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Evaluation of suspected Adverse drug reactions of oral antidiabetic drugs in type 11 diabetics mellitus in a tertiary care referral hospital

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ABSTRACT

The study was to evaluate and analyse ADRs in type II diabetic patients. Oral anti-diabetic drugs were evaluated prospectively over a period of six months in a tertiary care hospital located in north Malabar region. They were evaluated for incidence, frequency, severity and causality. ADR causality was graded according to WHO-UMC scale and Naranjo scale. Severity according to Modified Hartwig and Siegel scale and preventability based on Modified Schumock and Thornton Scale.A total of 58 ADRs were reported from 460 patients with female predominance over male. Patients undergoing treatment for a period of less than 5 years experienced more incidence of ADR. All the ADRs that were reported of type A and reported in biguanides especially in GI System. The suspected ADRs were assessed for their causality, (52) were probable, (6) possible as per WHO scale. Naranjo scale were (53) probable and (5)possible. In Modified Hartwig and Siegel scale (28) were mild and (30) moderate. Modified Schumock and Thornton Scale (58) ADRs were probably preventable. Considering the reporter status ADRs by physician (52), pharmacist (4) and nurses (2). In management of reported ADRs (42) majority of ADRs were managed by directly withdrawing the suspected drugs, in (11) no changes were done, dose was altered in (3) and symptomatic treatment was provided in (2) cases. Considering the outcomes of ADR, 45 of the ADRs were recovered and 13 reactions still continued. Results provide insight to the healthcare providers on the importance of monitoring and reporting ADR with DM

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. [1] Modern principles of management of diabetes focus 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. The conventional options for type II diabetes mellitus include drugs that have been relatively long on the market such as Biguanides, Sulfonylureas (SU), Alphaglucosidase inhibitors, Meglitinides, Thiazolidinedione (TZD), Dipeptidyl Peptidase 4 Inhibitors and Sodium Glucose Co-transport 2 Inhibitors. Drugs are the commonest medical interventions used to relieve sufferings but drugs themselves can prove fatal and result in adverse drug reactions (ADR). Inspite of their efficacy in achieving glycaemic control, there are some safety issues with antidiabetic drugs such as gastro intestinal problems, metabolic disorders, central nervous system (CNS) disorders, muscoskeletal disorders, genito-urinary disorders, peripheral oedema, nasopharyngitis, weight gain etc. [2]

World Health Organization (WHO) defines adverse drug reactions as any response to a drug which is noxious and unintended and occurs at doses normally used in man for

prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function. Thus this definition excludes over dose (either accidental or intentional), drug abuse, and treatment failure and drug administration errors. [3] The detection of adverse drug reactions (ADRs) has become increasingly significant because of introduction of a large number of potent toxic chemicals, as drugs in the last two or three decades. Adverse drug reactions occur almost daily in health care institutions and can adversely affect a patient's quality of life, often causing considerable morbidity and mortality.

WHO has intervened seriously in this matter and established an international adverse drug reactions monitoring centre at Uppsala, Sweden, which is collaborating with national monitoring centres in around 70 countries. The first ADR monitoring programme was started with 12 regional centres and India joined the WHO monitoring program Uppsala, Sweden in 1997 and three centres were started in medical colleges at New Delhi, Mumbai and Aligarh.

The study is planned to actively generate data on the safety profile of currently prescribed oral anti-diabetic drugs by monitoring ADR. After analysing the ADR, causality assessment of reported ADR is carried out using the Naranjo causality assessment scale and WHO-UMC scale. Preventability Criteria was evaluated by Modified Schumock and Thornton Scale and Severity assessment by Modified Hartwig and Siegel.Avoidable adverse effects will be reduced by more skilful prescribing and this means that doctors, among all the other claims on their time, must find time to understand drugs better, as well as to understand their patients and their diseases The study was to evaluate and analyse ADRs in type II diabetic patients. Oral anti-diabetic drugs were evaluated prospectively over a period of six months in a tertiary care hospital located in north Malabar region. They were evaluated for incidence, frequency, severity and causality.

