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## A PHARMACOVIGILANCE STUDY OF ANTIDIABETIC DRUGS IN HYPERTENSIVE PATIENTS IN A TERRITORY HOSPITAL IN COIMBATORE ZONE

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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 study was to evaluate Adverse Drug Reactions associated with anti-diabetic drugs in antihypertensive patients. The present study was an open, non-comparative, observational study done to monitor ADRs associated with anti-diabetes medications in diabetic hypertensive patients in a territory hospital. A total of 42 adverse drug reactions were observed in 102 diabetic hypertensive patients during December 2016 to June 2017. A high percentage of ADRs occurred in elderly and female patients. Of the 42 ADRs, 22 (52.3%) were mild, 16(38%) were moderate and 4 (9.5%) were identified to be severe. Combination therapy was associated with significantly less occurrence of ADRs, with a total of 17 (40.4%) as compared to monotherapy (n=25, 59.5%). Among the various anti-diabetic drugs used in hypertension patients, metformin were associated with higher number of ADRs (47.6%), followed by glimepride (26.19%), voglibose (16.6%) and pioglitazone (9.5%).

**Key words:** Adverse Drug Reaction, Diabetes, Hypertension.

### INTRODUCTION

Diabetes mellitus (DM) is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or a combination of insulin resistance and inadequate insulin secretion. Type 2 diabetes is the more common form for more than 90 percent of all diabetes cases. The World Health Organization (WHO), considers T2DM as an apparent epidemic which is especially increasing at an alarming rate in developing countries [1,2]. An oral anti-diabetic drug (OAD) is the first line of drug treatment for type 2 diabetes. However, the progressive nature of type 2 diabetes usually requires a combination of two or more oral agents in the long term. Safety and tolerability often limit the optimal use of OADs [3]. The use of anti-

diabetics has been increasing. However, sporadic reports of serious adverse effects associated with the use of these products have become a source of concern. Spontaneous adverse event reporting may be used to monitor the safety of these drugs [4]. 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 [5]. 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 specific treatment, or alteration of the dosage regimen, or withdrawal of the product [6]. 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 [7]. When the Food and Drug Administration (FDA) approve a new drug for marketing, its complete adverse profile may not be known for the reason that of the limitation of preapproval clinic trials. Usually, 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 although ADRs which are rare and those detected on long term use are not [8]. Since the majority trials exclude the elderly, pregnant women, children, patients with multiple diseases, and those on medication assumed of interaction with the study drug, the study population may not be true representative of the real world where the drug is eventually used [9]. Hence, there is a require to monitor the safety profile of all the medications on continuous origin and to evaluation their therapeutic rationale in the light of add on information emanate out of the pharmacovigilance activities [10].

## MATERIAL AND METHODS

This study protocol was approved by Institutional human ethical committee. This study was conducted various tertiary hospital in Tirupur city for six months from December 2016 to June 2017. 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 anti-diabetic medicines in hypertensive patients in a territory hospital. All newly diagnosed and old hypertensive patients receiving anti-diabetic 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 according to the "WHO Probability Assessment Scale".

## RESULTS

### Gender

Table 1 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 23 (52.3%) than males 20 (47.6%).

**Table 1:** Total number of ADRs among males and females in the tested sample

S.No	Gender	Number of patients	Number of ADRs	Percentage
1	Male	59	20	47.6%
2	Female	43	22	52.3%

### Age

Table 2 shows the total number of ADRs among different age groups in the tested sample. A total of 17 ADRs (40.4%) were observed in the patient age group of 61-70 years, followed by 10 (23.8%) in 51-60 years, 9 (21.4%) in 71-80 years, 5 (11.9%) in 41-50 years and 1 (2.3%) of ADRs in 30\_40 years of age group. The results show that most of the ADRs were observed in the age group of 61-70 years.

**Table 2:** Total number of ADRs among different age groups in the tested sample

S.No	Age Category	Number of patients	Number of ADRs	Percentage
1	30-40	4	1	2.3
2	41-50	17	5	11.9

3	51-60	25	10	23.8
4	61-70	41	17	40.4
5	71-80	16	9	21.4

### Severity of ADRs

Table 3 shows the severity of ADRs in the tested sample of the 42 ADRs observed in our study, 4 (9.5%) were identified to be severe, 16 (38%) were moderate and 22 (52.3) were mild. It was found that most of the ADRs observed were of mild severity.

**Table 3:** Severity of ADRs in the tested sample

S.No	Severity of ADRs	Number of patients	Percentage
1	Severe	4	9.5
2	Moderate	16	38
3	Mild	22	52.3

### ADRs among monotherapy and combination therapy

Table 4 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 17 (40.4%) as compared to monotherapy (n=25, 59.5%).

**Table 4:** Total number of ADRs among monotherapy and combination therapy in the tested sample

S.No	Drug therapy	Number of patients	Number of ADRs	Percentage
1	Monotherapy	38	25	59.5
2	Combination therapy	64	17	40.4

### Type of ADRs due to anti-diabetic drugs

Table 5 shows the type of ADRs due to anti-diabetic drugs observed in the tested sample. The results shows that the most commonly identified ADRs due to anti-diabetic drugs in hypertensive patients was dyspepsia in 11 (26.1%) patients followed by diarrhea in 7 (16.6%), hypoglycemia in 6 (14.2%), weight gain in 4 (9.5%), pedal edema in 3 (7.1%), vomiting in 2 (4.7%), giddiness in 2 (4.7%), edema in 2 (4.7%), sweating in 2 (4.7%), gastric irritation in 2 (4.7%) and head ache in 1 (2.3%) patients.

