Repaglinide is more efficient than glimepiride on insulin secretion and post-prandial glucose excursions in patients with type 2 diabetes. A short term study

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S U M M A R Y

Objectives: To compare the effect of Repaglinide (R) vs Glimepiride (G) on glucose- and meal-induced insulin secretion and on meal-test induced postprandial glucose excursions.

Methods: After 2 weeks washout period, a 3-month randomised, cross-over parallel group trial of R (1 mg × 2/die) vs G (2 mg/die) in 14 patients with type 2 diabetes “naïve” in diet treatment was made.

Results: Both R and G significantly but similarly lowered fasting glucose levels and improved fasting plasma insulin levels vs baseline. Hyperglycemic clamp showed that both 1st (129.15 ± 23.6 vs 106.90 ± 18.6 pmol/L; p = 0.01) and 2nd phase (189.42 ± 34.4 vs 144.21 ± 37.3 pmol/L; p = 0.003) β-cell response to glucose as well as area under the curve (52.07 ± 10.86 vs 39.54 ± 10.27 µmol/L x 120'; p = 0.005) were greater in R than G groups. Insulin action (4.0 ± 1.1 vs 3.2 ± 0.9 mg × Kg × 60'/µU/mL; p = 0.046) was also improved by R than G administration. In the meal test, R therapy produced a more rapid induction of insulin secretion during the first part. In fact, the mean rise in insulin secretion peaked at 45 min in R (p = 0.001 vs G) and at 60 min in G (p = 0.001 vs R). Consequently, glucose spike at 60 min was higher in G group compared to glucose spike at 45 min in R group (p = 0.002).

Conclusions: Our study demonstrates that R is more efficient that G on improving glucose- and meal-induced insulin secretion as well as on controlling for postprandial glucose excursion.

Key-words: Repaglinide - Glimepiride - Hyperglycemic glucose clamp - Meal test - Insulin secretion - Postprandial glycemia.


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R É S U M É

Le repaglinide est plus efficace que le glimépiride sur la sécrétion d’insuline et sur les excursions glycémiques post-prandiales de type 2. Une étude à court terme

Objectifs : Comparer l’effet du Repaglinide (R) vs Glimepiride (G) sur la sécrétion insulinaire induite par le glucose et le repas et sur les excursions glycémiques après repas test.

Méthodes : Après 2 semaines de washout, 14 patients diabétiques de type 2 « naïfs » de traitement diététique ont été randomisés dans un essai de 3 mois en groupes parallèles avec crossover entre R (1 mg × 2/jour) et G (2 mg/jour).

Résultats : Aussi bien R que G ont réduit de façon significative et similaire la glycémie à jeun et amélioré l’insulinémie à jeun vs les taux de départ. Le clamp hyperglycémique a montré que les phases 1 (129.15 ± 23.6 vs 106.90 ± 18.6 pmol/L ; p = 0.01) et 2 (189.42 ± 34.4 vs 144.21 ± 37.3 pmol/L ; p = 0.003) de la réponse β-cellulaire au glucose de même que l’aire sous la courbe (52.07 ± 10.86 vs 39.54 ± 10.27 µmol/L x 120’ ; p = 0.005) étaient supérieures dans le groupe R que dans le groupe G. L’action de l’insuline (4.0 ± 1.1 vs 3.2 ± 0.9 mg × Kg × 60'/µU/mL ; p = 0.046) était aussi mieux améliorée par R que par G. Lors du repas test, le traitement R a induit une sécrétion d’insuline plus rapide dans sa première partie. En fait, la montée moyenne de la sécrétion d’insuline a atteint un pic à 45 min sous R (p = 0.001 vs G) et à 60 min sous G (p = 0.001 vs R). En conséquence, le pic de glycémie à 60 min était plus élevé sous G par rapport au pic de glycémie à 45 min sous R (p = 0.002).

Conclusions : Notre étude démontre que R est plus efficace que G pour améliorer la sécrétion d’insuline induite par le glucose et le repas et pour contrôler les excursions glycémiques postprandiales.

