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A pharmacovigilance study of oral antidiabetic drugs in patients with type 2 diabetes mellitus

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***Abstract*---**The aim of the study to to evaluate and analyse ADRs in type II diabetic patients and to determine the causality and safety profile of all the prescribed medicationsMethods: A prospective study was carried out in diabetic patients visiting the Diabetic OPD and those fulfilling inclusion criteria were included in study. ADR observed were obtained from their Diabetic Diary and were recorded in the Case Record Form to evaluate the incidence,frequency, severity and causalityResults: A total of 81 ADRs were reported from206 patients. The class of drug responsible for causing more ADRs was found to be biguanides. The mostcommonly affected organ system was GI System. The suspected ADRs were assessed for their causality,it wasrevealed that 26 were probable and 55 were possible as per WHO Scale. Conclusions: The present study helps to understand importance of ADR reporting to ensure maximum benefits of drugtherapy. As the cases of new onset diabetes is also increasing in Indian scenario as well as newer drugs are also developed to target the

disease pathology, therefore active pharmacovigilance should be carried out for risk identification and management.

***Keywords*---**anti-diabetic drug, adverse drug reaction, who scale, causalty assessment.

Introduction

Diabetes mellitus (DM) is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency ofinsulin secretion or a combination of insulin resistance and inadequate insulin secretion. The World Health Organization (WHO), considers T2DM as an apparentepidemic which is especially increasing at an alarming rate in developing countries. [1,2] The management principles of diabetesfocus on disease prevention, screening high risk individuals and aggressive treatment of individuals in the pre-diabetic state. Pharmacological treatment remains the main option for most of these patients. [3] With rise in number of cases of patients with DM type 2, use of anti-diabetics drugs has been increasing but these drugs themselvescan prove fatal and can result in adverse drug reactions(ADR) which can be mild to serious.

World Health Organisation (WHO) defines adverse drug reactions as any response to a drug which is noxiousand unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseaseor for the modification of physiologic function. Thus, this definition excludes over dose (either accidental orintentional),drug abuse failure of treatment and errors of drug administration. [4,5,6] WHO-UMC scale is the causality assessment used by WHO Programme for International Drug Monitoring (PIDM). WHO-UMC scale based on clinical pharmacology knowledge, is widely used under the Pharmacovigilance Programme of India (PvPI). It is a composite assessment method that takes into account the clinical–pharmacological aspects and the quality of the documentation of the ICSR. [8]

The detection of Adverse Drug Reactions(ADRs) has become significant because of introduction of largenumber of drugs in the last two decades. Adverse drug reactions can result in looseof patients confidence leading to negative emotions toward their physicians treatment and can engage in self-treatment options, which may consequently precipitate additional ADRs. [7] There is a need to monitor the safety profile of all the medications on continuous origin and providing feedback to physicians on the possibility and details of such events, thereby protecting the patients from avoidable harmful effect. Hence, the present study is planned to generate data on the safety profile of currently prescribed oral anti-diabetic drugs bydoing monitoring of ADRs.

Method

This was an prospective observational study conducted over a period of 6 months on patients with type 2 Diabetes Mellitus attending Diabetic OPD of Medicine Department and Department of Pharmacology at NSCB Medical college Jabalpur (MP). All the participants included in the study were explained clearly about the

purpose and nature of the study in the language they understood and were included in the study only after obtaining a written Informed Consent.

Inclusion criteria

1. All cases diagnosed with diabetes mellitus (Old and New onset DM Type 2)
2. Patient with type 2 DM with associated Comorbidity
3. Patient receiving Oral anti diabetic drugs.
4. Patient more than 18 year of age

Exclusion criteria

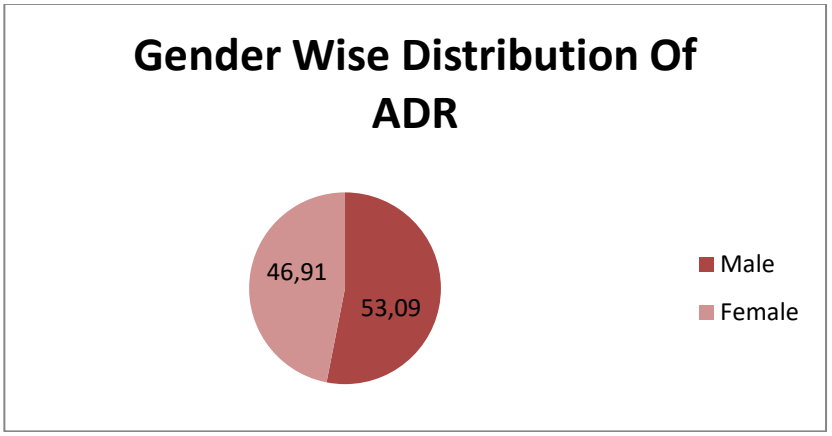
1. Pregnant and Lactating mothers
2. Patient diagnosed with Type 1 DM
3. Patient not receiving Oral Antidiabetic Agent

A total of 206 patients diagnosed with Diabetes Mellitus type 2 visiting Diabetic OPD were screened for the study. The detailed information of the participants pertaining to age, gender, relevant medical history, past history and drug therapy administered and ADR observed were obtained from their Diabetic Diary and were recorded in the Case Record Form to evaluate the incidence,frequency, severity and causality.
Statistical analysis – The collected data is expressed in the percentile form.

