Clinical Utilization Pattern of Multiple Strengths of Glimepiride and Metformin Fixed Dose Combinations in Indian Type 2 Diabetes Patients

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Abstract

Background: In Indian clinical set-up, modern sulfonylurea, particularly glimepiride is still preferred as an add-on to metformin due to its efficacy, safety and cost effectiveness. In view of this, a case-based questionnaire survey was conducted to analyze the clinical utility of multiple strengths of glimepiride and metformin fixed dose combination in type 2 diabetes mellitus (T2DM).

Methods: The case-based questionnaire survey was conducted with 174 health care professionals across India to assess the use of glimepiride and metformin fixed dose combination according to age, duration of diabetes, body mass index (BMI), diabetes complications, concomitant medications like insulin, and statin.

Results: Overall, data from 2248 patients taking multiple strengths of glimepiride and metformin fixed dose combination were analyzed. All the doses were prescribed across all the age groups and irrespective of duration of diabetes. Overall, 1429 diabetes patients had body mass index (BMI) ≥25 kg/m², among which 1176 (81.6%) patients were receiving combination of glimepiride 1 or 2 mg and metformin 500 or 850 or 1000 mg. Glimepiride and metformin fixed dose combinations were among the preferred choices in various complications like neuropathy, retinopathy, nephropathy, peripheral vascular disease, diabetic foot and cardiovascular disease. Insulin and statins were co-prescribed in 17.3% and 28.8% patients, respectively. Hypoglycemic episodes were reported in only a minority of patients, even with higher doses of glimepiride and metformin fixed dose combinations.

Conclusion: Multiple strengths of glimepiride and metformin fixed dose combinations are beneficial in T2DM, irrespective of age, duration of diabetes, BMI, diabetes complications, use of concomitant medications such as insulin and statin. Glimepiride and metformin fixed dose combinations were not associated with a significant risk of hypoglycemia.

Introduction

India is considered a major center for the global diabetes epidemic, home to 77 million adults with diabetes and the largest contributor to mortality (>1 million) attributable to diabetes and related complications. Metformin and Sulfonylurea (SU) like Glimepiride are one of the key pharmacotherapeutic agents in T2DM management. Several studies have reported the superiority of combination therapy consisting of SU and metformin for effective diabetes management. Glimepiride and metformin may be an ideal combination therapy, which promotes insulin secretion, improves insulin resistance, minimizes medication burden, improves treatment adherence and being cost effective. A real-world study showed that diabetes patients on glimepiride were associated with good clinical efficacy, lower mortality with reduced cardiovascular event risk. Similarly, glimepiride and metformin fixed-dose combination therapy is more effective in glycemic control than metformin up-titration, and is well tolerated in T2DM patients inadequately controlled on low-dose metformin monotherapy. Also, the Indian consensus recommends that SUs, as add-on to metformin, is a reasonable option for countries with high disease prevalence and resource constraints. In India, glimepiride and metformin fixed-dose combinations are widely used due to its availability in multiple strengths. This provides an ease of up-titration and down-titration for practicing physicians. To the best of our knowledge, no study has assessed the clinical usage pattern of multiple strengths of glimepiride and metformin fixed-dose combination in India. Therefore, a case-based questionnaire survey was conducted to analyze the clinical utility of multiple strengths of glimepiride and metformin fixed-dose combination in Indian T2DM patients.

Material and Methods

The case-based questionnaire survey was designed to assess the clinical utilization pattern of multiple strengths of glimepiride and metformin fixed-dose combination in T2DM. The survey questionnaire was administered to 174 health care professionals (endocrinologists, diabetologists, and physicians) across various geographical locations of India. Each doctor completed approximately 10 to 15 case profiles. A total of 2248 completed forms were collected and further descriptive analysis was performed. The results were expressed in percentages based on the responses for each question.

