Prescribing Trends of Drugs and Assessment of Adverse Drug Reactions in Patients with Diabetes

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Abstract

Objective: The present study was conducted to analyzethe prescribing pattern of anti-diabetics and to assess incidence of adverse drug reaction (ADR) in diabetic population at our hospital setting.**Methodology**: An observational study was conducted on Type 2 diabetes mellitus patients on oral antidiabetic agents, attending Tertiary Care Hospital in Bangalore between November 2015 and April 2016.Patient demographics, pattern of prescription including details of adverse event history, were recorded in ae-designed data collection form. The causality relationship was assessed by the World Health Organization-Uppsala Monitoring Centre criteria. **Results:**A total of 52.67% of patients received Oral Hypoglycemic agents alone. The incidence of adverse drug reactions (ADRs) amongst the study population was found to be 33.33%. Males experienced majority of ADRs (54%) followed by females (46%). Major ADRs included hypoglycemia (54.23%) followed by giddiness (10.17%) and weight loss (8.47%).The prescribing pattern of anti-diabetics was to be in line with recommendations by American Diabetes Association. **Conclusion:** Early detection and management of ADRs along with constant monitoring and active intervention ensures patient safety and better prognosis.

Key Words: *Diabetes, Adverse Drug Reaction, Oral Hypoglycemic Agents*

1. INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally and has reached widespread proportions in both the developed and developing countries[1,2]. Worldwide, 415 million people are diabetics and the number of people with the disease is set to rise beyond 642 million by 2040 [3]. In India, more than 65.1 million individuals have been diagnosed with the disease and the estimates suggest that 89 million patients may developby 2030[4,5]. The etiology of diabetes in India is multifactorial. This includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes[6] . Ideally, the initial management of diabetes should be based on dietary therapy combined with increased physical activity. However, pharmacological therapy (oral hypoglycemic agents or insulin) may be considered in the presence of marked hyperglycemia. Oral hypoglycemic drugs (OHA) are considered only after a regimen of dietary treatment combined with exercise has failed to achieve the therapy targets. There are two major groups of OHA: sulphonylureas (SUs) and biguanides (BGs). On unachieved glycemic control, introduction of insulin either alone or in combination with the oral agent is the preferred choice of therapy according to American Diabetes Association (ADA) [7]. Diabetes accounts for complications such as micro vascular and macro vascular. Intensification of treatment with more than

one diabetic agent with or without insulin is seen in patients who are predisposed to develop micro and macro vascular complications which may also potentiate the chances of developing adverse drug reaction (ADR). According to World Health Organization (WHO), ADR is defined as "a noxious, unintended, and undesirable effect that occurs as a result of dose normally used in man for diagnosis, prophylaxis, and treatment of disease or modification of physiological function.[8] Pharmacovigilance of anti-diabetic drugs can play a decisive role in detecting adverse drug reactions (ADRs) and providing feedback to physicians on the possibility and details of such events, thereby protecting the patients from avoidable harm. In India, pharmacovigilance activities are still in budding stage and initiatives are being taken for spontaneous ADR reporting under the Pharmacovigilance Programme of India[9].The present study was carried out to assess the prescribing pattern of anti-diabetics and ADRs at our hospital setting.

2. MATERIALS AND METHODS

The present, prospective, observational study was carried out at a tertiary care hospital in Bangalore, South India, between November 2015 to April 2016. All patients of either gender suffering from diabetes mellitus attending endocrinology OPD and those treated with insulin alone or OHAs alone or combination of insulin with OHAs were included in the study. The study population was further categorized into three different groups based on the prescribed medications such as Group-I (Insulin alone), Group-II (OHA alone) and Group-III (Insulin+OHA). The patients treated on inpatient basis and non-cooperative subjects were excluded. The study was approved by Institutional Ethics

Committee. The disease history and demographic details were taken and recorded in suitably designed data collection form. Complete data on medications were collected. In case of ADR details including the nature of reaction, date of onset, severity, treatment drugs, suspected drug including its dose, pharmaceutical form, route of administration and list of concomitant drugs were recorded in ADR documentation form. Any ADRs occurring in patients during the study period were reported using Central Drugs Standard Control Organization (CDSCO) adverse drug event reporting forms. Causality assessment was done as per the Naranjo's scale and WHO probability scale, severity assessment using Modified Hartwig and Siegel's scale and Preventability assessment as per Modified Schumock and Thornton Scale was conducted.

3. RESULTS AND DISCUSSION

A total of 150 patients were screened during the study. The patients were divided into 4 age groups and incidence of T2DM was highest in 41-60 years (54%) followed by 61-80 years (28%). 46.67% of the study population were found to be associated with either one or more diabetic complications. Among the different documented complications, diabetic foot ulcer 45.71%) was of greater occurrence followed by diabetic nephropathy (20%), diabetic retinopathy (18.57%) and diabetic neuropathy (15.71%). Majority of the patients belonged to group II as they received OHA alone (52.66%) (Table.1). Further, analysis of group II showed biguanides (39.74%) was the most prescribed OHA followed by sulfonylureas (20.53%), di peptidyl peptidase-4 inhibitors (8.6%) and alpha glucosidase inhibitors (3.98%). Metformin was the majorly prescribed drug (39.74%) in fact the only biguanide and the same was used in combination OHAs in higher frequency (96.55%).