Type 2 diabetes is a complex and heterogeneous metabolic disorder with insulin resistance and impaired insulin release as the main pathogenic factors. In order to compensate for such defects oral hypoglycaemic agents or insulin are used. The main target for such treatment is to control fasting blood glucose concentration and postprandial hyperglycaemia for preventing or delaying the development of secondary complications [1].

Repaglinide, a carbamylmethilbenzoil derivated acid, exerts its effects by binding to a site on the beta-cell plasma membrane, inhibiting ATP-sensitive K+ channels, thereby activating the Ca++ channels with increase in intracellular calcium ions influx [2]. This increase in intracellular calcium causes a more rapid and shorter insulin release. Due to its pharmacodynamic properties, repaglinide is able to achieve a strong metabolic control especially on postprandial glucose excursions [3]; in fact, insulin is more available during and just after meal, so reproducing the physiological pulsate profile of insulin secretion during meals [4]. Furthermore, repaglinide [5], as well as gliclazide [6] is also associated with a low risk of hypoglycaemic episodes.

Glimepiride, a new 3rd generation sulphonylureas, evokes insulin release with the advantage, over the other members of this group, of a low risk of hypoglycaemia and the possibility that it may increase insulin sensitivity [7]. Furthermore, glimepiride can be given once a day thus, it could be preferred by patients with type 2 diabetes for the easiness timing of administration [7]. Nevertheless, since glimepiride has a much longer pharmacodynamic profile than repaglinide, one should hypothesize glimepiride to have a smoother effect on postprandial glucose than repaglinide. Whether glimepiride and repaglinide have similar effects on glucose-mediated insulin secretion and postprandial glucose excursions is still not investigated.

In light of such evidences, we aimed at comparing the efficacy of a multiple daily dosage of repaglinide (1 mg at lunch and dinner) vs a single daily dose of glimepiride (2 mg/die) on glucose-induced insulin secretion and postprandial glucose concentrations. Additional data were also produced with regard to the effects of such drugs on insulin action.

**Research design and methods**

**Patients**

Fourteen patients with type 2 diabetes “naive” in diet treatment (9 men and 5 women; age range 50-80 years), volunteered for the study which was designed as a not blinded randomised cross-over parallel group trial of Repaglinide versus Glimepiride. Patients were informed about their therapy in both repaglinide and glimepiride phase.

The major exclusion criteria included: Type 1 Diabetes, hepatic dysfunction (as defined by alanine transaminase (ALT) or aspartate transaminase (AST) levels of 1.5 times the upper limit of normal) and renal failure (creatininaemia > 1.5 mg/dl), insulin therapy, the use of lipid lowering agents and contraceptive drugs, the occurrence or history of main cardiovascular diseases (angina pectoris, myocardial infarction, stroke, transluminal coronary angioplasty or bypass graft) and participation in other trials. All patients gave informed consent to participate in the trial which was approved by the Ethical Committee of our Institution.

After enrolment, all patients started a 2-week run-in period and were treated by hypocaloric diet which was maintained throughout the study. Then, patients were randomly assigned to receive repaglinide (1 mg × 2/die, before lunch and before dinner) or glimepiride (2 mg/die before the lunch) along 4 weeks.

At the end of such period, each patient underwent a meal test and a hyperglycaemic clamp. A 2 week wash-out period was planned before starting a cross-over treatment with glimepiride (2 mg/die before the lunch) and repaglinide (1 mg × 2/die, before lunch and before dinner) for a further 4 week period.

Due to the fact that all subjects enrolled were “naive”, in diet treatment and in good metabolic control, both repaglinide and glimepiride were used in the recommended usual starting dosage of 2 mg/die. Further studies using incremental doses and performed in appropriately selected patients will be necessary to verify a potential different dose response curve for repaglinide and glimepiride respectively.

At the end of the treatment a meal test and an hyperglycaemic clamp were repeated but in a different order compared to the 1st treatment period. In both occasions, hyperglycaemic clamp and meal test were conducted after an overnight fast and with an interval of at least 24 hours.

**Hyperglycaemic clamp**

All subjects underwent an hyperglycaemic clamp at basal, and after termination of both repaglinide and glimepiride treatment. Due to the fact that the tests were conducted in fasting patients, any medication was not administered before the test.

