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Original Article

Monitoring of Adverse Drug Reactions to Oral Hypoglycaemic Drugs in a Tertiary Care Hospital: A Prospective Study

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ABSTRACT

Background: ***Objective:*** *To monitor and evaluate adverse drug reactions (ADRs) of hypoglycemic drugs in type II diabetics by spontaneous ADR monitoring.* ***Methods:*** *450 diabetic patients on who are on oral Hypoglycemic drugs were evaluated prospectively in a cross-sectional study over a period of six months. Details of adverse event history, history of medication suspected of having caused the ADR were recorded in the format followed in the Pharmacovigilance Programme of India. The causality relationship was assessed by the scale prescribed by World Health Organization-Uppsala Monitoring Centre criteria..* ***Results:*** *A total of 450 patients were screened, of which 57 were suspected of having at least one ADR. Metformin contributed highest number of ADR reported, in the form of dyspepsia, vomiting and diarrhea, followed by glimepiride-induced hypoglycemia. SLGT-2 -induced Urinary Tract Infection, pioglitazone-induced pedal edema were also reported.* ***Conclusion:*** *ADRs due to hypoglycemic drugs is a frequent problem. ADR reporting is needed to develop a strong ADR database in India.*

Keywords: *Hypoglycaemic drugs, Adverse Drug Reaction, Pharmacovigilance.*

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INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally and has reached epidemic proportions in many countries.[1,2] Worldwide, 415million individuals have affected and therefore the range of individuals with the disease is about to rise on the far side 642 million by 2040.[3] In India, more than 65.1 million individuals have been diagnosed with the disease[4] and the estimates suggest 89 million patients by 2030 and about 56 per cent patients will be from urban regions.[5] Similar to alternative countries, the aetiology of polygenic disorder in India is complex and includes genetic factors as well as environmental influences like blubber related to rising living standards, steady urban migration and lifestyle changes.

The conventional options for type 2 diabetes mellitus include drugs that have been relatively long on the market such as biguanides, sulfonylureas, alpha-glucosidase inhibitors, meglitinides and thiazolidinedione. In spite of efficacy in achieving glycemic control, there are some safety issues with conventional antidiabetic drugs.

Apart from the conventional oral hypoglycaemic drugs which have been in the market for a long time, there are a number of new drugs that have been introduced during the last decade of which safety is established in clinical trials but there surveillance is needed for reporting newer adverse effects which are not documented yet.

Sodium glucose cotransporter-2 (SGLT-2) inhibitors are a new class of glucose-lowering agents that reduce hyperglycaemia in

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patients with T2DM by reducing renal glucose reabsorption, as a result, they increase urinary glucose excretion. The available data for SGLT-2 inhibitors: canagliflozin and dapagliflozin, suggests a good tolerability profile. The most frequently reported adverse events with these are female genital mycotic infections, urinary tract infections and increased urination. Owing to the fact that the newer oral anti-diabetic drugs have been in the market for last few years only, the data regarding their safety is limited particularly in Indian population.

Therefore, the detection of adverse drug reactions (ADR's) through Pharmacovigilance has become increasingly significant. Hence, the present study is planned to actively generate data on the safety profile of currently prescribed newer oral anti-diabetic drugs in diabetic Indian population by monitoring of ADR's.

METHODS

STUDY DESIGN

This study involved active Pharmacovigilance monitoring of prescribed oral anti-diabetic drugs in the outpatient department of Government Kilpauk Medical College Chennai between May to Oct 2018. The Study was conducted in accordance with the principles of good clinical practices (GCP).

All suspected ADR's were initially assessed by the attending Physician and subsequently the information was collected and analyzed by the pharmacologists for causality assessment. Patient details (age, sex, body weight), adverse event history, history of medication suspected of having caused the ADR, including its onset, duration, temporal association with drug intake if any and details of concomitant medication use, were recorded in the format followed in the Pharmacovigilance Programe of India [6]. The causality relationship among ADR and drug was assessed by the WHO-Uppsala Monitoring Centre (WHO-UMC) criteria.[7] Suspected ADRs with causality status less than "possible" were not analyzed further.

