Repaglinide improves blood glucose control in sulphonylurea-naive type 2 diabetes

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Abstract

The prandial glucose regulator repaglinide has a rapid onset of action, a short half-life and is metabolised mainly by the liver. Here we report the findings of a 10-week, double-blind, parallel, placebo controlled, randomised trial with repaglinide in 25 diet-treated, sulphonylurea-naive patients with Type 2 diabetes. Repaglinide was titrated, based on capillary blood glucose, from 0.5 mg to a maximum of 4 mg, preprandially with breakfast and dinner. After 10 weeks, repaglinide was associated with a decrease in HbA1c of 2.3%Hb relative to the placebo group ($P = 0.018$). This reflected a 30% decrease within the repaglinide group from a mean HbA1c of 7.0 to 4.9%Hb ($P < 0.002$). Repaglinide was also associated with a decrease in fructosamine, by 0.88 mmol/l, relative to placebo ($P < 0.001$), with a 20% decrease (from 3.80 to 3.04 mmol/l) within the repaglinide group ($P < 0.001$). Fasting and postprandial blood glucose concentrations decreased in association with repaglinide by 3.6 and 6.4 mmol/l, respectively, relative to placebo ($P < 0.001$ in each case). Within the repaglinide group fasting and postprandial blood glucose decreased by 3.9 and 6.2 mmol/l, respectively ($P < 0.001$ in each case). The number of patients reporting hypoglycaemia in the repaglinide group was similar to placebo (15 vs. 20, respectively; NS). Test meal assessments confirmed that repaglinide effectively controls glucose levels by stimulating mealtime insulin secretion. Fasting serum insulin concentration was not raised compared to baseline or placebo during repaglinide therapy, albeit that fasting glucose levels were decreased by repaglinide. Twice-daily meal-related insulin secretagogue therapy with repaglinide, a new short and rapid-acting prandial glucose regulator, is capable of improving all measures of glycaemic control without increased hypoglycaemia or fasting hyperinsulinaemia. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Type 2 diabetes; Repaglinide; Oral hypoglycaemic agents; Mealtime insulin secretion; Prandial glucose regulation

1. Introduction

Type 2 diabetes mellitus is a common metabolic disorder, accounting for more than 80% of all cases of diabetes. It is a serious, progressive disease in which insulin secretion is insufficient and
insulin action is impaired, resulting in hyperglycaemia [1]. Sulphonylureas stimulate insulin secretion and thereby reduce hyperglycaemia, with few side effects. Nevertheless, the long plasma half-life and the long-lasting effect of some sulphonylureas increase the risk of hypoglycaemia [2]. This risk is greatest in elderly patients and in patients with renal insufficiency [3]. The number of older people with diabetes is increasing [4] and the number of people with diabetes who also have renal disease is greater than previously assumed [5]. To reduce the risk of hypoglycaemia in these individuals, the American Diabetes Association and the European Diabetes Policy Group have recommended the use of short-acting oral hypoglycaemic agents [6,7]. Also, it has been hypothesised that the use of long-acting oral hypoglycaemic agents may contribute to islet β-cell exhaustion and the development of secondary failure to oral hypoglycaemic treatment [2].

Other arguments in favour of short- and rapid-acting hypoglycaemic agents, particularly when targeted in their use so as to limit postprandial hypoglycaemia, relate to the pathophysiology of Type 2 diabetes. Evidence suggests that a progressive loss of early phase insulin secretion in response to prandial stimuli is a fundamental aspect of the aetiology of Type 2 diabetes, contributing to both postprandial and fasting hyperglycaemia [8–11]. Furthermore, macrovascular pathological processes associated with diabetes may be accelerated during supraphysiological postprandial blood glucose excursions [12–15], and epidemiological evidence now implicates postprandial blood glucose levels as a better correlate of adverse cardiovascular outcomes than fasting blood glucose [16–18]. Therefore, short- and rapid-acting drugs when used to preferentially augment the prandial insulin response (and hence limit postprandial glucose excursions) might be expected to address a primary defect of Type 2 diabetes and have a positive influence on the progression of macrovascular disease whilst incurring a low risk of hypoglycaemia.

