The Efficacy of Repaglinide Monotherapy and in Combination with Metformin in Indonesian Type 2 Diabetes Mellitus Patients

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ABSTRACT

Aim: to investigate the efficacy and safety of repaglinide alone and in combination with metformin therapy.

Methods: seventy-two type 2 diabetes patients who were oral anti-diabetic drugs (OAD)-naïve or currently on OAD for ≤36 months with HbA1c ≤9% and fasting plasma glucose (FPG) ≤13 mmol/L were recruited. Patients were titrated for 6 weeks to a dose level which maintained fasting blood glucose at 4.4–7.0 mmol/L and continued treatment for 8 weeks. Dose regimen started with 0.5 mg repaglinide each main meal, progressing to 1.0 mg repaglinide, 1.0 mg repaglinide + metformin 500 mg b.i.d. and 1.0 mg repaglinide + metformin 500 mg t.i.d., depending on patients’ glycaemic status. Patients’ glycaemic control (HbA1c, FPG), body weight and other safety parameters were evaluated.

Results: thirty-seven patients completed the trial. Patients were overweight (mean BMI 25.5 ± 4.1 kg/m²) with mean age 52.5 ± 8.8 years and mean diabetes duration of 2.4 ± 3.8 years. Mean HbA1c (2.26 ± 0.22%, p<0.05) and FPG (3.31 ± 0.47 mmol/L, p<0.05) decreased significantly from baseline. Body weight did not change significantly (0.85 ± 0.45 kg, p=0.068). Of the 33 patients who had baseline FPG >7.0 mmol/L, it appeared that repaglinide alone at doses 0.5 or 1.0 mg achieved FBG <7.0 mmol/L in 67% of patients. The majority of the treatment emergent adverse events were mild and unlikely related to trial product. Episodes of symptomatic hypoglycaemia were low (9.3%) in frequency. The changes in haematology, clinical biochemistry and urinalysis were mostly minor or remained unchanged. Vital signs and the results of physical examination also remained unchanged. Three of the four withdrawals were due to adverse events but were unlikely related to trial product.

Conclusion: treatment with repaglinide alone and in combination with metformin was efficacious in glycaemic control in OAD-naïve or previous users. Most of the patients appeared to achieve good control with repaglinide alone. The treatment regimens were safe (317 words).

Key words: repaglinide, metformin, OAD-naïve type 2 diabetes mellitus, HbA1c, FPG.

INTRODUCTION

In patients with type 2 diabetes mellitus not adequately controlled by diet, monotherapy with an oral anti-diabetic drugs (OADs) will be initiated before moving to combination therapy when monotherapy failed. A host of OADs with different mechanisms of action are available in the market. Of these, repaglinide has been approved for use as monotherapy or in combination with metformin when lifestyle measures are inadequate while metformin could also be prescribed as either monotherapy or combination therapy. These two OADs differed in their mechanism of action and may provide synergistic effects when used in combination for treatment in patients with diabetes. Repaglinide acts by stimulating endogenous insulin output in line with glucose intake which places fewer restrictions upon the patient’s schedule since repaglinide is taken on an ‘as needed’ basis. A spin-off benefit of repaglinide therapy may be the opportunity to implement caloric restriction and avoid weight gain.

Metformin on the other hand, lowers blood glucose (BG) in diabetic patients without stimulating insulin secretion. There are advantages of combining metformin with sulphonylurea or repaglinide in type 2 diabetes patients inadequately controlled by sulphonylurea monotherapy or metformin monotherapy. At the level of glucose metabolism, metformin seems to preferentially improve insulin sensitivity (although the
precise mode of action is unknown) and thus may be considered the preferred medication for obese or hyperlipidemic type 2 patients.