**Table 5:** Type of ADRs due to anti-diabetic drugs observed in the tested sample

S.No	Type of reaction	Number of ADRs	Percentage
1	Hypoglycemic	6	14.2
2	Dyspepsia	11	26.1
3	Weight gain	4	9.5
4	Diarrhea	7	16.6
5	Vomiting	2	4.7
6	Giddiness	2	4.7
7	Edema	2	4.7
8	Sweating	2	4.7
9	Gastric irritation	2	4.7
10	Head ache	1	2.3
11	Pedal edema	3	7.1

### Total number of ADRs due to anti-hypertensive drugs

Table 6 shows the total number of ADRs due to anti-diabetic drugs. It was found that among the various anti-diabetic drugs used metformin were associated with higher number of ADRs (47.6%), followed by glimepride (26.19%), voglibose (16.6%) and pioglitazone (9.5%).

**Table 6:** Total number of hypertensive patients experiencing ADRs due to anti-diabetic drugs in the tested sample

S.No	Anti-diabetic drug	Total number of patients	Total number of ADRs	Percentage
1	Metformine	89	20	47.6
2	Glimepride	62	11	26.1
3	Voglibose	13	7	16.6
4	Piolutazone	9	4	9.5

### *Classification of antidiabetic drugs associated with ADRs*

Table 7 shows the classification of antidiabetic drugs associated with ADRs in the tested sample. The results shows that the most common identified ADRs due to metformin was dyspepsia in 6 (14.2%), followed by diarrhoea in 3 (7.1%), hypoglycemia 2 (4.7%), weight gain in 2 (4.7%), giddiness in 2 (4.7%), sweating in 2 (4.7%), vomiting in 1 (2.3%), gastric irritation in 1 (2.3%) and head ache in 1 (2.3%). The most commonly identified ADRs due to glimepride was hypoglycemia in 4 (9.5%), followed by dyspepsia in 2 (4.7%), weight gain in 2 (4.7%), diarrhea in 2 (4.7%) and gastric irritation in 1 (2.3%). The most commonly identified ADRs due to voglibose was dyspepsia in 3 (7.1%), diarrhea in 2 (4.7%) and edema in 1 (2.3%). The most common identified ADRs due to pioglitazone was pedal edema in 3 (7.1%) and edema in 1 (2.3%).

**Table 7:** Classification of anti-diabetic drugs associated with ADRs in the tested sample

S.No	Adverse effect	Metformin(89)	Glimepride(62)	Voglibose(13)	Pioglitazone(9)	Total
1	Hypoglycemia	2(4.7)	4(9.5)	0(0)	0(0)	6
2	Dyspepsia	6(14.2)	2(4.7)	3(7.1)	0(0)	11
3	Weight gain	2(4.7)	2(4.7)	0(0)	0(0)	4
4	Diarrhea	3(7.1)	2(4.7)	2(4.7)	0(0)	7
5	Vomiting	1(2.3)	0(0)	1(4.7)	0(0)	2
6	Giddiness	2(4.7)	0(0)	0(0)	0(0)	2
7	Edema	0(0)	0(0)	1(2.3)	1(2.3)	2
8	Sweating	2(4.7)	0(0)	0(0)	0(0)	2
9	gastric irritation	1(2.3)	1(2.3)	0(0)	0(0)	2
10	Head ache	1(2.3)	0(0)	0(0)	0(0)	1
11	Pedal edema	0(0)	0(0)	0(0)	3(7.1)	3

## DISCUSSION

In our study for evaluating the ADRs in hypertensive agents receiving anti-diabetic drugs, a total of 42 ADRs were observed in 102 diabetic hypertensive patients during the six months (December 2016-June 2017) 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 [11-13]. 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 [14-15]. The severity assessment showed that 22 ADRs were mild, 16 ADRs were moderate and 4 ADRs were severe. No lethal effects were observed or produced. Combination therapy was associated with significantly lesser occurrence of 17 ADRs, with a total of 25 as compared to monotherapy (n=25). In the HOT study, 76% of the patients assigned to the lowest target diastolic BP of 80 mm Hg or less required combination therapy [16]. In the UKPDS<sup>17</sup> 62% of those who were assigned to intensive BP control required combination therapy at a similar BP level. In our study, we found retinopathy, nephropathy, impotence, metabolic disorders, gastrointestinal tract disease, skin irritation, and muscle weakness. Previous studies by other researchers also suggest that nervous system side effects were reported to be high in diabetic hypertensive patients [18]. Among the various anti-diabetic drugs used, metformin were associated with higher number of ADRs followed by glimepride, voglibose and pioglitazone. The most

commonly identified ADRs on metformin was dyspepsia in 6 patients, on glimepride was hypoglycemia in 4 patients, on voglibose was dyspepsia in 3 patients and on pioglitazone was pedal edema in 3 patients [19]

## CONCLUSION

We conclude that, in diabetic hypertensive patients, intensive control of diabetes is very important. All the 4 drugs - metformin, glimepride, voglibose, and pioglitazone were effective in reducing morbidity and mortality. Most diabetic hypertensive patients will require combination therapy to achieve goal. Among the various anti diabetic drugs used, metformin were associated with higher number of ADRs followed by, glimepride, voglibose and pioglitazone. 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.

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