The evening before the tests, all patients were fed a standard diet (60% carbohydrate, 25% fat and 15% protein). Then, no food or drink other than water was permitted until completion of test.

In particular, for hyperglycaemic clamp, subjects were studied in the supin position with catheters insert in an antecubital vein for infusion of glucose and into a dorsal hand vein, in retrograde fashion, for drawing blood samples. After baseline samples were obtained, the hyperglycaemic clamp was initiated with an intravenous bolus of 20% glucose, administered over 1-2 minutes in a dose calculated to rapidly increase plasma glucose levels to 9.5 mmol/l. Plasma glucose values were determined using a bedside glucose analyser, and the glucose infusion rate was adjusted to maintain the target level of glycemia. The procedure was contin-
used for a total of 120 min after initiation of the glucose infusion. Sampling for glucose, insulin and C-peptide was performed at frequent intervals (0, 3, 5, 7, 10, 20, 40, 60, 80, 100 and 120 min). At the conclusion of the study the glucose infusion was discontinued, intravenous lines were removed.

As a measure of insulin sensitivity (SI Hyper Clamp) the ratio of metabolic rate to steady-state insulin (M/I) was calculated [8-10].

Meal test

In a different day all patients also underwent standard meal test (55% carbohydrate, 30% fat, and 15% protein with a caloric value of 500 Kcal) after each treatment. Patients received medication orally 15 min before the meal and then venous blood samples were taken at frequent intervals (0, 15, 30, 45, 60, 90, and 120 min) for measurement of plasma glucose, insulin, total cholesterol. Serial samples for triglycerides and FFA were obtained at baseline and at time 45, 60 and 120 min.

Analytical methods

Plasma glycosylated haemoglobin concentrations were determined by high-performance chromatography (Bio-Rad, Milan, Italy). Plasma glucose concentrations were determined by the glucose oxidase method. Plasma insulin and C-peptide concentrations were measured by radioimmunnoassay (Linco Resear. Labs, Italy). Plasma total cholesterol, triglycerides and FFA were measured by routine spectrophotometer methods.

Derived indices and Statistical analyses

First, second phase and steady state of insulin secretion and C-peptide levels were assessed during hyperglycaemic clamp as indices of glucose-stimulated pancreatic beta-cell secretory capacity. First phase of insulin and C-peptide was calculated as the mean of six measurements obtained during the first 20 min, 2nd phase as mean of six measurements from 20-120 min, and steady-state as the mean of the four determinations obtained from 60-120 min. The trapezoidal method was used for calculating the incremental area under the curve (AUC) for insulin and glucose values.

The C-peptide/insulin molar ratios for the first phase, second phase and steady-state of the hyperglycemic clamp were derived as indices of dynamic hepatic insulin clearance [11-14].

Analysis of variance (ANOVA) was used for evaluating differences between treatments.

P < 0.05 was considered statistically significant.

Results

Baseline data

At baseline patients were slightly overweight (25.7 ± 0.8 kg/m²) with a central body fat distribution (WHR = 0.86 ± 0.02) and were in sufficient metabolic control (HbA1c = 6.7 ± 0.3%; normal range = 4.0-6.2%). Compared to baseline both treatments resulted in a significant decline in fasting plasma glucose, total cholesterol, and triglycerides concentrations while the changes in fasting plasma insulin and C-peptide levels were no significant (Tab I). Furthermore, no significant difference in fasting plasma glucose, insulin, C-peptide and triglycerides levels were found after repaglinide and glimepiride respectively (Tab I).

Hyperglycaemic clamp

Plasma glucose and insulin levels during hyperglycemic clamp are shown in figure 1. Fasting plasma glucose values were immediately and similarly raised and kept with narrow range throughout the study in both experimental conditions, without difference between repaglinide and glimepiride groups. Incremental plasma insulin and C-peptide levels were significantly higher after repaglinide than glimepiride administration at different study times (Fig I) so that steady state plasma insulin levels (177.94 ± 33.7 vs 131.68 ± 37.3 pmol/L; p = 0.002) and C-peptide (4.0 ± 0.4 vs 3.4 ± 0.5 nmol/L; p = 0.006) were also more elevated after repaglinide administration. Categorizing insulin secretion in the different phases, incremental first and second phases of insulin and C-peptide were also more potentates by repaglinide than glimepiride administration (Tab II and IIIA).

