Repaglinide has more beneficial effect on cardiovascular risk factors than glimepiride: data from meal-test study

MR Rizzo, M Barbieri, R Grella, N Passariello, G Paolisso

SUMMARY

Aim our study is to compare the effects of repaglinide vs glimepiride administration on cardiovascular risk factors after meal test. Thus, after 2 weeks washout period, a 3-month randomised, cross-over parallel group trial of repaglinide (1 mg x 2/day) vs glimepiride (2 mg/day) in 14 patients with type 2 diabetes “naive” on diet treatment was made. Both treatments significantly declined plasma glucose, total-cholesterol, LDL-cholesterol, triglycerides, PAI-1, PAP levels and increased HDL-cholesterol. Lowering in plasma PAI-1 and PAP levels was significantly greater in repaglinide group. Furthermore, repaglinide administration resulted in a significant decrease in fasting plasma free fatty acids, fibrinogen, thrombin-antithrombin complex and reaction product of malondialdehyde with thiobarbituric acid (TBARS) levels, in absence of significant difference in fasting plasma insulin levels. Decrease in plasma TBARS levels correlated with the decrease in Plasminogen Activator Inhibitor-1 (r = 0.72; P < 0.003) and free fatty acids concentrations (r = 0.62; P < 0.01). Analysis of the insulin and glucose plasma concentrations throughout the meal test revealed that AUC for glucose (758 ± 19 vs 780 ± 28 mg/L/min; P = 0.02) was significantly lower after repaglinide than glimepiride administration despite similar AUC for insulin (2327 ± 269 vs 2148 ± 292 mg/L/min; P = 0.105). At time 120’ of meal test, repaglinide vs glimepiride administration was associated with a significant decline in plasma triglycerides, free fatty acids, fibrinogen, Plasminogen Activator Inhibitor-1, plasmin-alpha(2)-antiplasmin complex, thrombin-antithrombin complex, TBARS levels and increase in plasma HDL-cholesterol levels. In repaglinide group a negative correlation between insulin secretion during 1st phase of meal-test and in plasma HDL-cholesterol levels. In repaglinide group a negative correlation between insulin secretion during 1st phase of meal-test and plasma HDL-cholesterol (r = -0.48; P < 0.09). Such correlation was lost after adjusting for changes in postprandial hypoglycaemia (r = -0.48; P < 0.09).

In conclusion, our results support the hypothesis that repaglinide is more efficient than glimepiride on controlling for postprandial glucose excursion and may have beneficial effect on reducing cardiovascular risk factors.

Key-words: Repaglinide · Glimepiride · Cardiovascular risk factors · Meal test.

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RESUMÉ

Le répaglinide a plus d’effets bénéfiques sur les facteurs de risque cardiovasculaire que le glimépiride : données d’une étude par repas-test

L’objectif de notre étude était de comparer les effets de l’administration de répaglinide vs glimépiride sur les facteurs de risque cardiovasculaire après repas-test. Ainsi, après 2 semaines de washout, un essai de 3 mois, randomisé, en groupe parallèle avec cross-over a été mis en place utilisant répaglinide (1 mg x 2/jour) vs glimépiride (2 mg/jour) chez 14 patients diabétiques de type 2 “ naïfs” sous traitement diététique. Les deux traitements ont permis une baisse significative des paramètres plasmatiques suivants: glycéémie, cholestérol total, LDL-cholestérol, triglycérides, PAI-1, PAP, et une augmentation du cholestérol-HDL. La réduction des niveaux plasmatiques de PAI-1 et PAP était significativement plus marquée dans le groupe répaglinide. En outre, l’administration de répaglinide s’est accompagnée d’une diminution significative des facteurs plasmatiques suivants: acides gras libres, fibrinogène, complexe thrombine-antithrombine et produits de réaction du malondialdeide avec l’acide thiobarbiturique (TBARS), en l’absence de différence significative de l’insulinémie à jeun. La diminution des niveaux plasmatiques de TBARS était en corrélation avec la diminution des concentrations en Plasminogen Activator Inhibitor-1 (r = 0.72; P < 0.003) et en acides gras libres (r = 0.62; P < 0.01). L’analyse des insulinémies et des glycéémies au cours du repas-test a montré que l’aire sous la courbe (AUC) des glycéémies (758 ± 19 vs 780 ± 28 mg/L/min; P = 0.02) était significativement plus basse après répaglinide qu’après glimépiride malgré des AUC des insulinémies similaires (2327 ± 269 vs 2148 ± 292 mg/L/min; P = 0.105). Au temps 120’ du repas-test, l’administration de répaglinide vs glimépiride était associée à une diminution significative des niveaux plasmatiques de triglycérides, acides gras libres, fibrinogène, Plasminogen Activator Inhibitor-1, complexe plasmine-alpha(2)-antiplasmine, complexe thrombine-antithrombine, TBARS, et à une augmentation du cholesterol-HDL. Dans le groupe répaglinide, une corrélation négative entre la sécrétion d’insuline au cours de la phase 1 du repas-test et les taux plasmatiques de TBARS (r = -0.55; P < 0.03) a été observée au temps 120 min. Cette corrélation disparaissait après ajustement pour les modifications de l’hyperglycémie postprandiale (r = -0.48; P < 0.09). En conclusion, nos résultats confortent l’hypothèse selon laquelle le répaglinide est plus efficace que le glimépiride dans le contrôle des excursions glycéémiques postprandiales et peut avoir un effet bénéfique de réduction des facteurs de risque cardiovasculaire.

