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INCIDENCE OF ADVERSE DRUG REACTIONS AND DRUG INTERACTIONS OF ORAL HYPOGLYCEMIC AGENTS IN TYPE 2 DIABETIC PATIENTS AT GUWAHATHI MEDICAL COLLEGE HOSPITAL

Jyothirmayee Vattem*, Mangala Lahkar, Dipti Sharma

Department of Pharmacy Practice, NIPER – Guwahathi, Guwahathi – 781032, Assam, India.

*Corresponding author E-mail: jyothivattem@gmail.com

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ABSTRACT

To determine the incidence of adverse drug reactions and drug interactions due to oral hypoglycemic agents in patients suffering from type 2 diabetes. **Methodology**: Prior to the conduction of study, approval from institutional human ethics committee was obtained. The cross sectional, observational study was carried out in Guwahathi medical college hospital. Data collection was done over a period of five months through a pre-formulated case report form. Patients fulfilling all the inclusion criteria were selected randomly and interviewed for any objective and subjective evidence of ADR. For validation of ADR all the reactions were discussed and confirmed by practicing physician**. Results**: A total of 250 patients were included in the study and the data was tabulated in excel sheets and analyzed with appropriate statistical methods. The incidence rate of ADR was found to be 21.2% of which hypoglycemia is the predominant ADR. A combination of Glimepiride and Metformin caused more ADR than any other drug. Of all the ADR 30.2% are probable and 69.8% are possible. 10.4% ADR can be preventable accounting for DI. Of the 26 interactions 57.7% interactions were probable. All interactions were moderate in severity. A significant association was found between incidence of ADR and age, gender and polypharmacy. **Conclusion**: Improvement in patient-physician interaction time or the intervention of clinical pharmacist in educating patients about the disease and management of ADR will improve patient outcome.

1. INTRODUCTION

Diabetes is the most prevailing disorder and India is the diabetic capital of world[1]. Due to change in life style, number of patients with diabetes is increasing day by day and hence the use of drugs to treat this condition. Oral hypoglycemic agents are used to treat type 2 diabetes and most important ones are Sulfonylureas, Thiazolidinediones and Biguanides. The use of drugs is always associated with adverse effects. The International Conference on Harmonization defines an adverse drug reaction as "A response to a drug which is noxious and Unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function"[2]. Drug Interactions also cause ADR. When the effect of one drug is altered by co-administration of another drug or food or presence of disease then the phenomenon is called as drug interaction (DI). Type 2 Diabetes is also called as adult onset diabetes and mostly associated with diseases like hypertension, renal diseases and cardiovascular diseases that necessitate polypharmacy, which in turn leads to drug interactions. The unwanted effects caused by a drug may lead to prolonged hospital stay, increased health care costs and indirect

costs[3]. According to a study conducted at Hamdard university teaching hospital, New Delhi, in India, among 600 patients who attended OPD, 122 patients developed ADR and 10.7% of ADR are due to antidiabetic drugs only[4]. In one more study done at chattisghar, India, antidiabetic drugs accounted for 14.28% of 154 ADR[5]. As the field of pharmacovigilance is still in its infancy in this tertiary hospital, there was less study done on ADR and DI of oral hypoglycemic drugs. Therefore, the vision of undertaking the study is to find out the Incidence of Adverse Drug Reactions and Drug Interactions in type 2 diabetic patients on oral hypoglycemic agents.

METHODOLOGY

The observational study was retrospective, cross-sectional in nature with no follow up of patient. Approval of the Institutional Human Ethics Committee and permission from the superintendent of Guwahati Medical College and Hospital were obtained prior to the study initiation [Approval No. 190/2007/Pt-1181]. The study was conducted at both inpatient and outpatient departments of endocrinology and in patient departments of cardiology and neurology of Guwahathi medical college hospital. The data was collected over a period of five months i.e. from August 2010 to December 2010. The approval from all the Head of the Departments was taken. The professors and practicing physicians were requested to report any suspected ADR. The subjects are pre-existing type 2 diabetic patients on oral hypoglycemic agents of both sexes and all ages. Patients other than type 2 diabetes, too ill patients, patients with hearing problems and incomplete medical records, patients on their index visit and patients on alternative system of medicine were excluded from study. The patients fulfilling both inclusion and exclusion criteria were selected at random and interviewed for any subjective or objective evidence of ADR. The data was collected in standard CRF framed for this particular study. For validation of ADRs all reactions were discussed and confirmed with the practicing physicians. The causality assessment of ADR was done by Naranjo's causality assessment scale[6] that classifies ADR into "highly probable, probable, possible and unlikely". At the same time, severity and preventability of ADR were assessed using Hartwig's severity assessment scale[7] and Schumock and Thorntan ADR preventability scale[8] respectively. Probability of a reaction being a drug interaction was assessed using DIPS[9] (Drug Interactions Probability Scale) that classifies interactions into "highly probable, probable, possible and doubtful". All the data collected in study period was tabulated in Microsoft Excel sheet and analyzed. All the data was represented as average (±SEM) and percentages. Descriptive statistics were used for analysis. Graphpad Prism 5.0 was used for the statistical analysis of data. Fisher's exact test was used to determine the significant association between variable and Incidence of ADR. A p-value of <0.05 was considered as level of significance.