Discussion

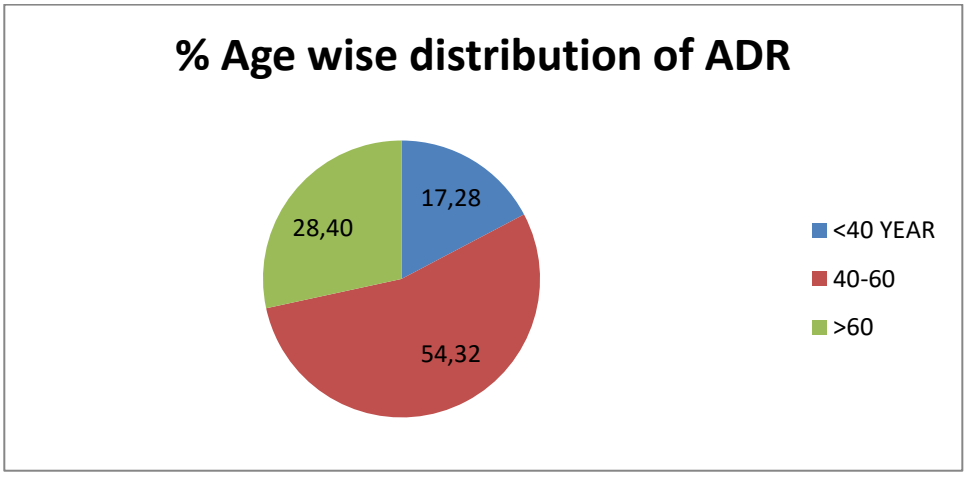
In the study a total of 206 diabetic patients were encountered and 81 ADRs were detected with a predominance of male gender (53.9%)over females (46.9%). [FIG 1]

Figure 1 Gender wise ADR distribution



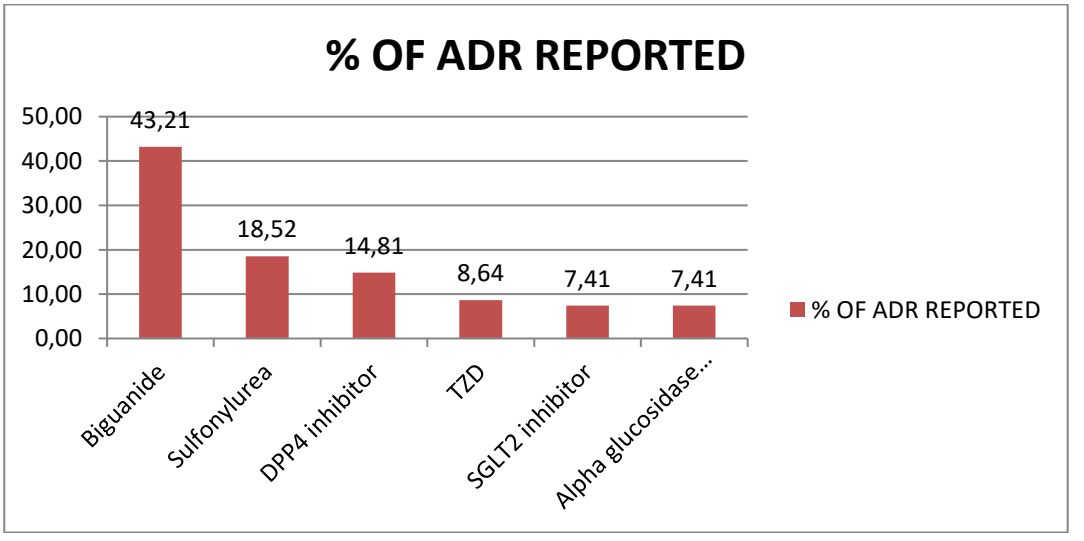
Patients in the age group of 40-60 years experienced maximum ADRs (54%), which is in accordance with the study of Bhattacharjee et al. which shows that the incidence of ADR is more in geriatric population. [9][FIG 2]

Figure 2 Percentage age wise ADR distribution



Themost commonly prescribed anti-diabetic medication was metformin, which was also responsible for causing more number of ADRs, but when analyzing the safety of drug, metformin was prescribed in 200 patients out of 206 but only 35 ADRs were reported, which is similar to study conducted by Tirthankar Debet et al.[10] Most commonly reported ADR were Gastric irritation, dyspepsia, diarrhea, hypoglycemia. [FIG 3]

