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A STUDY OF ADVERSE DRUG REACTIONS DUE TO ANTI-HYPERTENSIVE DRUGS IN DIABETIC PATIENTS IN A MULTISPECIALTY HOSPITAL

Beulah Samuel *[1], Uma Maheswara Reddy C[2]

[1]Vinayaka Mission University, Sankari Main Road, Ariyanoor, Salem 636308, Tamil Nadu, India.

[2]Sri. Ramachandra College of Pharmacy, Porur, Chennai 600116, Tamil Nadu, India.

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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 in diabetic patients. The present study was an open, non-comparative, observational study done to monitor ADRs associated with antihypertensive medications in diabetic patients in a multispeciality hospital. A total of 347 adverse drug reactions were observed in 740 diabetic hypertensive patients during 2008-2010. A high percentage of ADRs occurred in elderly and female patients. Of the 347 ADRs, 185 (53.3%) were mild, 122 (35.1%) were moderate and 40 (11.5%) were identified to be severe. Combination therapy was associated with significantly less occurrence of ADRs, with a total of 147 (42.3%) as compared to monotherapy (n=200, 57.6%). Among the various antihypertensive drugs used in diabetic patients, diuretics were associated with higher number of ADRs (37.1%), followed by ACE inhibitors (34.2%), beta blockers (18.1%) and calcium channel blockers (10.3%).

Keywords: *Adverse Drug Reaction; Hypertension; Diabetes; Angiotensin-converting enzyme inhibitors; Beta-blockers.*

INTRODUCTION

High blood pressure (BP) is an important cardiovascular risk factor. The currently accepted dividing line is systolic BP > or = 140 mm Hg and/or diastolic BP > or = 90 mm Hg based on epidemiological and intervention studies. In India, hypertension has become a major health problem. Epidemiological studies show a steadily increasing trend in hypertension prevalence over the last 40 years, more in urban than in the rural areas [1]. The frequency of hypertension (HTN) in diabetic population is almost twice as compared to non-diabetic general population [2]. The coexistence of hypertension and diabetes almost doubles the risk of cardiovascular events [3-4]. Patients of both type-1 and type-2 DM are prone to develop hypertension which accelerates cardiac, renal, and cerebral dysfunctions which are leading causes of death [5].

For the treatment of hypertension in diabetic patients, 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 compliance, 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 [6-7]. Aggressive treatment of hypertension can reduce cardiovascular events [8].

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 [9]. 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 [10].

When the Food and Drug Administration (FDA) approves a new drug for marketing, its complete adverse event profile may not be known because of the limitations of pre-approval clinical trials. Typically, clinical trials for new drugs are of short duration and are conducted in populations that number from a few hundred to several thousand; therefore, the most common dose-related adverse drug reactions are usually detected in the premarketing phase. Since most trials exclude the elderly, children, pregnant women,

***Correspondence :** beulah_milton@yahoo.com; profcumr@yahoo.co.in

patients with multiple diseases, and those on medications suspected of interaction with the study drug, the studies' participants may not be representative of the real world where the drug is eventually used [11]. An analysis of 192 randomized drug trials found that the quality and quantity of safety reporting may sometimes be presented erratically or may be missing altogether [12]. 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.

The objective of this article is to deal with the problems of hypertensive drugs in a diabetic patient and to highlight the important role of pharmacist in this task with the hope that this will stimulate and encourage increased reporting of serious adverse events associated with drugs. It is only with the help of alert and vigilant pharmacists that new risks of drugs are uncovered.

MATERIAL AND METHODS

The study protocol was approved by Apollo KH Institutional Review Board. The study was conducted between 2008 to 2010 by attending the medicine OPD on a daily basis. A written informed consent was obtained from the patients participating in the study. It was an open, non-comparative, observational study to monitor ADRs associated with antihypertensive medicines in diabetic patients in a multispecialty hospital. All newly diagnosed and old diabetic patients receiving antihypertensive medications between 30-80 years 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". 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

Demographic characteristics

Results of demographic characteristics of the tested sample are shown in Table 1. A total of 347 ADRs were observed in 740 diabetic hypertensive patients (380 male and 360 female) during the two year (2008-2010) study with a mean age of 61.52±12.10; mean BMI of 61.52±13.90 kg/m^2.