MATERIALS AND METHODS

Collected data was evaluated using various scales like WHO UMC scale, Naranjo scale, Modified Hartwig and Siegel scale , Modified schumock and Thornton scale.The study was conducted in out-patients of endocrinology department of tertiary care hospital located in north Malabar region. A prospective observational study was carried out in 460 patients with diabetes attending out patient endocrinology department to evaluate for the incidence, frequency, severity and causality.Patients undergoing treatment for type 2 diabetes mellitus. The study was carried out for a period of 6 months (May 2016-Nov2016). Data were collected from patients undergoing treatment of diabetes mellitus in endocrinology. All relevant data including various demographics, drugs received by patient, their dosage and duration of disease were collected. Patient consent was obtained using patient consent forms. Out-patients undergoing treatment of diabetes mellitus in endocrinology department were selected, and datawere entered in data entry form comprising the socio-demographic details of the patients, their medical and medication history, laboratory results etc were noted down. Data collected from the study was tabulated in Microsoft Excel 2010 and the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA).computer software version 17.0 for windows and analyzed

Table 1: List of ADR

SL.NO:	CLASS OF DRUG	NAME OF DRUG	NO: OF ADR	ADR
1	Sulfonylureas	Glimepride Glibenclamide Gliclazide	7 3 3	Hypoglycaemia, Weight gain, Dizziness, Gastric irritation. Hypoglycaemia, Weight gain Vomiting, Weight gain, Gastric irritation
2	DPP-IV inhibitors	Teneligliptine	4	Hypoglycemia, Weight gain, Oedema
3	SGLT2 inhibitors	Canagliflozin Dapagliflozin	1 1	Constipation Constipation
4	TZD	Pioglitazone	6	Weight gain, Oedema
5	Alpha-glucosidase inhibitors	Voglibose	4	Bloating, Dyspepsia, Gastric irritation, Diarrhoea
6	Biguanides	Metformin	28	Gastric irritation, Dizziness,Decreased appetite, Tiredness, Metformin Intolerance, Vomiting,Dyspepsia