In addition, AUC for insulin (52.07 ± 10.86 vs

<p>| Table I |
| Characteristics of study groups before and after treatment. |</p>
<table>
<thead>
<tr>
<th>Baseline before treatments</th>
<th>Baseline after Repaglinide</th>
<th>Baseline after Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Plasma Glucose (mmol/L)</td>
<td>7.2 ± 0.3</td>
<td>6.7 ± 0.3*</td>
</tr>
<tr>
<td>Fasting Plasma Insulin (pmol/L)</td>
<td>45.4 ± 15.2</td>
<td>57.1 ± 16.5</td>
</tr>
<tr>
<td>Fasting Plasma C-peptide (nmol/L)</td>
<td>1.24 ± 0.41</td>
<td>1.56 ± 0.46</td>
</tr>
<tr>
<td>Fasting Plasma Total Cholesterol (mmol/L)</td>
<td>5.1 ± 0.2</td>
<td>4.6 ± 0.1*</td>
</tr>
<tr>
<td>Fasting Plasma Triglycerides (mmol/L)</td>
<td>1.49 ± 0.14</td>
<td>1.26 ± 0.18*</td>
</tr>
<tr>
<td>Fasting Plasma Free Fatty Acids (mmol/L)</td>
<td>618 ± 60</td>
<td>561 ± 54*</td>
</tr>
</tbody>
</table>

Data are means ± SD. * = p < 0.05 vs baseline.
Figure 1
Glucose (A), Insulin (B) and C-peptide (C) plasma levels during hyperglycemic clamp. ‘Black circles’ = Repaglinide group; ‘White circles’ = Glimepiride group.
39.54 ± 10.27 μmol/L × 120’; p = 0.005) and for C-peptide (352.21 ± 63.43 vs 297.12 ± 64.01 nmol/L × 120’ p = 0.042) were also significantly more elevated during repaglinide than glimepiride administration.

Repaglinide produced a greater improvement in insulin action and hepatic insulin clearance than glimepiride (Tab II).

Meal Test
Along with meal test, incremental postprandial glucose and insulin concentrations were significantly different between repaglinide and glimepiride (Fig 2). In particular, repaglinide therapy produced a more rapid induction of insulin secretion. In fact, rise in insulin secretion peaked at 45 min in repaglinide group and at 60 min in glimepiride group. The glucose spike at 60 min was higher in glimepiride group (p = 0.002) compared to glucose spike at 45 min in repaglinide group (Tab IIIB). Analysis of insulin and glucose concentrations throughout the meal test revealed that AUC for glucose (42.07 ± 1.05 vs 43.29 ± 1.5 mmol/L × min; p = 0.02) was significantly lower after repaglinide than

Table II
Measures of insulin secretion, sensitivity and clearance during hyperglycemic clamp.

<table>
<thead>
<tr>
<th></th>
<th>Repaglinide</th>
<th>p</th>
<th>Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>First phase insulin (pmol/L)</td>
<td>129.11 ± 23.6</td>
<td>0.010</td>
<td>106.84 ± 18.6</td>
</tr>
<tr>
<td>Second phase insulin (pmol/L)</td>
<td>189.42 ± 34.4</td>
<td>0.003</td>
<td>144.21 ± 37.3</td>
</tr>
<tr>
<td>Steady-state insulin (pmol/L)</td>
<td>177.94 ± 33.7</td>
<td>0.002</td>
<td>131.68 ± 37.3</td>
</tr>
<tr>
<td>First phase C-peptide (nmol/L)</td>
<td>2.8 ± 0.5</td>
<td>0.21</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>Second phase C-peptide (nmol/L)</td>
<td>4.1 ± 0.5</td>
<td>0.021</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>Steady-state C-peptide (nmol/L)</td>
<td>4.0 ± 0.4</td>
<td>0.006</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>SI Clamp (mgxKgx60'/µU/mlL)</td>
<td>4 ± 1.1</td>
<td>0.046</td>
<td>3.2 ± 0.9</td>
</tr>
<tr>
<td>C-peptide/insulin first phase</td>
<td>0.15 ± 0.02</td>
<td>0.085</td>
<td>0.17 ± 0.01</td>
</tr>
<tr>
<td>C-peptide/insulin second phase</td>
<td>0.15 ± 0.02</td>
<td>0.027</td>
<td>0.18 ± 0.02</td>
</tr>
<tr>
<td>C-peptide/insulin steady-state</td>
<td>0.17 ± 0.03</td>
<td>0.030</td>
<td>0.19 ± 0.02</td>
</tr>
</tbody>
</table>