Figure 3 Percentage of ADR reported by different antidiabetic drugs



Organ system most commonly affected was gastro intestinal system (65.43%) which was similar to the study conducted by Singh H et al.[11] [FIG 4], [TABLE 1]

Figure 4 percentage of type of ADR

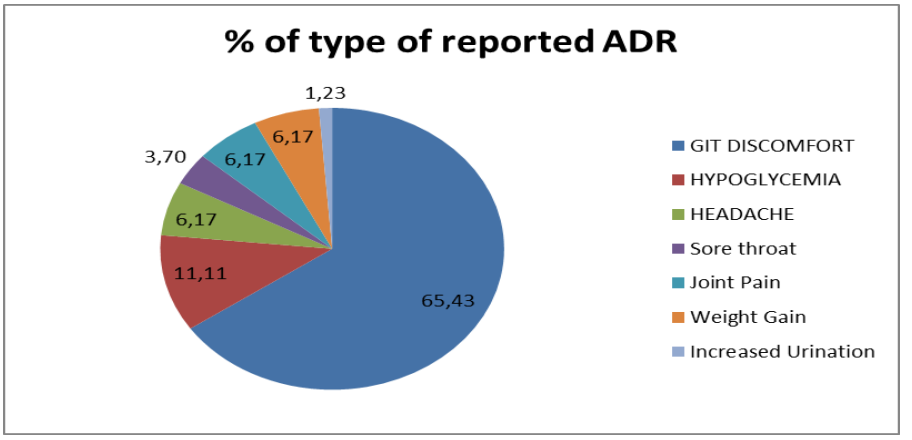


Table 1 SOC of ADRs with different classes of anti diabetic drugs

SOC Involved	ADR	Biguanide	Sulfonylurea	DPP4 inhibitor	SGLT2 inhibitor	TZD	Alpha glucosidase inhibitor	%
GI SYSTEM	GIT irritation	20	5	0	0	5	0	53 (65.4%)
	Dyspepsia	5	0	0	0	0	0	
	Diarrhoea	6	0	0	0	0	4	
	Nausea/Vomiting	0	0	0	0	0	0	
	Constipation	0	0	0	2	0	0	
	Flatulence	4	0	0	0	0	2	
METABOLIC DISORDER	Hypoglycemia	0	7	2	0	0	0	9 (11.1%)
CNS DISORDER	Headache	0	0	5	0	0	0	5 (6.1%)
OTHERS	Sore throat	0	0	3	0	0	0	14 (17.2 %)
	Joint Pain	0	0	2	3	0	0	
	Weight Gain	0	3	0	0	2	0	
	Increased Urination	0	0	0	1	0	0	
Total		35 (43.21%)	15 (18.52%)	12 (14.81 5)	6 (7.41 %)	7 (8.64%)	6 (7.41%)	81 (100 %)

The causality assessments of ADRs were also done according to WHO Scale which categorises ADRs as“certain”, “probable”, “possible”, “unlikely” and “unclassifiable’. It is seen that out of 81 ADRs reported with 26 were classified as probable and 55 ADRs as possible, whereas none could be categorized as certain or unlikely.[TABLE 2]

Table 2 Casualty assessment of ADR reported

DRUGS	CERTAIN	PROBABLE	POSSIBLE	UNLIKELY	UNCLASSIFIED
Biguanide	0	13	22	0	0
Sulfonylurea	0	7	8	0	0
DPP4 inhibitors	0	2	10	0	0
TZD	0	1	6	0	0
SGLT2 inhibitors	0	1	5	0	0
Alpha glucosidase	0	2	4	0	0

inhibitor					
Total	0	26	55	0	0

Those ADR classified as Probable dechallenge of the drug was done and patient recovered gradually well. While those classified as Possible were mild ADR hence dechallenge was not performed,symptomatic management was given and patient recovered gradaually well. No serious or life threatening ADR was reported. Monitoring of ADRs in patients taking oral anti-diabetic agents is very importantsince such medications have to be continued lifelong so it is very essential to monitor those drugs as it is well known to cause ADRs like GI disturbances, hypoglycemia, weight gain etc.

Conclusion

In our study, Gastro-intestinal, metabolic disorders were most common ADRs reported. Monitoring of ADRs inpatients taking oral anti-diabetic agents is very important, along with lifestyle modifications, these medicines will be needed for long time for management of type 2 DM. Hence evaluation of ADRs is important for the assessmentof risk factors to ensure maximum benefits of drugtherapy. As the cases of new onset diabetes is also increasing in Indian scenario as well as newer drugs are also developed to target the disease pathology, therefore active pharmacovigilance should be carried out for risk identification and management.

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