RESULTS

Out of 250 patients included in the study 53 patients developed one or more ADR. The incidence rate of ADR was 21.2%. Most of the ADR were mild in nature. Hypoglycemia was the predominant ADR accounting for 42.1% of total ADR. Multiple ADR were observed in the same patient. The incidence rates of different ADR were tabulated in Table 1. The patients reported with ADR were given 4 different drugs and 4 different combinations of OHA based on the differences in underlying disease. Table 2 represents the incidence of ADR with different OHA and their combinations prescribed to the ADR cases in Guwahati Medical College Hospital. The combination of Glimepiride with Metformin was mostly prescribed and is associated with more ADR (44.9%, Table 3). In the 250 subjects under study 88 were female and 162 were male. Percentage of ADR or incidence of ADR (29.5%) was more in female population compared to male (16.7%). The significance of association was found out using Fisher"s exact test. The association was statistically significant with a p- value of 0.023 at 95% confidence interval. The relation between the genders to the observed ADR was represented in table 4. Co-morbidities and polypharmacy also have significant association with the incidence of ADR. Incidence of ADR is more in patients having one or more co-morbidities (22.5%) than patients without co-morbidities (15.2%). The average number of drugs per prescription was 5.4 and around 66% of total ADR were observed in patients having polypharmacy.

Table I: Incidence of different ADR.

S.no	Types of ADR	Number of cases	% of ADR
1.	Hypoglycemia	42	42.1
2	Nausea	10	9.3
3	Weight gain	5	4.75
4	Allergic skin	2	1.9
5	Lethargy	6	5.6
6	Headache	2	1.9
7	Edema	5	4.75
8	Blurred vision	4	3.7
9	Constipation	13	12.1
10.	Anorexia	2	1.9
11	Weight loss	2	1.9
12	Diarrhoea	12	11.2
13	Vomiting	2	1.9

Table 2: Type and number of ADR associated with various OHA and their combinations

ADR	GLIMP+M	GLIMP	GLICLA+M	M	GLICLAZIDE	GLIBEN+M	V	PIO+M+GLIMP
Hypoglycemia	25	4	3	3	8	2		2
Constipation	10	2	1					
Diarrhea	2	2		4			2	2
Nausea	8			2				
Lethargy				4				
Edema								5
Blurred vision	3		1					
Vomiting					2			
Weight loss				2				
Weight gain		3			1			2
Allergic skin					2			
Headache		2						
Anorexia				2				
Total	48	13	5	17	13	2	2	11

Glimp: glimepiride**, M:** metformin, **Glicla:** glicalizide, Gliben: glibenclamide**, V**: voglibose, **Pio**: Pioglitazone

Table 3: Percentage of ADR with OHA and their combinations

S.no.	Drug or Combination	% ADR
1	Glimepiride+ Metformin	44.9
2	Metformin	14
3	Gliclazide	12
4	Pioglita-zone+Metformin+glimepiride	10.3
5	Glimepiride	9.9
6	Gliclazide+Metformin	4.7
7	Glibenclamide+Metformin	1.9
8	Voglibose	1.9

Table 4: Association between ADR and gender

S. No.	Gender	Total	ADR reported	No ADR	Percentage of ADR
1.	Female	88/250	26/53	62/197	29.5%
2.	Male	162/250	27/53	135/197	16.7%

Table 5: incidence of drug interactions with respect to precipitant drug

S. no.	**Class of precipitant drug**	**No. of drug interactions**	**Percentage of drug interactions**
1	Cardiovascular drugs	14	53.8
2	Thyroid hormones	5	19.2
3	Psychoactive drugs	2	7.7
4	NSAIDS	2	7.7
5	Alcohol	1	3.8
6	Insulin	1	3.8

ANNEXURE I: CASE REPORT FORM

Reg. no.: **Age:** **Sex:** **OPD/IPD:** **Ward:**

Weight: **Occupation:** **diabetic from:** **yrs** **DOA:**

Reason for admission/visit:

History:

- **History of illness (co-morbidities):**
- **Medication taken:**
- **Allergy/ADR to any drugs:**
- **OTC**
- **Smoking/alcoholism/gutka: how long?**

Physical examination:

- **P / I / E / C / D** ●**BP : ____** ● **Pulse Rate _____**
- **Chest**
- **Abdomen**
- **CVS**
- **CNS**

Lab reports:

Biochemistry	Imaging	Microbiology

Present diagnosis:

Medication:

Drug name & ROA	Dose & dosage	Date began	Reason for use

No. of drugs given:

- **Narrow therapeutic index drugs:**
- **Compliance**

	low	fair	high
Insulin			
Oral medication			
Diet			
Exercise			

- **Medication error: overdose/underdose**

Is there any ADE? If yes description:

Onset: acute _____ sub acute _____ latent _____

Type of ADR:

System involved:

When it occurred:

Measures taken:

Outcomes: recovered/not yet recovered/fatal/unknown

When it resolved:

No. of days of stay (if IPD):

Around 30.2% ADR were probable and 69.8% ADR were possible. 10.4% of ADR were preventable. Of the 250 prescriptions, 26 interactions were identified (incidence 10.4%). The effect of such interactions was hypoglycemia. Higher number of drug interactions was found with cardiovascular drugs (table 5). 57.7% of interactions were probable and the remaining were possible interactions. All the interactions were moderate in severity.