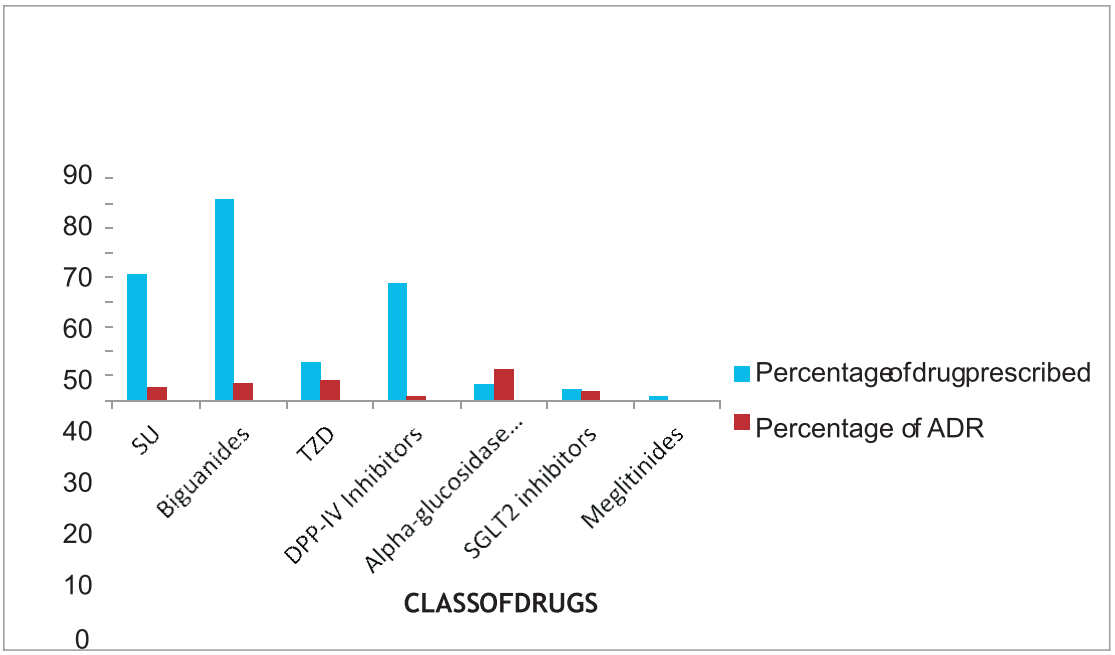

Fig. 1 : Incidence of ADR With Drugs Prescribed

by appropriate statistical methods.During the study period a total of 460 patients taking oral anti-diabetic drugs

RESULT

During the study period a total of 460 patient taking oral antidabetic drugs were enrolled. In gender distributions, 60.7% were female and 39.3%were male patients. Distribution based on age 30.2% of patients were in the age group of (50-59yrs).Patients were diabetics for less than 5 yrs were found to be more in the study. Among 480 patients,50 experienced ADR and out of that 8 patients had more than 1 ADR.In this study,58 ADR cases were detected from that 50 patient belongs to Type A category. More commonly Identified ADR were with biguanides followed by sulfonyl ureas,TZD,DDP-4 inhibitor,alpha glucosidase inhibitor and SGLT2 (Table 1).GI system organ was most effected due to the ADR(Table 2).

In the reporter status,52 cases were reported by physician, followed by pharmacist (4) and nurses (2).Drug withdrawn were found in 42 cases, dose altered in 3 cases and no changes were done in 11 cases.Systametic treatment were given for 2 cases. Causality assignment was evaluated using WHO scale (Figure 2)categorised as 52 ADR were probable and 6 possible. Assessment with Naranjo scale (Figure 3)indicated that majority of ADR 53 were probable and 5 possible. Severity assessment using modified hartwig and sigen scale indicated majority of ADR mild followed by moderated respectively. Preventability assessment using modified schumock and thornton scale revealed that all the ADR probably preventable 58 cases.

Table 2: Organ System Affected Due To ADR

System Affected	ADR	NUMBER OF ADRs	TOTAL
GI system disorders	Dyspepsia Diarrhoea Constipation Metformin Intolerance and gastric irritation Bloating Vomiting Decreased appetite	1 1 2 24 1 1 6	36
Metabolic disorders	Hypoglycaemia	6	6
CNS disorders	Dizziness	2	2
Others	Oedema Tiredness Weight gain	5 1 8	14