The effect of repaglinide and metformin combination therapy on glycaemia (HbA$_1c$ and fasting plasma glucose) and body weight were evaluated in type 2 patients who were not adequately controlled by OAD alone or who were OAD-naive. Prior to the conduct of the study, approval has been received from the Drug and Health Equipment Control and the Ethics Committee of the University of Indonesia. The study was conducted in Dr Cipto Mangunkusumo National General Hospital, Jakarta. An open-label design was adopted for the study since the efficacy endpoints assessed were biochemical parameters.

**METHODS**

**Inclusion Criteria**

In Indonesia, patients who were diagnosed with type 2 diabetes, according to the World Health Organisation criteria, aged 30 years or older, who were OAD-naive or who were not optimally controlled with OAD were enrolled to reflect the general type 2 diabetic population that have unsatisfactory glycaemic control (fasting plasma glucose ≥13 mmol/L [234 mg/dL] and HbA$_1c$ ≤9%) and are intended to begin combination therapy. For patients who were currently treated with OAD (sulphonylureas, biguanides and α-glucose inhibitors), the duration of treatment was limited to ≤36 months duration. Patients on sulphonylurea treatment must not be receiving daily doses of glibenclamide and glipizide exceeding 10 mg per day or gliclazide exceeding 160 mg per day. Patients must also be willing to record hypoglycaemic and adverse events in a diary and able to comply with trial protocol.

**Exclusion Criteria**

Patients who met the following criteria were not enrolled: cardiac problems (decompensated heart failure [NYHA III and IV], unstable angina pectoris, myocardial infarction within the last 12 months), body mass index (BMI) ≤19 kg/m$^2$, uncontrolled hypertension (systolic blood pressure ≥190 mmHg and/or diastolic blood pressure ≥105 mmHg), history of chronic treatment with insulin, known unawareness of hypoglycaemia, prior treatment with repaglinide, known contraindications to sulphonylureas, history of renal and/or liver disease, current treatment with systemic corticosteroids, known or suspected allergy to trial product or related products. In addition, females of childbearing potential or judged to be using inadequate contraceptive measures before or during the trial were excluded. Participation in any other clinical trial involving investigational products within 30 days prior to screening was not allowed.

**Withdrawal Criteria**

During the trial, patients were withdrawn if: their fasting capillary BG concentration was >15 mmol/L (270 mg/dL) during the titration period or >13 mmol/L (234 mg/dL) during the maintenance period; they were treated with systemic cortico-steroids for more than one week; severe hyperglycaemia or clinically unacceptable hypoglycaemic symptoms had occurred; they had initiation of insulin therapy or had participated in any other clinical trial.

**Treatment**

Patients who passed the screening were allowed a two-week wash-out/run-in period prior to the 6-week titration period. Patients were titrated for 6 weeks to a dose level which maintained optimal glycaemic control and continued treatment for 8 weeks (total of 14 weeks). During the titration period, patients whose fasting blood glucose level was >7.0 mmol/L$^3$ had their dosages increased. The dose regimen was: (I) 0.5 mg repaglinide each main meal, (II) 1.0 mg repaglinide each main meal, (III) 1.0 mg repaglinide each main meal + metformin 500 mg b.i.d. or (IV) 1.0 mg repaglinide each main meal + metformin 500 mg t.i.d. All patients started at dose level I regardless of their level of glycaemic control.

The variables assessed for efficacy included HbA$_1c$, FPG, change in body weight. HbA$_1c$ was analysed by ion-exchange high performance liquid chromatography using Bio-Rad VARIANT Hemoglobin Testing System. Glucose levels were assessed using the enzymatic method (Gluco-quant®Glucose/HK, Roche). Safety variables recorded included adverse events, hypoglycaemic episodes, vital signs, clinical biochemistry, haematology, urinalysis, physical examinations and fasting blood glucose. Hypoglycaemic episodes were classified as: major – BG <2.8 mmol/L with reversal of symptoms after food intake or glucagons/i.v. glucose administration; minor – symptoms present with confirmation of BG <2.8 mmol/L [50 mg/dL] or asymptomatic BG < 2.8 mmol/L (50 mg/dL); asymptomatic – symptoms present but not confirmed by BG measurement.

