Epidemiologic Surveillance of Glycemic Response to a Scored, Breakable, Extended Release, Fixed Dose Combination of Gliclazide and Metformin in Persons with Type 2 Diabetes

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Abstract

Background: The combination of metformin and a sulphonylurea has been recommended for treatment of type 2 diabetes. A, scored, breakable, extended release, once daily fixed dose combination (FDC) of gliclazide and metformin is available in India.

Objective: To assess the initial blood glucose lowering efficacy, glycemic control and patient acceptability of the fixed dose combination of original gliclazide 60mg and metformin 500mg in an extended release, scored and breakable formulation (in a range of 1, 1½, and 2 tablets) among Indian patients in day to day practice.

Methods: In a multi-center epidemiologic surveillance protocol of 60 days, patients with type 2 diabetes were prospectively prescribed 1 to 2 tablet of gliclazide 60mg + metformin 500mg during the course of study. The possibility of breaking the tablet in two equal halves enabled administration of 1½ tablets wherever required. Primary data on fasting plasma glucose response and adverse events was extracted for analysis from the case records of patients kept with the investigators. The primary outcome was the proportion of patients achieving glycemic control, defined as fasting plasma glucose of 90-130 mg/dl at the end of the study.

Results: Of the 759 patients treated with an extended release FDC of gliclazide 60mg + metformin 500mg, the number (%; 95% CI) which achieved glycemic control was 474/759 (62.5%, 59.0% to 65.8%). The proportion controlled with 1 tablet was, 252/759 (33.2%, 29.9% to 36.6%); with 1½ tablets, 149/298, (50.0%, 44.3% to 55.6%); and with 2 tablets, 73/94, (77.5%, 68.2% to 85.0%). Mean (95% CI) FPG mg/dl decreased from baseline by 48.7 (45.0 to 51.4) with 1 tablet; by 71.3 (66.0 to 76.6) with 1½ tablets; and by 86.3 (75.7 to 96.9) with 2 tablets. Frequency of hypo-glycaemia was 0.7%.

Conclusion: Extended release FDC of gliclazide 60mg + metformin 500mg, a scored, breakable, once daily, formulation was effective in controlling blood glucose in a large proportion of type 2 diabetes with a low risk of hypoglycaemia.

Editorial Viewpoint

• Various combinations of metformin and sulphonylurea are being used in type 2 diabetes.

• This study specifically assesses gliclazide with metformin and finds it effective with a low risk of hypoglycaemia.

Introduction

In Indian metro cities, every one in five persons has diabetes, and this proportion is growing at an alarming rate of 28%.¹ Of these patients, about 80% receive an oral hypoglycemic treatment. However, with a low compliance rate of 41%, only 37% have their blood glucose under control.² Most patients are diagnosed and treated by general physicians in primary care practice, and a major concern is to make the treatment of type 2 diabetes more effective in this setting.

Towards this goal, recent treatment guidelines recommends dual drug medication that includes metformin to rapidly achieve glycemic control.³⁵ To make this strategy more effective, a single tablet with dual drug formulation may offer greater efficacy because

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of better patient compliance than two drugs given separately.7

Among the sulphonylureas (SU), gliclazide is a good option for combination with metformin because of its association with significantly less cardiovascular risk,8 comparatively infrequent hypoglycemia9 and proven long term ability to achieve and maintain tight glycemic control.10

An FDC of gliclazide extended release 60mg and metformin extended release 500mg is available in India. The novelty of this formulation is that both agents have similar pharmacokinetic attributes that support once daily administration. Further, the tablet is scored and breakable into two identical halves. This has the potential to allow a simple 2 step up titration from 1 to 1½ to 2 tablets (gliclazide 60, 90, 120mg and metformin 500, 750, 1000mg respectively) of both drugs simultaneously for rapid glycemic control.

The aim of this surveillance was to monitor initial glycemic control in type 2 diabetic patients receiving treatment of FDC of gliclazide extended release 60mg + metformin extended release 500mg, in daily practice.