Mots-clés : Répaglinide · Glimépiride · Facteurs de risque cardiovasculaire · Repas-test.

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Introduction

Several longitudinal studies have shown a relationship between meal-time glycemic excursion and development of cardiovascular disease [1-2]. In light of such evidence a strong reduction in post meal glucose excursion could be the main target of anti-diabetic therapy for preventing the rise and worsening of cardiovascular disease.

Repaglinide, a carbamoylmethylbenzoin derivated acid, has recently been introduced for controlling postprandial hyperglycaemia since it binds on beta-cell plasma membrane closing voltage-sensitive potassium channels, thereby activating the Ca++ channels with increase in intracellular calcium ions influx [3]. Such latter event is responsible for an increase in intracellular calcium which, in turn, causes a burst in plasma insulin release [4-5].

Glimepiride, in contrast to repaglinide, is a long-action sulphonylurea, which can be given once a day [6] and it may increase insulin sensitivity. Nevertheless, since glimepiride has a much longer pharmaco-dynamic profile than repaglinide, one should hypothesis glimepiride to have a smoother effect on postprandial glucose excursion than repaglinide.

Due to the fact that postprandial glucose excursion is a strong cardiovascular risk factor in diabetics [7-10], one cannot rule out that repaglinide has also an impact on metabolic and coagulative factors related to cardiovascular risk.

Whether glimepiride and repaglinide have similar effects on postprandial glucose excursions and on cardiovascular risk factors is still not investigated.

Thus, we aimed at 1) comparing the efficacy of multiple daily dosage of repaglinide (1 mg at lunch and dinner) vs. a single daily dose of glimepiride (2 mg/day) on postprandial glucose concentrations; 2) investigating whether repaglinide and glimepiride have a different impact on cardiovascular risk factors.

Material and methods

Patients

Fourteen type 2 diabetics “naive” on diet treatment, 9 men and 5 women, with age range 50 to 80 years, volunteered for the study which was designed as a randomised cross-over group trial of repaglinide (1 mg twice/day) versus glimepiride (2 mg/day). Patients were informed about their therapy in both repaglinide and glimepiride phase.

All patients were required to comply with the protocol and carry out home blood glucose monitoring. The major exclusion criteria included Type 1 Diabetes (ADA criteria), impaired hepatic function (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), the use of lipid lowering agents, insulin therapy and contraceptive drugs, the occurrence of main cardiovascular diseases (Heart failure-NYHA class III-IV-, unstable angina pectoris, recent myocardial infarction, uncontrolled/unthreatened hypertension - SBP > 180 mmHg — DBP > 105 mmHg-) 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 only by hypocaloric diet which was maintained throughout the study. Then patients were randomly assigned to receive repaglinide (1 mg 2 /day, before lunch and before dinner) or glimepiride (2 mg/day before the lunch) along 4 weeks. At the end of such period, each patient underwent a meal test. A 2 week wash-out period was planned before starting a cross-over treatment with glimepiride (2 mg/day before the lunch) and repaglinide (1 mg 3 /2/day, before lunch and before dinner) for a further 4 week period. At the end of this latter treatment period a meal test was repeated. In both occasions, meal test were conducted after an overnight fast.