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Multiple strengths of glimepiride and metformin fixed-dose combination

Based on the strength of glimepiride in the combination, five groups were formed for analysis:
- Group 1 (Glimepiride 0.5 mg + Metformin 500 or 1000 mg)
- Group 2 (Glimepiride 1 mg + Metformin 500 or 850 or 1000 mg)
- Group 3 (Glimepiride 2 mg + Metformin 500 or 850 or 1000 mg)
- Group 4 (Glimepiride 3 mg + Metformin 850/1000 mg)
- Group 5 (Glimepiride 4 mg + Metformin 1000 mg)

Analysis parameters

The therapeutic utilization of multiple strengths of glimepiride and metformin fixed-dose combination was analyzed based on the age of the patient, duration of diabetes, Body Mass Index (BMI), diabetes complications, hypoglycemic episodes, and concomitant medications (insulin and statin).

Results and Discussion

Strength usage

Overall data from 2248 subjects was evaluated and the usage pattern is as shown in Figure 1. A strength of glimepiride 2 mg + metformin 500/850/1000 mg combination was most widely used in 44% diabetes patients, followed by strength of glimepiride 1 mg + metformin 500/850/1000 mg combination in 38%, a strength of glimepiride 0.5 mg + metformin 500/1000 mg combination in 9%, and glimepiride 3 mg + metformin 850/1000 mg combination in 7% patients; the least used strength was glimepiride 4 mg + metformin 1000 mg combination, in only 2% of diabetes patients.

Clinical usage pattern of multiple strengths of glimepiride and metformin fixed-dose combinations

Age of type 2 diabetes patients

Diabetes is a progressive disease and there exists a difference in the pathophysiology of T2DM in older and younger individuals. In India, unlike the western countries, diabetes is characterized by an early onset at a relatively young age, which might be due to insufficient β-cell mass, functional defects of β-cells, or both. Therefore, the American Diabetes Association (ADA) advises the use of early combination therapy including drugs with a complementary mechanism.6

In our survey, 18.2% patients belonged to the age group of 18–44 years, 60.8% to the 45–64 years and 21% belonged to ≥65 years. The analysis showed that all the available strengths of glimepiride and metformin fixed dose combinations were safely prescribed for diabetes management in the young as well as the elderly population. In the elderly population (≥65 years), Glimepiride (1–2 mg) + Metformin (500–850–100 mg) combinations were the most commonly prescribed strengths by physicians (Table 1).

Duration of diabetes

The duration of diabetes has significant clinical and public health-related implications.1 Published evidence suggests that SUs may lose durability over the years due to β-cell exhaustion. However, SUs and metformin combination has been studied for glycemic control durability for 5 years7 and >10 years.8 A study by Srivanichakorn W et al., suggested that there is no rationale for withdrawing the SU component even after 17 years of combination therapy.9 In the most recent cardiovascular outcome trial (CVOT) CAROLINA, the median duration of diabetes at baseline was 6.3 years in the linagliptin group (n = 3001) and 6.2 years in Glimepiride group and later, medication exposure was 5.9 years in both the groups.10

In the current survey, 5.71% of patients were newly diagnosed, 26.97% patients had diabetes for <5 years, 40.7% patients had diabetes for 5–10 years, and 19.88% patients had diabetes for >10 years. Results showed that all the strengths of glimepiride and metformin combination were used across diabetic patients irrespective of duration of diabetes. However, newly diagnosed patients and patients with <5 years of diabetes duration received relatively lower doses of glimepiride and metformin fixed dose combination, as compared to diabetes patients with >10 years diabetes duration. In group

![Table 1: Usage of glimepiride and metformin fixed dose combinations based on age](image)
1. 64.1% patients were newly diagnosed or had diabetes for <5 years, while 79% and 82% diabetes patients had diabetes duration of >5 years in group 4 and 5, respectively (Figure 2).

BMI of diabetes patients

Obesity is one of the major risk factors for T2DM. Being overweight and especially obese, particularly at younger ages, substantially increases the lifetime risk of diabetes. Data from clinical trials showed that long-term use of metformin stabilizes the BMI and improves body composition in the adolescent obese patients while the modern SUs are weight neutral.