RESULTS

A total of 450 patients were screened for the study, of which 57 (11.2%) was suspected to have at least one ADR to oral hypoglycemic agents. On causality assessment, 19 of these 57 cases (33.92%) were considered to have insufficient evidence about causality (WHO-UMC causality status "unlikely") and they were excluded from further analysis. Out of the remaining 37 patients analyzed, 37 suspected ADRs were detected. Few patients had reportable the presence of quite one ADR, either due to single drug use or due to multiple antidiabetic drug use.

No ADR encountered was found to be fatal, life-threatening, or required hospitalization for management. None of the ADRs was labelled "Certain" as rechallenge in the same dose, was not attempted by the attending physician, once a drug was withdrawn. Out of 450 patients, 262 were male, and 238 were female. The average age of the patients were 42.62 among 57 patients, who had ADR, 26 patients were male, and 31 were female. Percentage of ADR occurrence among all male patients was 45.61%, and among female, it was 54.38%. Out of 450 patients, 463 patients were given metformin dose varied from 450 mg/day up to 2 g/day.

Out of them, total 28 patients (11.21%) reported one or more adverse effect after use of this drug. Among them, there were 16 incidents of dyspepsia, 4 incidents of diarrhoea, and 8 incidents of nausea, vomiting. A total of 428 patients were given glimepiride in the study group; dose varied from 1 to 2 mg/day. Among them, 6 patients had some symptoms of hypoglycemia (sweating, tremor and dizziness) and 2 patients complained about weight gain after the use of glimepiride. Hence, total 8 patients (12.74%) had some adverse event due to glimepiride use. A total of 32 patients were given SLGT 2 for controlling postprandial hyperglycemia. Among them, 3 patients (27.76%) reported to have Urinary Tract Infection. And 2 patients reported Halitosis. Pioglitazone was given in 7 patients. 2 of them (16.31%) had complained about pedal edema. All of them occurred in the dose of 15 mg/day.

DISCUSSION

The present study has reported the incidence and attempted to profile suspected ADRs due to antidiabetic drugs in the diabetes OPD setting in a tertiary care Hospital. Evaluation of ADRs is an important criteria to be included during the assessment of risk factors to ensure maximum benefits of drug therapy. More data on prescribed drugs and their side effects will help in reducing the ADR occurrence and ensure patient safety. In our study also, dyspepsia and diarrhea were the most common adverse effect reported by patient to doctors, mostly due to metformin, followed by glimeperide. Glimepiride alone or its combination with antidiabetic caused many incidence of symptom, all of them have occurred if glimepiride was used with dose of two mg/day.

Metformin-induced dyspepsia occurred only if it was used in dose more than 1000 mg/day. In our study no serious events recorded, may be due to insulin was kept out of the measurement, which is the most common agent to cause hypoglycemia. Most of the adverse effects were managed by reducing the dose of the drug, and in some cases by stopping the drug such as stopping glimepiride if patient had prolonged hypoglycemia.

Our study had some limitations, the patients were screened on one fixed day of each week, and this could introduce potential bias in the sample. Being an OPD-based study, it is likely that we have missed ADRs that were transient or too mild to motivate the patient to report to the doctor on the next hospital visit. ADRs can perhaps also be reduced using less medication and with adequate knowledge of drug interactions8. An ant diabetic drug ADR database built up on the basis of such studies conducted across multiple centers, through active collaboration of diabetologists and pharmacologists can be a worthy long-term goal in the Indian context.

CONCLUSION

ADRs due to Oral hypoglycaemic Agents are quite common. Though they are not likely to be life-threatening, they can cause various discomforts in patients who consume it. Notifying ADRs to adverse events monitoring centres can help in the safe use of drugs. Even though the population involved in this study were very less it gives an idea about the prevalence of ADRs with oral hypoglycaemic agents with their causal relationship with drug and severity. Large scale studies will surely help in bringing out the more Unknown ADR's.

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