Due to the fact that all subjects enrolled were “naive”, on diet treatment and in good metabolic control, both repaglinide and glimepiride were used in the recommended usual starting dosage of 2 mg/day.

Anthropometrics determination

Weight and height were measured using a standard techniques according to WHO guidelines. Body mass index (BMI) was calculated as body weight divided by height squared.

Meal test

All patients underwent standard meal test (55% carbohydrate, 30% fat, and 15% protein with a caloric intake of 500 Kcal) after repaglinide and glimepiride treatments. Patients received medication orally (repaglinide 1 mg or glimepiride 2 mg) 15 min before a standard 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 and HDL cholesterol. At time 120 min of the test measurements of plasma free fatty acids (FFA), fibrinogen, Plasminogen Activator Inhibitor-1 (PAI-1), plasmin-alpha(2)-antiplasmin complex (PAP), thrombin-antithrombin complex (TAT), reaction product of malondialdehyde with thiobarbituric acid (TBARS) levels were made. First, second phase and steady state of insulin secretion were assessed during meal test as indices of glucose-stimulated pancreatic beta-cell secretory capacity. As usually recommended [11] first phase of insulin 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.
Analytical methods

Plasma glucose concentrations were determined by the glucose oxidase method. Plasma insulin concentrations were measured by radioimmunoassay (Linco Research Labs, Italy). Glycated haemoglobin levels were determined by high-performance chromatography (Bio-Rad, Milan, Italy). Plasma total cholesterol, triglycerides and FFA were measured by routine spectrophotometer methods. PAI-1 Ag levels were measured by enzyme-linked immunosorbent assay (ELISA) technique (Byk Gulden, Milan, Italy). PAP and TAT were assayed by ELISA (Behring Werke, Marburg, Germany). Serum oxidative stress was measured as the reaction product of malondialdehyde with thiobarbituric acid (TBARS).

Statistical analyses

Results are presented as mean ± SD. To predict the adequacy of sample size the nQuery test was used. Analysis of variance (ANOVA) was used for evaluating differences between the two treatments. Simple correlation by the Pearson method allowed us to assess univariate relations. Partial correlation analysis allowed us to evaluate the association among metabolic variables after controlling for changes in post-prandial (45 min) hyperglycaemia. P < 0.05 was considered statistically significant.

Results

Baseline and fasting data

At baseline, patients were slightly overweight (25.7 ± 0.8 kg/m²) with a central body fat distribution (waist circumference: 94.3 ± 5.2 cm) and were in sufficient metabolic control (HbA1c = 6.7 ± 0.3%). Compared to baseline values, both repaglinide and glimepiride treatments resulted in a significant decline in fasting plasma glucose, total and LDL-cholesterol, triglycerides, PAI-1 and PAP levels and in a significant increase in plasma HDL-cholesterol levels (Tab I). Indeed, plasma PAI-1 and PAP levels were significantly lower in repaglinide than in the glimepiride group (P < 0.05 and P < 0.001 respectively). In addition, repaglinide, but not glimepiride administration, significantly decreased fasting plasma FFA, fibrinogen, TAT and TBARS levels, in absence of significant differences in fasting plasma insulin levels (Tab I). Noteworthy, decrease in plasma TBARS levels correlated with the one in plasma PAI-1 (r = 0.72; P < 0.003) and FFA (r = 0.62; P < 0.01) concentrations.

Meal Test

Along with meal test, incremental post prandial glucose and insulin concentrations were significantly different between repaglinide and glimepiride groups (Fig 1). In particular, repaglinide therapy produced a more rapid induction of insulin secretion than glimepiride treatment. 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. Analysis of the insulin and glucose concentrations throughout the meal test revealed that AUC for glucose (758 ± 19 vs 780 ± 28 mg/Lxmin; P = 0.02) was significantly lower after repaglinide than glimepiride administration despite similar AUC for insulin (2327 ± 269 vs 2148 ± 292 mU/Lxmin; P = 0.105).