Repaglinide, a carbamoylmethyl benzoic acid (CMBA) derivative (2-ethoxy-4-[[3-methyl-1-[2(1-piperidinyl)phenyl]-butyl]amino]-2-oxoethyl] benzoic acid), is a novel antidiabetic agent that differs from sulphonylureas in molecular structure, profile of action, and excretion mechanism [19,20]. The rapid onset and short duration of action of repaglinide are well suited for mealtime dosing, when it stimulates a pulse of insulin secretion that mirrors the physiological response to meals in non-diabetic individuals [21]. Repaglinide binds to a specific site on the pancreatic β-cell, blocking ATP-dependent potassium channels to stimulate insulin release without suppressing cellular protein synthesis [22,23]. The drug has a rapid absorption and a fast elimination profile with a plasma half-life of less than 1 h in healthy volunteers. It is metabolised in the liver into inactive substances that are excreted in bile [19].

Because it provides a close approximation to physiological insulin secretion profiles, mealtime dosing with repaglinide may be expected to maintain acceptable glycaemic control with a lower risk of hypoglycaemia than longer-acting insulin secretagogues [24,25]. The present study was designed to test this hypothesis by investigating the degree of overall glycaemic control that can be achieved with this strategy using repaglinide in a multiple-dose titration study in sulphonylurea-naïve Type 2 diabetes.

2. Materials and methods

2.1. Patients and design

The study, a single-centre, multiple-dose, double-blind, parallel-group trial, was approved by the Medical Ethical Committee of the University Hospital, Antwerp, and performed in accordance with the Declaration of Helsinki. Patients with Type 2 diabetes entering the study gave written informed consent. Inclusion criteria included a body mass index (BMI) > 20.0 kg/m², fasting blood glucose (FBG) > 7.8 mmol/l (140 mg/dl) and a glycated haemoglobin (HbA₁c) < 10.0%. Only sulphonylurea-naïve, diet-treated patients, known to have had Type 2 diabetes for at least 1 year, were included. No concomitant medication known to influence insulin secretion or glucose metabolism was permitted during the trial period.
Patient characteristics are given in Table 1; there were no significant differences between study groups. In summary, 11 men and 15 women entered the trial. Their mean age was 60, duration of diabetes, 6.5 and BMI 30.1 kg/m².

2.2. Dose regimens and titration

Twenty-six patients were randomised to receive repaglinide, 0.5 mg, or placebo, taken preprandially with breakfast and dinner. Each patient was seen on seven occasions over a 10 week period (baseline and weeks 1, 2, 3, 4, 7 and 10). Patients attended fasting for these early morning visits bringing with them 24-h urine samples. At each visit the patient’s fasting and 2-h postprandial capillary blood glucose values were measured (using Glucometer®, Bayer, Leverkusen, Germany) by the investigator. Based on these values the dose was doubled if the fasting blood glucose was > 7.8 mmol/l (140 mg/dl) or the 2-h postprandial blood glucose > 8.9 mmol/l (160 mg/dl), to a maximum of 4 mg twice daily. Venous blood was also taken for central analysis at these times. To achieve standardisation, patients were advised to take all study drugs 15 min before meals, commencing the day after the baseline visit.

2.3. Meal profiles

On three occasions (baseline, weeks 4 and 10) patients attended fasting as normal, but in addition to the usual measurements, venous blood was taken 15 min before, and at 15, 30, 60, 90, 120, 180 and 240 min after a standard breakfast to determine blood glucose and plasma insulin profiles (the −15 min blood samples were also used for HbA1c calculation). The standard breakfast constituted 15 g of breakfast cereal, 200 ml of skimmed milk, 60 g of whole-wheat bread, 9 g butter, 50 g lean meat and 250 ml of orange juice. This was calculated to provide approximately 500 kCal (2160 kJ) with 58% carbohydrates, 24% fat and 18% protein.