The incidence of ADR in the study population was found to 33.33% (50/150) with a male predominance (54%). A total of 60 reactions was identified wherein major ADRs included hypoglycemia (54.23%), followed by giddiness (10.17%), weight loss (8.47%), tiredness (6.78%), diarrhea (5.08%), constipation (3.39%), fatigability (3.39%), acanthosis Nigricans (3.39%), weight gain (1.7%), heartburn (1.7%) and gastritis (1.7%).

Classification of ADRs according to drug class denoted that 47.45% of drug was a combination of Oral hypoglycemic agent with Insulin preceded by Metformin (23.72%), and Insulin alone (22.03%), Glimepiride (5.08%) and Voglibose (3.39%).(Table.2)

Assessment of causality of ADRs using Naranjo and WHO probability scales showed 45.7% and 28.8% as probable respectively. Majority of ADRs were found to be severe (54.25%) followed by mild (30.50%) and moderate (15.25%) upon severity assessment (Fig1). The reactions were categorized reactions as definitely preventable (66.1%), probably preventable (15.25%) and non-preventable (18.25%) by using Modified Schumock and Thornton Scale. None of the ADRs were fatal.

Amongst the subjects with ADRs, 23.7% of the subjects were continued with the suspected drug without any active intervention while drug dose adjustments were done in 54.2%, symptomatic treatment was provided for 22% of the subjects.

Diabetes mellitus, a metabolic disorder requires long term treatment with anti-diabetics with or without insulin along with life style modification to prevent the life threatening complications. Selection of anti-diabetic therapy depends on the type and severity of the disease. In our study setting maximum number of patients received by OHA + Insulin (47%) followed by OHA alone (37%). Among the patients who received OHA, biguanides and sulfonyl ureas was found to be 39% and 20.53% which is in contrast to study by Bela[10].The incidence of ADR in our study was encountered to be 33.33% while a study done by Singh and Dwivedi showed 11.8%[11]. The percentage of ADRs was found to be the highest (47.45%) in patients receiving both Insulin and OHA. This might reflect the usage of multiple drugs in order to treat the concurrent complications in diabetic patients. Among OHAs metformin attributed to 23.72% of ADRs while a study conducted by Sheehan reported it as 30% wherein the main side effect of metformin reported was gastrointestinal disturbances (nausea, abdominal pain, diarrhea)[12].

Table 1. Showing categorization of patients based on treatment

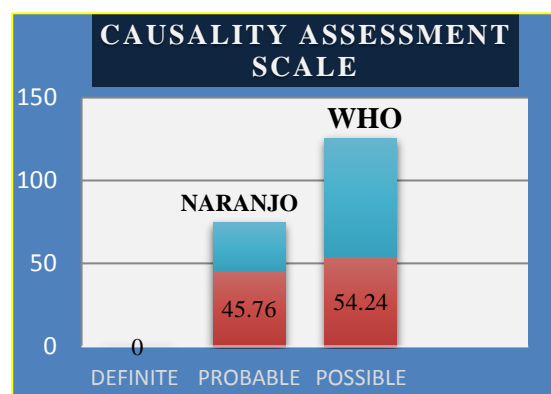| Treatment groups	N	%
Group I (insulin alone)	22	14.67
Group II (OHA alone)	79	52.67
Group III (insulin+ OHA)	49	32.66
TOTAL	**150**	**100**

OHA- Oral hypoglycemic drugs

Fig. 1 ADR causality assessment

This can be reduced, by slowly increasing the dose i.e. by 500mg per day every 1 to 2 weeks and also by counselling the patient to take the drug with food.Hypoglycemia was the commonest ADR (54.2%) reported andhighest (22%) in patients receiving insulin compared to other anti-diabetics which is consistent to a study conducted by Yale in 2005 (34%)[13].

Table 2. Drugs involved and their adverse reaction details

Drugs involved	Reaction details*	Total % of patients
Insulin	Hypoglycemia (n=5), Acanthosis nigricans (n=2), Giddiness (n=3), Tiredness (n=2), Fatigability (n=1)	22.03 ± 0.08
Metformin	Weight loss (n=5), Diarrhoea (n=2), Constipation (n=2), Hypoglycemia (n=2), Heartburn (n=1), Tiredness (n=1) Fatigability (n=1)	23.72 ± 0.05
Glimepiride	Hypoglycemia (n=2), Weight gain (n=1)	5.08 ± 0.01
Voglibose	Gastritis (n=1), Diarrhoea (n=1)	3.39 ± 0.03
Ohers (Insulin/ Combination OHAs)	Hypoglycemia (n=23), Giddiness (n=3), Tiredness (n=2)	47.45 ± 0.09

Hypoglycemic episodes have a major negative impact on the quality of life and safety of people with DM. In T2DM the use of OHA, inadequate calorie intake, exercise, medication use errors, and intercurrent illness contributes to hypoglycemic events[14]. In severe conditions hypoglycemia can cause seizures, coma and death more frequently in patients with T1DM as compared to T2DM[15]. The other frequently monitored adverse events are diabetic ketoacidosis (0.43%), weight gain (2.1%), lipodystrophy (1.17%) and injection site reactions[16].

4. CONCLUSION

Diabetes is a disease of metabolic dysregulation that presents with abnormal glucose metabolism, accompanied by long term complications. Early detection and tight glycemic control is advocated in diseased individuals using lifestyle modification and anti-diabetics in order to prevent the macro and micro vascular complications. ADRs due to antidiabetic drug although not fatal may cause a sense of aversion towards the therapy which may lead to discontinuation of the medications. Further studies can be conducted in other health care settings to identify the prescribing behavior of anti-diabetics and pattern of ADRs.

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