Patients and Methods

Selection of Patients
Participants diagnosed with type 2 diabetes by each investigator in their daily practice were identified. Of these, patients who could prospectively receive, in the clinical judgment of the investigator, 1 tablet of FDC of gliclazide extended release 60mg + metformin extended release 500mg, were selected for surveillance.

Surveillance
Primary data was extracted from the case records of selected patients kept by the investigators. Information was collected on demographic, clinical and fasting plasma glucose (FPG) at the start of treatment. At follow up visits after 15, 30 and 60 days - FPG, the prescribed dose of FDC of gliclazide extended release 60mg + metformin extended release 500mg (1, 1½ or 2 tablets) and adverse events were ascertained.

Statistical Analysis
The primary outcomes were the number of patients achieving glycemic control (FPG 90-130mg/dl) on an intention to treat basis, mean change in FPG from baseline and frequency of side effects. Categorical data was expressed as percentages with their 95% confidence interval (CI), and changes in FPG as means with their 95% CI.

Results

Eighteen investigators maintained surveillance on FPG and adverse effects in 759 type 2 diabetic patients who received 1 tablet, or subsequently, the stepped up doses of 1½ and 2 tablets of FDC of gliclazide extended release 60mg + metformin extended release 500mg over 60 days (Table 1).

At baseline, the mean (SD) age of the patients was 50.0 (±10.0) years, of whom 293 (39.3%) were females.

Table 1: Surveillance flow chart

<table>
<thead>
<tr>
<th></th>
<th>Day 15</th>
<th></th>
<th>Day 30</th>
<th></th>
<th>Day 60 end of surveillance</th>
</tr>
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<tbody>
<tr>
<td>Lost to follow up</td>
<td>40</td>
<td>3</td>
<td>1</td>
<td></td>
<td>1 lost to follow up</td>
</tr>
<tr>
<td>FPG target</td>
<td>252 at FPG target</td>
<td>467 not at FPG target</td>
<td>298 prescribed 1½ Tablets*</td>
<td>73 at FPG target</td>
<td></td>
</tr>
<tr>
<td>Prescribed</td>
<td>1½ Tablets*</td>
<td></td>
<td></td>
<td>2 Tablets*</td>
<td>20 not at FPG target</td>
</tr>
</tbody>
</table>

*An FDC of gliclazide extended release 60 mg and metformin extended release 500 mg FPG = Fasting plasma glucose

Table 2: Baseline status characteristics of patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=759</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>50.0 +/- 10</td>
</tr>
<tr>
<td>Females</td>
<td>293 (39.3%)</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>23 +/- 38</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>199.5 +/- 52.9</td>
</tr>
<tr>
<td>Untreated</td>
<td>212 (30.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>281 (37.0%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>218 (28.7%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>265 (34.9%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>38 (5.0%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>5 (0.66%)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>11 (1.4%)</td>
</tr>
</tbody>
</table>

± values mean plus or minus standard deviation. All other values are number of patients with percentage of the group in parenthesis. MI=myocardial infarction

Mean FPG was 199.5 (±52.9) mg/dl. The number (%) with obesity was 265 (34.9%); Hypertension 281 (37.0%); dyslipidaemia 218 (28.7%); and renal impairment 11 (1.4%) (Table 2).

759 patients received the initial dose of 1 tablet. At the second visit on day 15, the number (%) with obesity was 252 (33.2%, 29.9 to 36.6%); 40 were lost to follow up and 298 received the up-titrated dose of 1½ tablets. At the third visit on day 30, the glycemic target was reached in 149 (50.0%, 44.3 to 55.6%); 3 were lost to follow up and 94 received the further up-titrated dose of 2 tablets. At the fourth visit on day 60, 73 (77.5%, 68.2 to 85.0%) could be brought under glycemic control. These rates for the three dosage strengths are mutually exclusive. Overall, 474/759 (62.5%, 59.0 to 65.8%) patients achieved glycemic control (Table 1, Figure 1).