Table 1: *Results of demographic characteristic of the tested sample (n=740)*

S.No	Patient characteristics	Mean±standard deviation
1	Age (years)	61.52±12.10
2	Weight (kg)	67.78±12.45
3	Height (cm)	157.86±11.18
4	Body mass index (kg/m2)	61.52±13.90

Gender

Table 2 shows the total number of ADRs among the males and females in the tested sample. It was found that a higher percentage of ADRs occurred in females 190 (54.7%) than males 157 (45.2%).

Table 2: *Total Number of ADRs among males and females in the tested sample*

Gender	Number of Patients	Number of ADRs	Percentage
Male	380	157	45.2
Female	360	190	54.7

Age

Table 3 shows the total number of ADRs among different age groups in the tested sample. A total of 121 ADRs (34.8%) were observed in the patient age group of 61-70 y, followed by 101 (29.1%) in 51-60 y, 78 (22.4%) in 71-80 y, 39 (11.2%) in 41-50 y and 8 (2.3%) of ADRs in 30 - 40 y age groups. The results show that most of the ADRs were observed in the age group of 61-70 years.

Table 3: *Total Number of ADRs among different age groups in the tested sample*

Age Category	Number of Patients	Number of ADRs	Percentage
30-40	20	08	2.3
41-50	76	39	11.2
51-60	192	101	29.1
61-70	296	121	34.8
71-80	156	78	22.4

Severity of ADRs

Table 4 shows the severity of ADRs in the tested sample. Of the 347 ADRs observed in our study, 40 (11.5%) were identified to be severe, 122 (35.1%) were moderate and 185 (53.3%) were mild. It was found that most of the ADRs observed were of mild severity.

Table 4: *Severity of ADRs in the tested sample*

S.No	Severity of ADRs	Number of Patients	Percentage
1	Severe	40	11.5
2	Moderate	122	35.1
3	Mild	185	53.3

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ADRs among monotherapy and combination therapy

Table 5 shows the total number of ADRs among monotherapy and combination therapy in the tested sample. It was found that combination therapy was associated with significantly lesser occurrence of ADRs, with a total of 147 (42.3%) as compared to monotherapy (n=200, 57.6%).

Table 5: *Total number of ADRs among monotherapy and combination therapy in the tested sample*

Drug Therapy	Number of Patients	Number of ADRs	Percentage
Monotherapy	268	200	57.6
Combination therapy	472	147	42.3

WHO probability assessment (causality assessment) scale for ADRs

Table 6 shows the WHO probability assessment scale for ADRs in the tested sample. On the causality scale of WHO, 61 (17.5%) ADRs were classified certain, 114 (32.8%) probable, 134 (38.6) possible, 14 (4.0%) unlikely, 4 (1.1%) conditional and 20 (5.7) could not be categorized (unclassifiable).

Table 6: *WHO probability assessment (causality assessment) scale for ADRs in the tested sample*

S.No	Category	Number of ADRs	Percentage
1	Certain	61	17.5
2	Probable	114	32.8
3	Possible	134	38.6
4	Unlikely	14	4.0
5	Conditional/unclassified	4	1.1
6	Inaccessible/unclassifiable	20	5.7

Type of ADRs due to antihypertensive drugs

Table 7 shows the type of ADRs due to antihypertensive drugs observed in the tested sample. The results shows that the most commonly identified ADRs due to antihypertensive drugs in diabetic patients was cold and numb hand in 55 (15.8%) patients followed by erectile dysfunction in 42 (12.1%), cough in 41 (11.8%), fatigue in 40 (11.5%), edema in 30 (8.6%), kidney failure in 20 (5.7%), hyponatremia in 20 (5.7%), bronchospasm in 20 (5.7%), gastrointestinal tract disease in 19 (5.4%), headache in 14 (4.0%), intermittent claudication in 14 (4.0%), depression in 13 (3.7%), allergic reaction in 12 (3.4%), hypokalemia in 4 (1.1%) and rash in 3 (0.8%) patients.