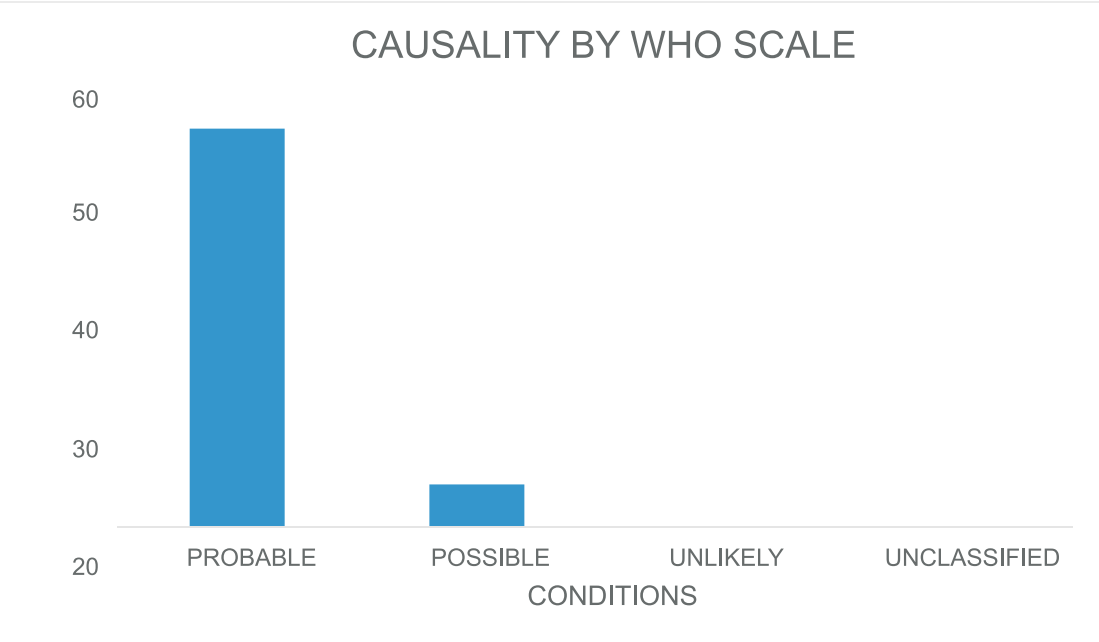

Fig. 2 : WHO Causality Assessment

DISCUSSION

In this study, a total of 460 diabetic patients were encountered and 58 ADRs were detected from 50 patients with a predominance of female gender (60.7%) over males (4.8%).Majority of patients included in the study was also females. Patients in the age group of 60-69 years experienced maximum ADRs (18), which is in accordance with the study of Bhattacharjee et al [4], which shows that the incidence of ADR is more in geriatric population. Majority of the ADR cases were seen in patients taking medication for a period of less than 5 years which is similar to the study carried out by Javedh Shareef et al [5] Only type A ADR were reported in all the cases. The most 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 375 patients but only 28 ADRs were reported, which is similar to study conducted by Tirthankar Debet et al [6].Organ system most commonly affected was gastro intestinal system (36) which was in accordance to the study conducted by Singh H et al [7]. Rate of reporting ADR by various health professionals were observed as 53 by physicians, 3 by pharmacist and 2 by nurses. As a part of management in 42 cases the drug was withdrawn, no changes were done in 11 cases, dose altered in 3 cases and symptomatic treatment was provided in 2 cases. Adverse drug reactions encountered were treated and the final outcome was measured. About 45 ADRs were recovered and 13 were continuing. To strengthen and further emphasize the validity of the study, causality assessment was done using Naranjo scale and WHO-UMC scale. The assessment showed that out of 58 ADRs, (52) were probable and (6) were possible as per WHO scale and Naranjo scale indicated that majority of the ADRs (53) were probable and (5) were possible. These findings are similar to the

Table 3: Incidence of ADR With Drugs Prescribed

CLASS OF DRUGS	NUMBER OF DRUGS PRESCRIBED	PERCENTAGE OF DRUGS PRESCRIBED	ADR REPORTED	PERCENTAGE OF DRUG PRESCRIBED WITH ADR (%)
SU	234	50.9	13	5.6
Biguanides	375	81.5	28	7.5
TZD	73	15.9	6	8.2
DPP-IV inhibitors	219	47.6	4	1.8
Alpha-glucosidase inhibitors	31	6.7	4	12.9
SGLT2 inhibitors	49	5	2	4.1
Meglitinides	2	0.4	0	0