Data are means ± SD.

Table III
Insulin secretion and postprandial glucose levels after repaglinide and glimepiride treatment in each patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Insulin secretion (1st phase) (pmol/L)</th>
<th>Postprandial glucose levels (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Repaglinide</td>
<td>Glimepiride</td>
</tr>
<tr>
<td>1</td>
<td>118.96</td>
<td>94.95</td>
</tr>
<tr>
<td>2</td>
<td>111.81</td>
<td>86.87</td>
</tr>
<tr>
<td>3</td>
<td>138.76</td>
<td>114.08</td>
</tr>
<tr>
<td>4</td>
<td>93.75</td>
<td>74.86</td>
</tr>
<tr>
<td>5</td>
<td>138.24</td>
<td>104.48</td>
</tr>
<tr>
<td>6</td>
<td>133.04</td>
<td>113.35</td>
</tr>
<tr>
<td>7</td>
<td>168.25</td>
<td>145.29</td>
</tr>
<tr>
<td>8</td>
<td>128.05</td>
<td>107.17</td>
</tr>
<tr>
<td>9</td>
<td>148.60</td>
<td>94.71</td>
</tr>
<tr>
<td>10</td>
<td>113.92</td>
<td>113.72</td>
</tr>
<tr>
<td>11</td>
<td>174.35</td>
<td>131.06</td>
</tr>
<tr>
<td>12</td>
<td>92.08</td>
<td>94.71</td>
</tr>
<tr>
<td>13</td>
<td>121.51</td>
<td>95.07</td>
</tr>
<tr>
<td>14</td>
<td>136.32</td>
<td>125.44</td>
</tr>
</tbody>
</table>

media ± SD (n=14) 129.11 ± 23.6 106.84 ± 18.6 9.16 ± 0.3 9.71 ± 0.5

Postprandial glucose was evaluated as the highest glucose excursion for each patients after meal administration.
Figure 2
Glucose (A) and Insulin (B) plasma levels during meal test. ‘Black circles’ = Repaglinide group; ‘White circles’ = Glimepiride group.
glimepiride administration despite similar AUC for insulin (16.69 ± 1.93 vs 15.41 ± 2.09 μmol/L × 120; p = 0.105).

Plasma triglycerides and FFA concentrations were similar in fasting but more suppressed at the end of the test after repaglinide administration while plasma total cholesterol had a similar trend in both experimental conditions (Fig 3).

**Hypoglycaemic events**

Only five adverse event reported were considered related to the study. In fact, three patients reported one mild symptomatic hypoglycaemic event during repaglinide therapy and two patients during glimepiride treatment.

**Discussion**

Our study provide evidence that repaglinide is more efficient than glimepiride on improving glucose and meal-induced insulin secretion and on controlling for postprandial glucose excursion. Furthermore, our data demonstrate that repaglinide has more advantageous effects than glimepiride on insulin action.

Glimepiride is a sulphonylurea that acts by stimulating insulin release from pancreatic B-cells and possible via extra-pancreatic mechanisms. Furthermore, as well as repaglinide, glimepiride is also initiating insulin secretion by closing K-ATP channel. In isolated perfused rat pancreas [15], glimepiride has been demonstrated to stimulate biphasic insulin release [16], with a more rapid initial peak followed by a slower sustained second phase.