2.4. Biochemical analysis

For the test-meal profiles, glucose measurements were performed by the hexokinase method (Hitachi 717), insulin by radio-immunoassay and HbA1c by ELISA (normal range 2.7–4.9%) at BARC (Bioanalytical Research Corporation, Gent, Belgium).

2.5. Statistical analysis

Blood glucose and plasma insulin profiles were characterised by the area under the curve (AUC0–4 h), maximum concentration (Cmax), minimum concentration (Cmin), time of maximum concentration (Tmax), and time of minimum concentration (Tmin). AUC0–4 h was calculated by the trapezoidal method. AUC0–4 h and Cmax for blood glucose and plasma insulin were analysed using logarithmically-transformed values because the variation in these parameters is multiplicative in nature. Between-group differences over the 10-week period were evaluated by two-tailed t-tests. Within-group changes from week 0 to 10 were evaluated by Student’s paired t-test. A P value < 0.05 was considered as significant. All statistical analyses were made using SAS version 6.04 software. Unless otherwise noted, the results are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the 25 patients completing the study</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Repaglinide (n = 13)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.4 ± 10.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.2 ± 3.7</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>6.7 ± 3.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.98 ± 2.76</td>
</tr>
<tr>
<td>Fructosamine (mmol/l)</td>
<td>3.80 ± 0.68</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td>13.08 ± 4.02</td>
</tr>
<tr>
<td>Postprandial blood glucose (mmol/l)</td>
<td>19.20 ± 5.32</td>
</tr>
</tbody>
</table>

* Mean ± SD.
3. Results

Twenty-five patients completed the trial; one patient in the placebo group withdrew after the first day for personal reasons. After 10 weeks, five of the 13 patients in the repaglinide group received the maximum dose of 4 mg with breakfast and dinner, while seven patients were receiving 1 or 2 mg with meals, and one patient remained on the initial dose of 0.5 mg with meals. In the placebo group, six of the 12 patients ended the study on ‘maximum’ dose levels, but the remainder who ended the study on ‘lower dose’ levels were technically protocol violations who should have had earlier dose increments by the glycaemic criteria based on venous blood. This was also true for four of the repaglinide-treated patients, who therefore ended the study on suboptimal doses.

3.1. Glycaemic control

Changes in HbA\textsubscript{1c}, fasting blood glucose, postprandial blood glucose, urinary glucose and fructosamine over the study period for repaglinide versus placebo are shown graphically in Fig. 1.

Relative to placebo, HbA\textsubscript{1c} decreased by −2.3\% Hb in the repaglinide group ($P = 0.018$). Over the 10-week study period, there was a 30\% decrease in HbA\textsubscript{1c}, from 7.0 to 4.9\% Hb ($P = 0.002$), in the repaglinide group, whereas there was no significant change in the placebo group (6.0–6.1\%). Similarly, repaglinide was associated with a significant decrease from baseline in fructosamine of −0.88 mmol/l relative to placebo ($P < 0.001$). This was due to a 20\% decrease (from 3.80 to 3.04 mmol/l, $P < 0.001$) in the repaglinide group during the 10-week trial period, with a non-significant 4\% increase in the placebo group.
Fasting and postprandial blood glucose concentrations also decreased in the repaglinide group relative to the placebo group, by 3.6 and 6.4 mmol/l, respectively ($P < 0.001$ in each case). The 10-week decreases within the repaglinide group were 3.9 and 6.2 mmol/l, respectively ($P < 0.001$ in each case). A significant 15% decrease in fasting blood glucose, from 13.1 to 11.1 mmol/l ($P < 0.001$), was observed after only 1 week of treatment with repaglinide even at the low dose of 0.5 mg preprandially with breakfast and dinner.