Table I

Metabolic characteristics of study groups before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Baseline before treatment</th>
<th>Repaglinide</th>
<th>Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>131 ± 6</td>
<td>122 ± 7*</td>
<td>125 ± 6*</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>6.33 ± 2.12</td>
<td>7.96 ± 2.33</td>
<td>7.78 ± 2.07</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>5.04 ± 0.4</td>
<td>4.68 ± 0.2*</td>
<td>4.83 ± 0.2*</td>
</tr>
</tbody>
</table>
| HDL-Cholesterol (mmol/L) | 1.08 ± 0.06     | 1.36 ± 0.06*| 1.25 ± 0.07*|%
| LDL-Cholesterol (mmol/L) | 3.62 ± 0.44     | 3.14 ± 0.43*| 3.26 ± 0.43*|
| Triglycerides (mmol/L) | 1.49 ± 0.14      | 1.26 ± 0.18*| 1.34 ± 0.06*|
| FFA (mmol/L)      | 618 ± 60                | 561 ± 54*   | 583 ± 58    |
| Fibrinogen, (mg/dl) | 283 ± 45*              | 304 ± 42    |
| TBARS (nmol MDA/ml plasma) | 0.41 ± 0.04*   | 0.43 ± 0.05 |
| PAI -1 (ng/ml)    | 55.2 ± 331              | 37 ± 5.4*   | 50.1 ± 6.3* |
| PAP (ng/ml)       | 482 ± 0.46              | 436 ± 49*   |
| TAT (ng/ml)       | 3.62 ± 0.44             | 3.23 ± 0.51*| 3.30 ± 0.50 |

*P < 0.05 vs baseline. All metabolic parameters were determined in plasma after overnight fast.
At time 120' of meal test, a significant difference in plasma HDL cholesterol, triglycerides, FFA, fibrinogen, PAI-1, PAP, TAT and TBARS levels was found between repaglinide and glimepiride groups (Tab II). In repaglinide, but not in glimepiride group, a negative correlation between insulin secretion during 1st phase of meal test and plasma TBARS levels at time 120' was found (r = -0.55, P < 0.03). Such correlation was lost after adjusting for changes in post-prandial hyperglycaemia (r = -0.48; P < 0.09).

In addition, changes in plasma TBARS levels and in TAT concentration were significantly correlated after repaglinide treatment (r = 0.612; P < 0.020).

Discussion

Our results provide evidence that repaglinide is more efficient than glimepiride on controlling for post-prandial glucose excursions and may have beneficial effects on reducing cardiovascular risk factors. It is likely that such effect of repaglinide may be explicated through a reduction in oxidative stress parameters.

Several recent epidemiological data [7-9] provided evidence that postprandial glucose excursions, rather than fasting hyperglycaemia, play a major role as risk factor for cardiovascular diseases in type 2 diabetics. In particular, it has been demonstrated that postprandial glucose is the main cardiovascular risk factor when compared to fasting plasma glucose and glycosylated haemoglobin [10]. Thus, in order to prevent the development and worsening of cardiovascular diseases, a strict metabolic control of post-prandial glucose excursion is required. Accordingly, several pharmacological treatments have been designed. Glimepiride is a sulphonylurea that may be given in a single daily dose. It acts by stimulating insulin release from pancreatic B-cells and possible via extrapancreatic mechanisms. Furthermore, as well as repaglinide, glimepiride is also initiating insulin secretion by closing K-ATP channel. Compared to placebo, the maximum effects of glimepiride in decreasing blood glucose and increasing insulin levels [12] are obtained during the first 4 hours after the dose [13]. Repaglinide induces insulin secretion by closing K-ATP channels and provokes a rapid post prandial insulin response [5]. Due to the short half -life, repaglinide is given before each meal and is not detectable in the circulation, 4 h after a dose [5].

Our data provide evidence that repaglinide is more efficient than glimepiride on potentating meal-induced insulin secretion. Such a difference might be related to their diverse pharmaco-dynamic and -kinetic properties. In fact, due to the fact that postprandial glucose excursions are mainly targeted by the early phase insulin secretion, the strong and quick improvement of 1st phase of insulin secretion found after repaglinide treatment appears to be a clear metabolic advantage for getting a good metabolic control in type 2 diabetic patients. In addition, the benefit in terms of metabolic control deriving from an early insulin peak after repaglinide than glimepiride administration, it was also demonstrated by the occurrence of a lower area under the curve for glucose throughout the mixed meal.

In addition to the diverse effects on mixed meal-induced plasma glucose excursion and insulin secretion, a different impact of repaglinide and glimepiride treatment on cardiovascular risk factors has been also demonstrated.

