male gender predominance over females in our study, which was in contrast to many studies reported in the literature. [13-15] This can be due to higher number of male admission during the study period. 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. [16] Age wise distribution of ADRs showed majority of ADRs were reported in older patients i.e. more than 50 years (n = 105) as compared to younger ones i.e., less than 50 years (n = 55). Compromised organ functions, decreased BMR (basal metabolic rate), concomitant disease conditions and multiple drug

regimens might be assigned as likely reasons for higher incidence of ADRs in older patients. In a study conducted by Khurshid [17] and Hussain [16] in Delhi, reported maximum ADRs among 41-50 years. In our study BBs were the most frequently associated drugs with ADRs which was in accordance with the previous studies which mention beta-blockers as the drug category most often implicated with ADRs [18,19] but our results were in contrast to other studies which reported CCBs to be the leading cause of ADRs [20,21] Among individual drugs Atenolol was found to be the commonest drug associated with ADRs in our study, while Amlodipine was associate in the study reported in literature. [22] The most common organ system associated with ADRs in our study was respiratory system followed by musculo-skeletal system. This finding is in contrast with previous studies which have reported CNS [23,24], gastrointestinal system [25] and CVS [16] to be involved in the majority of ADRs.

4.1 Limitations of the Study

There is a possibility that many ADRs would have been unrecognized or un-reported in the study and were not recorded in the study data. The complete causality assessment could not be done due to not practicing the 'de-challenge' test. Hence causality results such as 'definite' could not be concluded.

Table 11. Miscellaneous drugs and the ADR reported

Drug	No of ADRs	ADR	Individual no
Hydrochlorothiazide	13 (56.52)	Hyponatremia	4
		Hypokalemia	3
		Vomiting	2
		Giddiness	2
		Nausea	1
		Hyperlipidemia	1
Clonidine	5 (21.73)	Increase sleep	2
		Dry cough	2
		Postural hypotension	1
Prazosin	3 (13.04)	Weakness	2
		Postural hypotension	1
Sod. Nitroprusside	2 (8.69)	Vomiting	2
Total	23 (100)		23

Table 12. ADRs and individual drugs

Class of drugs	Drug	No of ADRs observed (%)
Beta blockers	Atenolol	26 (16.25)
	Metoprolol	18 (11.25)
	Propranolol	4 (2.5)
	Nebivelol	3 (1.87)
Calcium channel blockers	Amlodipine	19 (11.87)
	Nifedipine	13 (8.12)
Angiotensin converting enzyme inhibitors (ACEI)	Enalapril	25 (15.62)
	Ramipril	6 (3.75)
	Lisinopril	3 (1.87)
	Perindopril	1 (0.625)
Angiotensin receptor blockers (ARBs)	Losartan	14 (8.75)
	Telmisartan	3 (1.87)
	Olmesartan	1 (0.625)
Miscellaneous	Hydrochlorothiazide	13 (8.12)
	Clonidine	5 (3.12)
	Prazosin	3 (1.87)
	Sodium Nitroprusside	2 (1.25)
Total		160 (100)

Table 13. Organ system affected due to ADRs

Organ system	No of ADRs (%)
Central nervous system	20 (12.5)
Musculoskeletal system	36 (22.5)
Gastro intestinal system	19 (11.87)
Respiratory system	40 (25)
Cardiovascular system	29 (18.12)
Dermatological system	3 (1.8)
Metabolic	12 (7.5)
Renal	1 (0.625)
Total	160 (100)

5. CONCLUSION

The present work is a part of ongoing pharmacovigilance program and is the maiden pharmacovigilance study of its kind conducted in our hospital. Among the antihypertensive drug, maximum ADRs (30%) were reported for beta blockers. Most ADRs of antihypertensive drugs were moderate in severity and the causality analysis revealed them as 'probable'. The results of the above study would be useful for the physicians in rational selection of drug therapy for treatment of hypertensive patients. This may enhances patient adherence with the therapy by selecting medicines of lesser ADRs profile and thus reducing unnecessary economic burden to the patients due to unwanted effects of the therapy. This study also emphasizes the need for constant monitoring and more of such kind of study in the future.

CONSENT

Written consent was taken from patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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