Twenty four hour urinary glucose was also significantly reduced, from 31.8 to 3.6 g/24-h in the repaglinide group ($P < 0.002$), without significant changes in the placebo group.

### 3.2. Meal studies: insulin and glucose

Fasting insulin levels did not change significantly in the repaglinide group (from $77 \pm 148$ to $80 \pm 54$ pmol/l), and were comparable to the placebo group (from $81 \pm 43$ to $69 \pm 42$ pmol/l).

As expected, postprandial insulin levels were markedly increased in patients treated with repaglinide after 10 weeks (Fig. 2).

Compared to placebo, there was a significant decrease in the magnitude and duration of postprandial glucose excursions in association with repaglinide between baseline and week 10 (Fig. 2), confirmed by the derived parameters of $\text{AUC}_{0-4 \text{h}}$ and $C_{\text{max}}$ for blood glucose (Table 2). These parameters, as well as blood glucose $T_{\text{max}}$, also

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**Fig. 2.** Mean blood glucose and plasma insulin profiles following a standardised test meal (----- Week 0, — Week 10) in patients receiving repaglinide or placebo. The change in FPG, PPG and PPG–FPG was significant between groups. The change in all three parameters was significant for recipients of repaglinide, but not placebo.
Table 2
Changes in derived parameters for blood glucose and plasma insulin during the study*  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Repaglinide</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Glucose AUC_{0–4 h} (mmol h^{-1})</td>
<td>−23.03 ± 2.81_{b,d}</td>
<td>−2.62 ± 3.61</td>
</tr>
<tr>
<td>C_{max} (mmol/l)</td>
<td>−5.44 ± 0.73_{b,d}</td>
<td>0.06 ± 0.69</td>
</tr>
<tr>
<td>T_{max} (min)</td>
<td>−16.15 ± 8.05_{c}</td>
<td>0.00 ± 6.40</td>
</tr>
<tr>
<td>Insulin AUC_{0–4 h} (mU h^{-1})</td>
<td>61.28 ± 19.60_{b,e}</td>
<td>−9.16 ± 9.98</td>
</tr>
<tr>
<td>C_{max} (mU/l)</td>
<td>25.97 ± 7.73_{b,e}</td>
<td>−1.47 ± 3.45</td>
</tr>
<tr>
<td>T_{max} (min)</td>
<td>−16.15 ± 11.07</td>
<td>0.00 ± 11.08</td>
</tr>
</tbody>
</table>

* Mean ± SE.

b P < 0.001 vs. baseline.

c P < 0.05 vs. baseline.

d P < 0.001 between groups.

e P < 0.05 between groups.

4. Discussion

The value of good glycaemic control in Type 2 diabetes was shown beyond doubt by the UK Prospective Diabetes Study (UKPDS), which confirmed a number of previous studies in Type 2 diabetes [26–28]. As shown in the UKPDS, conventional oral therapies such as sulphonylureas are able to maintain glycaemic control in many people with Type 2 diabetes for much of the course of the disease. However, conventional therapies have limitations. In the case of sulphonylureas, the most important of these are the well-established risk of hypoglycaemia resulting from the non-physiological, chronic insulin secretion that they induce, and restrictions on eating patterns that may inconvenience patients, compromise compliance and confound dietary management.