Total Number of ADRs due to antihypertensive drugs

Table 8 shows the total number of ADRs due to antihypertensive drugs. It was found that among the various antihypertensive drugs used diuretics were associated with higher number of ADRs (37.1%), followed by ACE inhibitors (34.2%), beta blockers (18.1%) and calcium channel blockers (10.3%).

Table 7: *Type of ADRs due to antihypertensive drugs observed in the tested sample*

S.No	Type of Reactions	Number of ADRS	Percentage
1	Fatigue	40	11.5
2	Edema	30	8.6
3	Gastrointestinal tract disease	19	5.4
4	Kidney failure	20	5.7
5	Cough	41	11.8
6	Erectile dysfunction	42	12.1
7	Headache	14	4.0
8	Depression	13	3.7
9	Rash	3	0.8
10	Allergic reaction	12	3.4
11	Cold and numb hand	55	15.8
12	Hypokalemia	4	1.1
13	Hyponatremia	20	5.7
14	Intermittent claudication	14	4.0
15	Bronchospasm	20	5.7

Table 8: *Total Number of diabetic patients experiencing ADRs due to antihypertensive drugs in the tested sample*

S.No	Antihypertensive drugs	Total number of patients	Total number of ADRs	Percentage
1	ACEI	552	119	34.2
2	BB	436	63	18.1
3	CCB	132	36	10.3
4	Diuretic	192	129	37.1

Classification of antihypertensive drugs associated with ADRs

Table 9 shows the classification of antihypertensive drugs associated with ADRs in the tested sample. The results shows that the most commonly identified ADRs due to ACE inhibitors was cough in 35 (10.0%) patients, followed by fatigue in 25 (7.2%), edema in 15 (4.3%), gastrointestinal tract disease in 12 (3.4%), allergic reaction in 10 (2.8%), kidney failure in 9 (2.5%), erectile dysfunction in 5 (1.4%), head ache in 4 (1.1%), depression in 2 (0.5%) and rash in 2 (0.5%). The most commonly identified ADRs due to beta blockers was bronchospasm in 20 (5.7%) patients, followed by fatigue in 15 (4.3%), intermittent claudication in 14 (4.0%), erectile dysfunction in 5 (1.4%), gastrointestinal tract disease in 4 (1.1%), head ache in 2 (0.5%), allergic reaction in 2 (0.5%), and depression in 1 (0.2%). The most commonly identified ADRs due to calcium channel blockers was edema in 15 (4.3%) patients, followed by headache in 8 (2.3%), cough in 6 (1.7%), gastrointestinal tract disease in 3 (0.8%), erectile dysfunction in 2 (0.5%), kidney failure in 1 (0.2%) and rash in 1 (0.2%). The most commonly identified ADRs due to diuretics was cold and numb hand in 55 (15.8%) patients followed by erectile dysfunction in 30 (8.6%), hyponatremia in 20 (5.7%), kidney failure in 10 (2.8%), depression in 10 (2.8%) and hypokalemia in 4 (1.1%).

DISCUSSION

In our study for evaluating the ADRs in diabetic patients receiving anti-hypertensive drugs, a total of 347 ADRs were observed in 740 diabetic hypertensive patients

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Table 9: *Classification of antihypertensive drugs associated with ADRs in the tested sample*