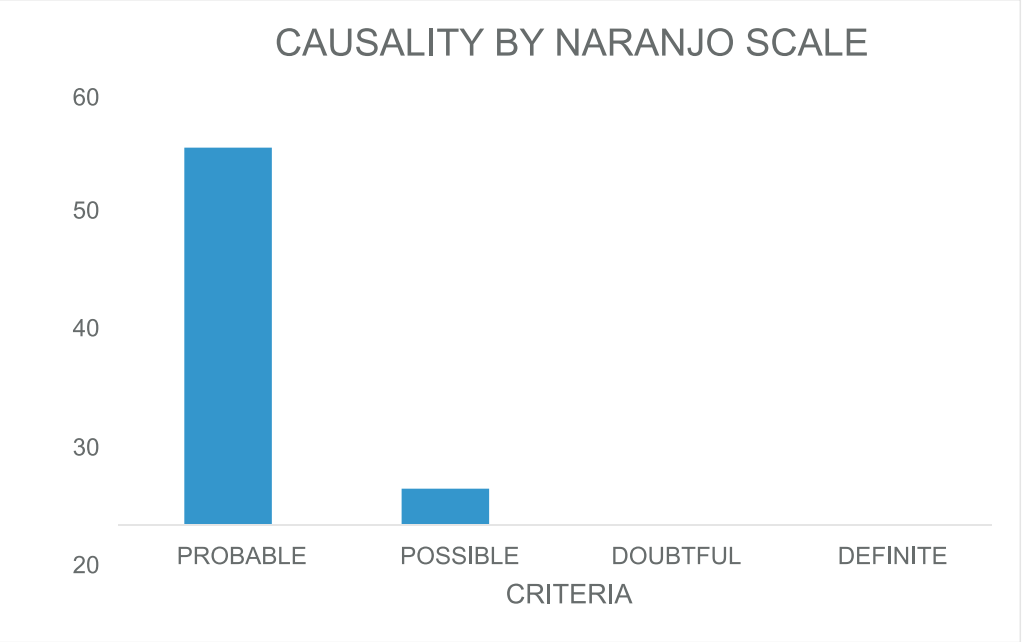

Fig. 3 : Naranjo Causality Assessment

study carried out by Javedh Shareef et al [8] which stated that most of the ADRs belong to category probable. On the evaluation of the severity of ADRs by the Hartwig and Siegel severity assessment scale, it was evident that most of the ADRs reported in the study were moderate (30) in nature followed by 28 were mild No lethal outcomes were observed or produced during the study period. Assessment of the preventability of the ADRs using modified Schumock and Thornton scale revealed that 58 ADRs were probably preventable.[9-11]

When analyzing the safety of drugs, in the study more number of ADRs (28) were reported with biguanides, similarly most commonly prescribed drug (375) was found to be metformin. Therefore the incidence rate of ADR with the drug is comparatively less ie only 7.5% , whereas in case of Thiazolidinedions 6 ADRs were reported from 73 prescriptions and the incidence rate of ADR with Thiazolidinedions was 8.2%. In case of Alpha-glucosidase inhibitors 4 ADRs were reported from 31 prescriptions and the incidence rate of ADR with Alpha-glucosidase inhibitors is 12.9%. Therefore metformin is considered as the safest drug when compared to the newer classes of drugs and is prescribed more commonly.

CONCLUSION

ADRs are one of the drug related problems being considered as the important challenge for drug safety. The stimulated spontaneous reporting used in the present study turned out to be a pragmatic method which allowed the detection and characterization of ADRs. The present study has provided baseline information about the prevalence of ADRs and their distribution among different age groups, genders, organ systems affected, and therapeutic classes of medicines. The data presented here will be useful in future, long term and more extensive ADR monitoring in the hospital and will be useful in framing policies towards rational use of drugs. However, monitoring of adverse drug reactions is an ongoing, ceaseless and continuing process. Since newer and newer drugs hit the market, the need for pharmacovigilance grows more than ever before. Monitoring of ADRs in patients using anti-diabetic agents is a matter of importance since such medications have to be taken lifelong so it is very essential to monitor since it is well known to cause ADRs like GI disturbances, edema, hypoglycemia, weight gain etc.. On balance, this study suggests that hospital- based monitoring is a good method to detect known and unknown links between drug exposure and ADRs. A close relationship also needs to be created between doctors and pharmacovigilance centers, and the attitudes of residents and doctors to ADR monitoring must change so that they perceive this as an integral part of their clinical activities. There is a need to inform the treating doctors about the importance of observing for ADR following pharmacotherapy, recording them meticulously, and reporting them to the concerned authority. This practice will prove to be very valuable in making the drug therapy safer and rational. So in future a comprehensive sensitization Programme is required in each step of health care system right from treating doctors, nurses, paramedics, and drug dispensing pharmacist to ensure better and safe pharmacotherapy and improve compliance of patients.

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