We have shown in this study that repaglinide treatment yields significant and clinically useful improvements in all measures of glycaemic control tested, without increasing the risk of hypoglycaemia above that with placebo, when administered in a convenient meal-related dosing regimen. The results of this study thereby confirm the hypothesis that effective control of mealtime blood glucose excursions is sufficient to control fasting blood glucose and urinary glucose, as well as medium- and long-term measures of glycaemic control such as fructosamine and HbA1c. The meal-related action of repaglinide was evident from insulin measurements: the absolute fasting plasma insulin levels in the repaglinide group remained unchanged over the 10-week period and were comparable to the placebo values, although it should be noted this was in the context of reduced fasting blood glucose levels. Furthermore, this observation could be considered consistent with a previous study in which repaglinide, 2 mg twice daily, showed a reduction of median fasting plasma insulin by over 15%, when compared with glibenclamide, despite similar glycaemic control [20]. Effective stimulation of mealtime insulin secretion by repaglinide was evident in our study from the 10-week observation of markedly higher postprandial insulin level compared with placebo over the first two postprandial

Patient: showed significant changes from baseline in the repaglinide group: AUC_{0–4 h} decreased by 34%, C_{max} by 27% and T_{max} by 16 min. Similarly, the AUC_{0–4 h} and C_{max} for plasma insulin increased significantly in the repaglinide group relative to placebo as well as from baseline (by 38 and 48%, respectively), although a repaglinide-associated reduction of 16 min in the insulin T_{max} did not reach significance (Table 2).

3.3. Hypoglycaemia and adverse events

No serious clinical adverse events or major hypoglycaemic episodes occurred in either treatment group. Some 15 patients in the repaglinide group, and 20 in the placebo group, reported mild to moderate hypoglycaemic episodes, defined as symptoms of hunger. Blood glucose values were not recorded during any of these episodes.

Patients treated with repaglinide showed a small but significant weight gain of 2.1 ± 0.5 kg (P < 0.01), whereas placebo-treated individuals were characterised by a non-significant weight loss of 0.8 kg over the 10-week period.
hours, despite lower blood glucose levels (Fig. 2). A comparison of the postprandial glucose and insulin curves suggests that patients in the repaglinide group, on average, had more severe disease than those in the placebo group; the baseline prandial insulin response of the former was lower with a correspondingly greater blood glucose excursion. This observation was consistent with the baseline HbA1c data (Table 1), which, although not significant, also suggest that patients in the repaglinide group may have been in poorer glycaemic control. The better glycaemic control outcomes of repaglinide-treated patients are therefore all the more impressive, and this despite some patients being on suboptimal doses due to titration protocol deviation. The significant reduction in glucose $T_{\text{max}}$ (and non-significant reduction in insulin $T_{\text{max}}$) associated with repaglinide are also welcome observations given the importance of attenuated early prandial insulin secretion in the pathophysiology of Type 2 diabetes [8–11].

Importantly, the improvement in glycaemic control with repaglinide was not associated with any increase in hypoglycaemic events compared with the placebo group. The weight gain that occurred in the repaglinide group, however, was statistically significant, although it may simply have reflected improving glycaemic control in these patients. Weight gain is a well recognised side-effect during sulphonylurea therapy that may, in part, relate to the need to consume snacks in order to avert hypoglycaemia. Large-scale placebo-controlled [29] and open [30] assessments of prandial repaglinide have not confirmed an increased risk of weight gain with this treatment strategy.

Responses to repaglinide treatment in practice might well exceed those observed in this study because our subjects received repaglinide, 0.5–4 mg, with breakfast and dinner but not with other main meals. Current practice with repaglinide adopts a flexible meal-related dosing principle, in which patients receive one dose of repaglinide with each main meal daily (up to a maximum of four doses of 4 mg), but omit or delay the dose of repaglinide if a meal is skipped or delayed. This regimen provides an even closer approach to the physiological diurnal insulin profile than that in our study. A recently published, placebo-controlled study, in which repaglinide was used in this way in 408 patients, showed repaglinide to be associated with improved glycaemic control, as assessed by HbA1c and fasting plasma glucose, and a low risk of hypoglycaemia that were independent of patients’ preferred daily meal patterns [29].

In conclusion, the encouraging results of the present study show that repaglinide, a new short-acting insulin secretagogue, is capable of improving conventional measures of glycaemic control through its prandial action without increasing hypoglycaemia or fasting hyperinsulinaemia.

Acknowledgements

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References