Several mechanisms have been hypothesized for explaining the link among hyperglycaemia, atherogenesis and cardiovascular diseases: gluco-oxidation of the extracellular matrix that induces accelerated atherosclerosis [14], endothelial dysfunction with a decreased production or inactivation of NO [15], a thrombogenic tendency with...
increase in PAI-1 and platelet aggregation [16], high plasma triglycerides and LDL cholesterol levels and low HDL plasma levels [17].

In our study, plasma total-cholesterol, tryglycerides, PAI-1, PAP levels had a similar decline after both repaglinide and glimepiride treatments. Nevertheless, fasting plasma FFA, fibrinogen, and TAT levels were more affected by repaglinide than glimepiride group. Of note, the strongest decrease of plasma FFA in post meal test after repaglinide than glimepiride treatment, has doubtless advantage in terms of minor negative impact of such parameter on insulin secretion [18], sensitivity [19] and prevention of arrhythmias [20]. Indeed, the modest difference between the two compounds in terms of FFA at 120 min although statistically significant, is probably insufficient to result in clinically relevant effects such as changes in insulin secretion, sensitivity and prevention of arrhythmias as the deleterious role of FFA was demonstrated in experimental circumstances using higher FFA concentrations or greater differences.

Due to the well known relationship among hyperglycaemia, free radical generation and macroangiopathy [21-22], the potential role of repaglinide and glimepiride administration on oxidative stress indices, was also investigated. Interestingly, repaglinide, but not glimepiride administration, resulted in a significant reduction in plasma TBARS levels. Furthermore, repaglinide group had plasma TBARS levels at time 120' negatively correlated with measures of insulin secretion during the 1st phase of meal test, being such association dependent on postprandial glucose levels. Such data are in agreement with previous finding showing that repaglinide administration is associated with an increase in total serum antioxidant capacity [22] and suggest the beneficial effects of repaglinide in reducing cardiovascular risk factors to be related to the antioxidant effects, which, in turn, are linked to the impact of such drug on post-prandial glucose. Such hypothesis is supported by the reduction of plasma TBARS levels after repaglinide treatment which was positively associated with the decrease in some of the major cardiovascular risk factor such as plasma PAI-1 and FFA concentrations.

Indeed, it is implied that the improvement of fibrinolytic, lipid and TBARS parameters observed after repaglinide treatment could be due to both a direct effect of the drugs and an indirect effect through a post prandial glucose control.

In conclusion, our study demonstrates that multiple daily doses of repaglinide are more efficient than glimepiride on improving glucose — and mixed meal — induced insulin secretion and have a more beneficial effects in reducing cardiovascular risk factors mainly through an antioxidant role. The anti-oxidant effect of repaglinide seems related to a more tight control of post-prandial plasma glucose excursions. However, long-term studies will need to determine whether greater improvements in those cardiovascular risk factors will translate into a reduced incidence of cardiovascular diseases.

References


Table II
Plasma levels of metabolic, coagulative and oxidative stress parameters at time 120’ min of meal test.

<table>
<thead>
<tr>
<th></th>
<th>Repaglinide</th>
<th>Glimepiride</th>
</tr>
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<tbody>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>5.66 ± 0.4</td>
<td>5.79 ± 0.4</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/L)</td>
<td>1.49 ± 0.05</td>
<td>1.44 ± 0.06*</td>
</tr>
<tr>
<td>LDL-Cholesterol (mmol/L)</td>
<td>3.05 ± 0.48</td>
<td>3.18 ± 0.42</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.63 ± 0.18</td>
<td>1.77 ± 0.15*</td>
</tr>
<tr>
<td>FFA (mmol/L)</td>
<td>610 ± 99</td>
<td>635 ± 97*</td>
</tr>
<tr>
<td>Fibrinogen, (mg/dl)</td>
<td>299 ± 41</td>
<td>328 ± 31*</td>
</tr>
<tr>
<td>TBARS (nmolMDA/ml plasma)</td>
<td>0.42 ± 0.04</td>
<td>0.45 ± 0.04*</td>
</tr>
<tr>
<td>PAI -1(nmol/ml)</td>
<td>49 ± 4.9</td>
<td>53.4 ± 6*</td>
</tr>
<tr>
<td>PAP (ng/ml)</td>
<td>424 ± 49</td>
<td>463 ± 46*</td>
</tr>
<tr>
<td>TAT (ng/ml)</td>
<td>3.25 ± 0.25</td>
<td>3.6 ± 0.4*</td>
</tr>
</tbody>
</table>

*Statistically significant differences were: P < 0.05