Sl No	Adverse effects	ACEI (n= 552)	BBs (n= 436)	CCBs (n= 132)	Diuretics (n= 192)	Total
1	Fatigue	25 (7.2)	15 (4.3)	0 (0)	0 (0)	40
2	Edema	15 (4.3)	0 (0)	15 (4.3)	0 (0)	30
3	Gastrointestinal tract disease	12 (3.4)	4 (1.1)	3 (0.8)	0 (0)	19
4	Kidney failure	9 (2.5)	0 (0)	1 (0.2)	10 (2.8)	20
5	Cough	35 (10.0)	0 (0)	6 (1.7)	0 (0)	41
6	Erectile dysfunction	5 (1.4)	5 (1.4)	2 (0.5)	30 (8.6)	42
7	Headache	4 (1.1)	2 (0.5)	8 (2.3)	0 (0)	14
8	Depression	2 (0.5)	1 (0.2)	0 (0)	10 (2.8)	13
9	Rash	2 (0.5)	0 (0)	1 (0.2)	0 (0)	03
10	Allergic reaction	10 (2.8)	2 (0.5)	0 (0)	0 (0)	12
11	Cold and numb hand	0 (0)	0 (0)	0 (0)	55 (15.8)	55
12	Hypokalemia	0 (0)	0 (0)	0 (0)	4 (1.1)	04
13	Hyponatremia	0 (0)	0 (0)	0 (0)	20 (5.7)	20
14	Intermittent claudication	0 (0)	14 (4.0)	0 (0)	0 (0)	14
15	Bronchospasm	0 (0)	20 (5.7)	0 (0)	0 (0)	20

during the two year (2008-2010) study. It was found that a higher percentage of ADRs occurred in females than males. The result confirms previous reports that the occurrence of ADRs is on the higher side in females [13-15].

Age was found to be important criteria in the fact that the patients in the age group 61 to 70 years experienced maximum ADRs followed by patients in the age group between 51 to 60 and 71 to 80 years. Previous studies have also shown that a larger percentage of ADRs was reported from geriatric populations which were similar to our results [16-17]. The severity assessment showed that 185 ADRs were mild, 122 ADRs were moderate and 40 ADRs were severe. No lethal effects were observed or produced.

Combination therapy was associated with significantly lesser occurrence of ADRs, with a total of 147 as compared to monotherapy (n=200). In the HOT study, 76% of the patients assigned to the lowest target diastolic BP of 80 mm Hg or less required combination therapy [18]. In the UKPDS [19] 62% of those who were assigned to intensive BP control required combination therapy at a similar BP level.

The assessment done by using WHO scale revealed that out of 347 ADR's 61 ADRs were identified as certain, 114 probable, 134 possible, 14 unlikely, 4 conditional and 20 could not be categorized (unclassifiable).

In our study, we found nervous system side effects were high followed by respiratory system, renal system, sexual dysfunction, metabolic disorders, gastrointestinal tract diseases, dermatological system, and muscular system. Previous studies by other researchers also suggest that nervous system side effects were reported to be high in diabetic hypertensive patients [20].

Among the various antihypertensive drugs used, diuretics were associated with higher number of ADRs followed by ACE inhibitors, beta blockers and calcium channel blockers. The most commonly identified ADRs on ACE inhibitors was cough in 35 patients, on beta blockers was bronchospasm in 20 patients, on calcium channel blockers was edema in 15 patients, and on diuretics was cold and numb hand in 55 patients. Previous studies by other researchers were also similar to our results [20-21].

CONCLUSION

We conclude that, in diabetic hypertensive patients, intensive control of BP to levels lower than 130/85mmHg reduces the risk of cardiovascular events. All 4 drug classes—diuretics, beta blockers, ACE inhibitors, and calcium antagonists were effective in reducing morbidity and mortality. Most diabetic hypertensive patients will require combination therapy to achieve goal BP. Among the various antihypertensive drugs used, diuretics were associated with higher number of ADRs followed by, ACE inhibitors, beta blockers and calcium channel blockers. Diabetic hypertensive patients are at inevitable risk of bad effects of drugs due to sub-optimal functionality of their organ systems. This necessitates careful organ function analysis prior to prescribing any medication. One of the essential reasons of wide prevalence of ADRs in diabetic hypertensive patients is that they are elderly and are often on multiple drug therapy. The results of the above study would be useful for the physicians in rational selection of drug therapy for treatment of diabetic 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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