Mean (95% CI) FPG mg/dl, decreased from baseline by 48.7 mg/dl (45.0 to 51.4) with 1 tablet; by 71.3mg/dl (66.0 to 76.6) with 1½ tablets and by 86.3mg/dl (75.7 to 96.9) with 2 tablets (Figure 2).

Hypoglycaemia and generalised weakness were reported by 2
patients (0.7%), but did not lead to discontinuation of treatment.

**Discussion**

In the primary care setting of India, about a third of persons diagnosed with type 2 diabetes identified for surveillance were obese, had hypertension, or gave a history of myocardial infarction. In these patients, treatment of type 2 diabetes with FDC of gliclazide extended release 60 mg + metformin extended release 500 mg was beneficial to patients. Within the range of 1 tablet (gliclazide 60 mg and metformin 500 mg) that could be up-titrated to 1½ tablets (gliclazide 90 mg and metformin 750 mg) and 2 tablets (gliclazide 120 mg and metformin 1000 mg), average FPG decreased by nearly half from baseline and about 6 out of 10 patients could be brought under glycemic control. This was achieved quickly and easily because of the simple two step titration of gliclazide and metformin simultaneously. Less than 1 out of 10 patients complained of symptoms suggestive of hypoglycaemia that were mild and did not lead to withdrawal of treatment.

The evidence suggests that gliclazide may be the preferred SU to pair with metformin, particularly for patients at high cardiovascular risk. Recent high quality observational data has shown that compared to metformin - glimepiride, glibenclamide and glipizide were significantly associated with increased all-cause and cardiovascular mortality. In contrast, results for gliclazide and repaglinide were not statistically different from metformin for both outcomes. This may be related to less hypo-glycaemia with gliclazide. In a rare direct head to head randomized comparison, glimepiride was associated with a seven fold greater risk of severe hypo-glycaemia than gliclazide.

Furthermore, in the ADVANCE study, intensive treatment with gliclazide safely reduced HbA1c to 6.5%, and significantly reduced the composite cardiovascular end point. The molecular basis for these observations may be related to the fact that unlike glibenclamide and glimepiride, gliclazide has an azabicyclo-octyl ring instead of a benzamido moiety that precludes its binding to cardiomyocytes.

The observed reduction in FPG is close to the upper 95% CI of the efficacy of SUs when added separately to metformin. In a meta-analysis of 27 trials, SUs added to maximum dose metformin decreased HbA1c by up to 0.97%. When HbA1c is in the range of 6-9%, this decrease is approximately equal to a FPG reduction of up to 104 mg/dl. Minimizing risk of hypo-glycaemia, prevents long term complications: The low frequency of hypo-glycaemia reported by patients is consistent with the previously reported risk with gliclazide, as being about half that of glimepiride and glipizide.

Against the backdrop of recent treatment guidelines that recommend dual drug treatment that includes metformin, for speedier blood glucose control, the possibility that a single tablet with dual drug formulation may offer greater efficacy and safety than the two drugs given separately has been reported. The FDC formulation of gliclazide extended release 60 mg + metformin extended release 500 mg as a single scored and breakable tablet for once daily administration, together with a two step up-titration involving between 1 to 2 tablets may serve to explain its high hypoglycemic efficacy within a short interval of time.
The surveillance has limitations. Patients were not randomly selected and many uncontrolled patients did not receive the up-titrated doses of gliclazide extended release 60mg + metformin extended release 500mg FDC. The results are limited in scope to initial blood glucose response to treatment and reported side effects. However, patients received treatment under conditions reflective of primary care practice, and responded with a two-fold increase in glycemic control over the prevailing rate in the community.2

The results of this study suggest that FDC of gliclazide extended release 60mg + metformin extended 500mg is effective in achieving glycemic control over the short term with a low frequency of hypo-glycaemia in the setting of primary care. It can be useful in the guideline recommended management of type 2 diabetes.

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References