**Statistical Analysis**

The last-observation-carried-forward principle was used to manage missing data in the intention-to-treat (ITT) and safety analyses. All patients who were
exposed to at least one dose of trial product and who had returned for at least one visit after treatment indication were included in the ITT analyses.

The null hypothesis was that the difference between the start and end value of HbA1c equals zero, that is, there was no treatment effect. The change in HbA1c from baseline was analysed for treatment effect using paired t-test. Descriptive statistics were used to evaluate the safety endpoints. PC SAS® version 6.12 was used for the analysis.

RESULTS

Patient Disposition

Of the 72 patients who were screened, 41 were exposed to trial drug and 37 completed the trial (90%). Four patients withdrew during the trial, three due to adverse events and one due to non-compliance with protocol.

The characteristics of the study population are shown in Table I. The patients were recently diagnosed diabetes patients with 56% of them being OAD-naïve. A higher proportion of females (63%) were recruited. The majority of the patients were free of diabetic complications, however, 75% were diagnosed with neuropathy.

Exposure to Treatment

All 41 patients started at dose level I and at the end of the titration period, dose information was available in 38 patients, that is, the start of the maintenance period. After the titration period, 46% of the patients continued on dose level I to control their blood glucose levels during the maintenance period. Seven percent of patients had their dose level increased to level IV.

Glycaemia and Body Weight

After 14 weeks of treatment, glycaemia was significantly improved; HbA1c decreased by 2.26 ± 0.22% and FPG decreased by 3.31 ± 0.47 mmol/L (Table 2 and Figures 1a and b).

The proportion of patients who achieved HbA1c and FPG values that were considered to be optimal according to the guidelines of the Asia-Pacific Type 2 Policy Group was analysed. Prior to titration, 85% of the patients have poor control of HbA1c (>7.5%) and 2% had HbA1c values in the optimal range (<6.5%). At the end of the 14 week treatment, the proportion of patients who had poor control of HbA1c was reduced to 11%. The proportion of patients who had borderline (from 12% to 37%) and optimal control (from 2% to 52%) increased. Similar to the trend observed for HbA1c, at the end of the treatment period, the proportion of patients with poor control of FPG (>7.0 mmol/L) was reduced from 85% to 37%. Correspondingly, the proportion of patients who achieved borderline (from 12% to 26%) and optimal control (from 2% to 37%) increased.

Mean body weight was increased by 0.85 ± 2.81 kg at the end of the treatment period. The change however, was not statistically significant (Table 2).

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Repaglinide and Repaglinide + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients exposed</td>
<td>41</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>52.2 ± 8.8 (32.0-72.0)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>25.2 ± 4.1 (19.2-36.1)</td>
</tr>
<tr>
<td>Mean duration of diabetes, years</td>
<td>2.4 ± 3.8 (0.0-15.0)</td>
</tr>
<tr>
<td>Baseline glycaemic status</td>
<td></td>
</tr>
<tr>
<td>Mean HbA1c, %</td>
<td>8.7 ± 1.5 (6.2-12.4)</td>
</tr>
<tr>
<td>Mean FPG, mmol/L</td>
<td>9.8 ± 2.8 (3.3-16.3)</td>
</tr>
<tr>
<td>Complication status</td>
<td></td>
</tr>
<tr>
<td>Retinopathy, n (%)</td>
<td>5 (12.2%)</td>
</tr>
<tr>
<td>Nephropathy, n (%)</td>
<td>16 (39.0%)</td>
</tr>
<tr>
<td>Neuropathy, n (%)</td>
<td>31 (75.6%)</td>
</tr>
<tr>
<td>Macro-angioplasty, n (%)</td>
<td>5 (12.2%)</td>
</tr>
</tbody>
</table>