Due to its pharmacodynamics and -kinetics properties, glimepiride is usually given as monotherapy or in combination with metformine or exogenous insulin in type 2 diabetic patients with secondary beta-cell failure. Compared to placebo, glimepiride decreases blood glucose and increases insulin levels, with maximum effects during the first 4 hours after the dose [17]. Recently, it has been shown in patients with type 2 diabetes that the hypoglycaemic effect can be attributed to an increase in fasting, 1st and 2nd phases of insulin secretion while non significant improvement in insulin sensitivity were found [18].

Recent epidemiological data [19, 20] have demonstrated that postprandial glucose excursions rather than fasting hyperglycaemia play a major role as risk factor for cardiovascular diseases in patients with type 2 diabetes. Thus, in order to prevent the development and worsening of cardiovascular diseases a strict metabolic control of postprandial glucose excursion is required. Repaglinide, has been shown to initiate insulin secretion by closing K-ATP channel and inducing a rapid postprandial insulin response [4]. Due to the short half-life repaglinide is given before each meal and is not detectable in the circulation 4 h after a dose [4]. Thus, multiple daily doses of repaglinide [21] might be more appropriate than a single daily dose of glimepiride to control for post-prandial glucose excursion. Our data provide evidence that repaglinide is more efficient than glimepiride on potentiate either glucose-induced and mixed meal-induced insulin secretion. Such a difference might be related to the their diverse pharmacodynamic and -kinetic properties. Interestingly, repaglinide had also a stronger and quicker effect on glucose-induced 1st phase of insulin secretion. Due the fact that post-prandial glucose excursion are mainly targeted by the early phase insulin secretion, a strong and quick improvement of 1st phase of insulin secretion seems a clear metabolic advantage for getting a good metabolic control. In addition, it should be pointed out that mixed meal test confirmed and improved our knowledge about the different timing effects of β-cell response once exposed to repaglinide and glimepiride. In fact, mixed meal test showed that repaglinide and glimepiride are both associated to an improvement in insulin secretion with a similar total amount of insulin secreted throughout the test. Nevertheless, the beneficial effects in terms of metabolic control deriving from an early insulin peak after repaglinide administration, it was also demonstrated by the occurrence of the lower area under the curve for glucose throughout the mixed meal. In addition, mixed meal test also demonstrated that repaglinide vs glimepiride administration was associated with lower plasma triglycerides and FFA concentrations at the end of the study, a result having doubtless advantage in terms of minor negative impact of lipids on insulin secretion [22] and sensitivity [23] as well as on prevention of arrhythmias [24].

Interestingly enough, repaglinide administration was also associated to a better insulin sensitivity. To the best of our knowledge, no study have investigated the potential differences in insulin sensitivity between a multiple daily dose and short-acting drug (repaglinide) vs a single daily dose and long-acting drug (glimepiride). The different profile of insulin secretion within the two drugs might provide an explanation for such difference. In fact, insulin is normally secreted in pulsatile manner (either at fasting and after meals) and such pulsatility optimises the hormone action as demonstrated in healthy subjects [25]. In patients with type 2 diabetes alterations or lack in pulse mass, pulse frequency and orderliness of insulin pulse have been demonstrated while a restoration of insulin pulses contributes to improve insulin sensitivity [26]. It can be hypothesized that short-acting insulin secretagogues, given at multiple daily dosage before meals, might contribute to reproduce and mimic the daily pulsatile insulin pattern, a phenomenon which does not occur when long-acting sulphonylureas are given once a day. Such hypothesis is strengthened by recent data showing the lack of effect of glimepiride on insulin action in patients with type 2 diabetes [18]. Notwithstanding, only future studies specifically designed to address such point could provide a sure pathophysiologically interpretation for such results.

In conclusion our study demonstrates that multiple daily doses of repaglinide are more efficient that glimepiride on improving glucose — and mixed meal — induced insulin

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Figure 3
Triglycerides (A), FFA (B) and total cholesterol (C) plasma levels during meal test. ‘Black circles’ = Repaglinide group; ‘White circles’ = Glimepiride group.
secretion as well as on insulin action and that such effects have an advantageous impact on fasting and postprandial plasma glucose levels.

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References