DISCUSSION

Type 2 diabetes was also referred as adult onset diabetes as it is usually diagnosed in older patients. This disease is associated with co-morbidities like cardiovascular diseases and renal failure. Increasing age, co-morbidities, polypharmacy and poor medication adherence all contribute to the occurrence of ADR and DI. Hypoglycemia was the predominant ADR accounting for 41.2% of total ADR followed by constipation (12.1%) and diarrhoea (11.2%). A combination of Metformin with glimepiride is associated with more ADR (44.9%) followed by Metformin (14%). This correlates with a randomized, double blind study conducted in France to detect the improvement in glycemic control by adding glimepiride to Metformin monotherapy, superior glycemic control was observed compared to their monotherapies, but the incidence of ADR was more compared to their monotherapies[10]. A study done to compare the efficacy of glimepiride, Metformin and rosiglitazone monotherapy in Korean population, the predominant ADR was hypoglycemia (29%) [11]. Incidence of ADR was associated with gender, co-morbidities and polypharmacy. No such association was found with age. It may be because most patients belong to the age of 40-50 years group and the average age of the patients was 51 years. Hence, the occurrence of ADR is predominant in that age group.

The incidence of ADR was more in female (29.5% of female population) compared to male (16.7% of male population). Previous studies also reported that the occurrence of ADR is more in female[12]. This may be because of difference in body weight and Basal Metabolic Rate, hormonal changes that are unique to female and the effect of these changes in metabolism. Polypharmacy was correlated with the incidence of ADR. 66% of total ADR were observed in patients taking more than 4 drugs. A study done in medicine department of tertiary care hospital in Chattisghar had shown similar result. In that study, 51.29% of total ADR were observed in female and polypharmacy was accounted for 64.28% of total ADR[12]. Co-morbidity was more common in DM and 79% of total ADR occurred in patients with co-morbidities. A secondary data analysis in Mexico reported that co-morbidities are one of the risk factor for the occurrence of ADR. Increased number of co-morbidities encourages polypharmacy resulting in increased incidence of DI and hence ADR[13]. A total of 1350 drugs were prescribed to the 250 patients and the average no. of drugs given to each patient was 5.4. 26 patients (10.4%) suffered adverse effect because of drug interactions. The results were consistent with the prospective study conducted in the inpatient department of a hospital in Norway that had shown 8.8% of DI[14]. However, the incidence of DI depends on the patient's underlying diseases and the drug utilization pattern of that particular hospital. 100% of interactions were moderate in severity. 57.7% of interactions were probable in nature. There were credible reports in the literature on the interactions observed in the study in human and the interactions were consistent with known interactive properties of both drugs. As the study is retrospective, observational in nature, as with ADR, re-challenge with offending drug and test for serum drug concentrations in human could not be done in patients. Incidence rate of drug interactions in the sample was more in female (57.7%) compared to male (42.3%). Interactions with Cardiovascular drugs (53.8%) were more prominent. The results were consistent with the previous studies. A cross-sectional study conducted in Brazil had shown similar result[15]. In that study, 69.8% of total interactions were found in female. Cardiovascular drugs accounted for 47.5% of total interactions. In one more study conducted in Nepal on diabetic patients cardiovascular drugs accounted for 49.5% of total DI[16]. Most interactions (accounting for 16 % of total population) occurred in patients in the age group of 51-60 which is consistent with the prospective observational study done in Nepal (23.1%). The study was conducted for a short span in small sample size. It has provided baseline information about the prevalence of ADR of OHA and their distribution among different age groups, genders and therapeutic classes of drugs. The data presented here will be useful in future for long term, extensive ADR monitor-

ing in the hospital and will be useful in framing the policies towards the rational use of drugs. The study on the global prevalence of diabetes indicated the increased prevalence of diabetes in male. The present study evidenced the above data. The incidence of ADR is more in this region. The patients are mostly from rural area and of lower economic groups. Most of them lack the knowledge about the disease, medication and their complications. There are no proper tools for patient education. All of them might have influenced the results.

Polypharmacy was found to be one of the risk factor for the incidence of ADR. Hence, it should be discouraged. One cannot withhold the drug from treatment when it is needed. Ambulatory patients should be advised to monitor for symptoms of hypoglycemia and necessary precautions to be take when they experience them. The patient to physician ration is more in this study setting which gives less time for communicating with the patient. Improvement in patient-physician interaction time or the intervention of clinical pharmacist in educating patients about the disease and management of ADR will improve patient outcome.

Conflict of interest: None.

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