All mean express as mean: standard deviation (minimum–maximum)

Table 2. Change in Glycaemia and Body Weight from Baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Repaglinide and Repaglinide + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td></td>
</tr>
<tr>
<td>Baseline (n=41)</td>
<td>8.7 ± 1.5</td>
</tr>
<tr>
<td>End of treatment (n=38)</td>
<td>6.6 ± 0.8</td>
</tr>
<tr>
<td>Change in HbA1c after 14 weeks of treatment (n=38)</td>
<td>-2.26 ± 0.22 (-2.71; -1.81)*</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
</tr>
<tr>
<td>Baseline (n=41)</td>
<td>9.8 ± 2.8</td>
</tr>
<tr>
<td>End of treatment (n=38)</td>
<td>6.7 ± 1.5</td>
</tr>
<tr>
<td>Change in FPG (mmol/L) after 14 weeks of treatment (n=38)</td>
<td>-3.31 ± 0.47 (-4.26; -2.37)*</td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
</tr>
<tr>
<td>Baseline (n=41)</td>
<td>61.5 ± 10.7</td>
</tr>
<tr>
<td>End of treatment (n=38)</td>
<td>61.8 ± 10.6</td>
</tr>
<tr>
<td>Change in body weight (kg) after 14 weeks of treatment (n=39)</td>
<td>0.85 ± 0.45 (-0.06; 1.76)</td>
</tr>
</tbody>
</table>

Mean glycaemia and body weight presented as mean SD
Change in glycaemia and body weight presented as mean SEM (95% C.I.) *p<0.05 (paired t-test)
Dosing Guideline for Repaglinide

One of the secondary objectives of the trial was to determine the dose of repaglinide and metformin at the end of the treatment based on FPG value before and during the trial period. Since the target of 200 patients required for analysis was not met, a cross-tabulation of baseline FPG versus dosing level which maintained FPG £7.0 mmol/L after the 6-week titration period was tabulated. Of the 33 patients who had baseline FPG >7.0 mmol/L, it appeared that dose level I (0.5 mg repaglinide with each main meal) was sufficient to maintain FPG £7.0 mmol/L in 14 patients (42%). Eight patients (24%) were able to maintain glycaemia on 1.0 mg repaglinide therapy. Eleven patients (33%) were required to be maintained on a combination regimen of 1.0 mg repaglinide and 500 mg metformin b.i.d. (8 patients) or t.i.d. (3 patients) at the end of the titration period.

Safety

Thirty-one patients (76%) reported 86 treatment emergent adverse events (TEAEs), including hypoglycaemia. The 86 TEAEs consisted of two serious adverse events, eight episodes of symptomatic hypoglycaemia (five patients, 12%) and 76 other adverse events. Upper respiratory tract infection (10 patients, 15 events), headache (nine patients, 14 events) and toothache (five patients, six events) were the most commonly reported adverse events with 35% incidence. The majority (72 events, 92%) of the adverse events were mild in severity.

Three patients withdrew during the trial because of adverse events and one due to non-compliance with protocol. The adverse events suffered by these three patients included abortion threatened, peripheral gangrene and bone fracture. All three patients subsequently recovered from the adverse events which were all considered unlikely related to trial product.

Changes in haematology, clinical biochemistry and urinalysis were mostly minor or remained unchanged. Clinically significant test results were due to concomitant illnesses or the result of adverse events. No changes to the body systems and vital signs were observed at the end of the treatment period.

DISCUSSION

The effect of repaglinide alone and in combination regimen with metformin on glycaemia (HbA1c and FPG) and body weight in patients with type 2 diabetes who were OAD-naïve or previously treated with OAD for three years or less was assessed. Glycaemia was effectively controlled in this group of patients as shown by the reduction in HbA1c and FPG levels after the 14-week treatment period. The treatment regimen was able to reduce glycaemia without any change in body weight.