In this survey, 16.9%, 19.5% and 63.6% of the diabetes patient population had BMI ≤23, 23–25 and ≥25 kg/m², respectively. Overall, 1429 diabetes patients had BMI of ≥25 kg/m²: among whom 119 (8.3%) patients were on glimepiride 0.5 mg + metformin 500–1000 mg combination, 509 (35%) patients were on glimepiride 1 mg + metformin 500–850–1000 mg combination, 667 (46.6%) patients were on glimepiride 2 mg + metformin 500–850–1000 mg combination, 99 (6.9%) patients were on glimepiride 3 mg + metformin 850–1000 mg combination and 35 (2.4%) patients were on glimepiride 4 mg + metformin 1000 mg combination (Table 2). Our result was also in accordance with a SUs consensus statement of South Asia (SAFES), which recommends the use of modern SUs (glimepiride) over conventional SUs even in overweight/obese T2DM patients.

Diabetes Patients with Complications

Diabetes patients are at risk of developing micro- and macro-vascular complications due to inadequate glycemic control as well as multiple cardiovascular (CV) risk factors. In the present survey among 2248 diabetes patients, 27% had neuropathy, 14.5% had retinopathy, 9.3% nephropathy, 6.3% had peripheral vascular disease, 6% had diabetic foot, while 15.7% had cardiovascular disease (CVD). In this population with diabetes related complications, multiple strengths of glimepiride and metformin fixed dose combinations were among the preferred choice of drugs for blood glucose control and to reduce diabetic complications (Table 3).

Concomitant Statin Therapy

Diabetes is considered coronary heart disease (CHD) risk equivalent. Statin therapy should be added to lifestyle therapy, regardless of the baseline lipid levels for patients with diabetes. High-dose statin therapy is recommended by the ADA for all patients with diabetes with a history of clinical atherosclerotic CVD or with at least one additional CVD risk factor. Moderate-dose statin therapy is suggested for patients younger than 40 or older than 70 years, who have CVD risk factors. The benefits of statin therapy in primary and secondary prevention in patients with diabetes is well established and supported by robust data from randomized, controlled trials and national and international guidelines.

In the current survey, only 648 patients (28.8%) were on statins. Statin treatment was used along with glimepiride and metformin fixed dose combinations in 24%, 25.6%, 32.8%, 26.7% and 31.5% patients in Group 1, Group 2, Group 3, Group 4 and Group 5, respectively. There is an urgent need to improve statin usage in diabetes patients, especially as primary prevention to ensure more cardio-protection.

Hypoglycemia in Diabetes Patients

Hypoglycemia is a major limiting factor in tight glycemic management.
of diabetes and may increase vascular events in addition to other possible detrimental effects. The risk of severe hypoglycemia is higher in the elderly patients. However, a consensus statement of South Asia recommends modern SUs (glimepiride) over conventional SUs in T2DM patients due to less risk of hypoglycemia.

In this case-based questionnaire survey, out of 2248 patients, only 142 patients (5.8%) experienced a hypoglycemic event (in the last 12 months); no hypoglycemia was observed in low-dose glimepiride 0.5 mg + metformin 500 mg combination group (Figure 4).

Conclusion

Glimepiride and metformin fixed dose combinations are widely used in clinical practice due to good glycemic control, minimal risk of hypoglycemia and weight gain, neutral nature with respect to cardiovascular risk, and cost effectiveness. The current case-based questionnaire analyzing data from 2248 patients showed that multiple strengths of glimepiride and metformin fixed dose combinations are prescribed in T2DM patients irrespective of age, duration of diabetes, BMI, diabetes complications, use of concomitant medications such as insulin and statins, and is devoid of risk of hypoglycemia.

Limitation

In our study, we could not correlate the glycemic control achieved by different glimepiride and metformin fixed dose combinations, as glimepiride and metformin fixed dose combinations have been prescribed with other oral antidiabetic drugs. Also, the daily frequency of dose administration was different for different patients and lastly, the duration of treatment period was not defined.

What’s New

- In clinical practice, high doses of glimepiride (2/3/4 mg) and metformin (500/850/1000 mg) fixed dose combinations are widely used even in patients with BMI ≥25 kg/m², highlighting its weight neutral benefit.
- In elderly population (>60 years), glimepiride and metformin fixed dose combinations are widely prescribed, highlighting the safety.
- High doses of glimepiride (2/3/4 mg) and metformin (500/850/1000 mg) fixed dose combinations are also used in combination with Insulin, highlighting its weight neutrality and less hypoglycemic risk.

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