Moses et al² showed that HbA1c and FPG were significantly improved in the combination therapy of repaglinide and metformin compared with treatment with either drug as monotherapy. In their study, 60% of patients receiving combination therapy achieved optimal glycaemic control (HbA1c <7.1%) compared to patients receiving either drug as monotherapy (22% and 20% in repaglinide and metformin monotherapy respectively). Also, none of the patients receiving combination therapy had poor control (HbA1c >9%) compared to 26% and 20% in repaglinide and metformin monotherapy respectively. The significant improvement in glycaemia demonstrated by the combination therapy suggested a synergistic effect of repaglinide and metformin. The clinical significance of this possible synergism is that patients who suffered unacceptable side effects while on metformin monotherapy could have repaglinide added and the dose of metformin reduced without any compromise in glycaemic control.

Compared to Moses et al’s study,² who recruited patients who were inadequately controlled (HbA1c
>7.1%) on metformin for more than six months, the present study included patients who were either OAD-naïve or who were treated with OAD for three years or less and whose HbA1c was ≤ 9%.

Although this trial was not designed to compare the efficacy of monotherapy and combination therapy, to observe for any effect of increasing dose level of repaglinide or metformin on glycaemia and body weight, additional analysis comparing three treatment groups was performed (data not shown). As glycaemia becomes more difficult to control, the dose level of repaglinide or metformin was increased according to the titration guidelines. The repaglinide and metformin combination therapy probably included patients whose glycaemia were uncontrolled and thus difficult to treat. As a result, only a small improvement is seen as compared to patients treated in the repaglinide monotherapy groups. When analysed by repaglinide monotherapy and repaglinide and metformin combination therapy, the synergistic effect of combination therapy observed by Moses et al2 was not consistently seen in this trial. In their study, patients uncontrolled (HbA1c >7.1%) on 1–3 g per day of metformin were recruited. The doses of repaglinide (0.5 or 4.0 mg) and metformin (patients were maintained on pre-study dose) used during titration were different from the present trial. In addition, a different titration guideline was used. The dose of repaglinide was increased when fasting blood glucose was >7.8 mmol/L.

Although the synergistic effect of repaglinide and metformin combination therapy was not observed in this group of diabetes patients, repaglinide alone at doses of 0.5 or 1.0 mg was able to control blood glucose below 7.0 mmol/L in two-thirds of the patients. In type 2 diabetes, the early phase of insulin response is delayed and diminished during prandial needs. This early response is instrumental in the suppression of endogenous glucose production. Therefore in these patients, endogenous glucose production continues despite prandial intake and the continued insufficiency of insulin response results in postprandial hyperglycaemia.7,8,9 Since glucose regulation is most compromised during the prandial phase, increasing insulin levels early in the prandial phase with a rapid-onset, short-acting insulin secretagogues such as repaglinide given flexibly at mealtimes would be a logical approach. Repaglinide had been shown to be at least as effective as metformin,2 and glibenclamide10 and superior to glipizide11 and troglitazone12 and offered flexibility in patients’ eating schedule. In OAD-naïve13 or previously treated patients,14 repaglinide was efficacious irrespective of the number of meals consumed per day.

In the study by Moses et al,2 no serious side effects were observed and the majority of the adverse events were mild or moderate in severity, similar to the findings of the present trial.

CONCLUSION

The present treatment regimen appeared to be safe and well tolerated with no clinically relevant changes in laboratory tests, physical examination and vital signs observed. There were only eight occurrences of symptomatic hypoglycaemic episodes during the trial period. In this group of Indonesian patients with type 2 diabetes mellitus with a relatively short duration of diabetes, and half of whom were OAD-naïve, repaglinide and repaglinide combination therapy with metformin was efficacious in improving glycaemia (HbA1c and FPG) without any change in body weight. Repaglinide alone appeared to achieve good control of glucose levels in most patients.

REFERENCES


