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RESEARCH ARTICLE

Compared to glibenclamide, repaglinide treatment results in a more rapid fall in glucose level and beta-cell secretion after glucose stimulation

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Abstract

Background The more rapid onset of action and the shorter half-life of repaglinide may reduce the post-load glucose excursion and limit sustained insulin secretion compared to sulphonylurea (SU) derivatives.

Methods We studied 12 patients with type 2 diabetes (age 62 ± 2 years, BMI 28.3 ± 1.3 kg m^{-2}, HbA_{1c} $6.7 \pm 0.2\%$) on SU monotherapy at submaximal dose. Patients were treated for 3 weeks with repaglinide or glibenclamide in a randomized, crossover trial. At the end of each treatment period, patients underwent a 60-min hyperglycaemic clamp (glucose 12 mmol L^{-1}) followed by 4-h observation (60–300 min) with frequent blood sampling for determination of glucose, insulin, proinsulin and C-peptide levels. Before the clamp (5 min for repaglinide, 30 min for glibenclamide), patients ingested their usual morning drug dose.

Results After the end of the hyperglycaemic clamp, mean plasma glucose fell to a level of 5 mmol L^{-1} after approximately 150 min with repaglinide, and after approximately 190 min with glibenclamide. While initially quite similar, in the period from 240 to 300 min, insulin, proinsulin and C-peptide levels were lower during repaglinide treatment (insulin 133 ± 20 vs 153 ± 25 pmol L^{-1} ($P < 0.05$), proinsulin 14 ± 3 vs 19 ± 4 pmol L^{-1} ($P = 0.06$) and C-peptide 0.81 ± 0.19 vs 1.14 ± 0.18 nmol L^{-1} ($P = 0.05$) for repaglinide vs glibenclamide, respectively).

Conclusions Following glucose stimulation, plasma glucose levels, and insulin concentration decrease more rapidly after repaglinide treatment than after glibenclamide. Proinsulin and C-peptide secretion tended to fall more rapidly as well. These findings are consistent with a more rapid onset and shorter duration of beta-cell stimulation associated with repaglinide.

Keywords repaglinide; sulphonylurea; type 2 diabetes; insulin secretion; hyperglycaemic clamp; beta-cell

Introduction

For more than 30 years, sulphonylurea derivatives (SU) have been a cornerstone in the treatment of type 2 diabetes mellitus [1,2]. SU bind to the SU receptor of the beta-cell (SUR1). Binding closes the ATP-dependent potassium channels in the plasma membrane, which in turn

induces depolarization of the cell membrane and through several subsequent steps causes insulin release [3]. Glibenclamide, the most widely used SU, has a plasma half-life of 14 h and long-acting metabolites with hypoglycaemic properties.

Repaglinide represents a new class of insulin secretagogues, with a chemical structure different from SU, but a mechanism of action quite similar to that of SU; closure of ATP-dependent potassium channels triggers insulin release. Repaglinide appears equally effective at lowering HbA_{1c} as glibenclamide [4–6]. The shorter half-life (1 h) may decrease the frequency of hypoglycaemic events and may have the advantage that, after a meal, insulin levels decline rapidly when blood glucose concentrations drop, decreasing the tendency of persistent hyperinsulinaemia and/or sustained beta-cell stimulation.

In the present randomized, controlled study, we compare the effects of repaglinide and glibenclamide on glucose dynamics, and on insulin, proinsulin and C-peptide secretion profiles after standardized glucose stimulation in patients with type 2 diabetes mellitus.

Patients and methods

Study population

The study population consisted of 12 patients with type 2 diabetes mellitus, selected from our outpatient clinic, from our database or by advertisement. All patients met the following inclusion criteria: treatment with submaximal doses of SU derivatives or metformin (glibenclamide $\leq$ 10 mg, glipizide $\leq$ 10 mg, glimepiride $\leq$ 4 mg, gliclazide $\leq$ 160 mg, tolbutamide $\leq$ 1500 mg or metformin $\leq$ 1000 mg a day), stable oral glucose-lowering drug dose for at least 8 weeks before entry into the study, fair glycaemic control ($HbA_{1c} \leq$ 8%), BMI 23 to 40 kg m^{-2} and age between 40 and 75 years. Submaximal oral glucose-lowering treatment and a $HbA_{1c} \leq$ 8% should ensure selection of a group of patients with type 2 diabetes mellitus with fair residual insulin secretion capacity. Exclusion criteria were allergy to glibenclamide or repaglinide, pregnancy and treatment with diazoxide (because of its interference with beta-cell function).

The study was carried out in accordance with the Declaration of Helsinki and was approved by the hospital ethics committee. All subjects gave their written informed consent.

Protocol

The study had a single-centre randomized crossover design, and consisted of two periods: a 3-week treatment with orally administered repaglinide (1.0- or 2.0-mg tid) and a 3-week oral glibenclamide treatment (2.5- or 5.0-mg bid).

All patients received a glucose meter and were instructed to measure 7-point glucose day profiles once a week. We contacted the patients every week, allowing adjustment of the dose of the study medication, if required, according to the glucose day profiles. Target glycaemic levels were 5 to 8 pre-prandial and 6 to 10 mmol L^{-1} post-prandial. After each 3-week treatment period, an experimental procedure (hyperglycaemic clamp) was performed. This artificial insulin secretion stimulus was used because it allows optimal standardization, clearly superior to a high carbohydrate meal.

Hyperglycaemic clamp procedure

The hyperglycaemic clamp procedures were performed in a patient observation room, after an overnight (10 h) fast. On the mornings of the tests, patients took no medication. Two intravenous cannules were inserted. One was positioned retrogradely into a dorsal hand vein, which was placed in a Plexiglas box, ventilated with heated air and used for sampling of arterialized venous blood [7]. The second cannula was inserted in an antecubital vein of the contralateral arm for infusion of insulin and glucose.

At the start of the experiment, blood was sampled for measurement of glucose, HbA_{1c}, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride concentration.

Initially, the fasting hyperglycaemia was corrected by an appropriate insulin infusion, aiming at a euglycaemic blood glucose level of 5.0 mmol L^{-1}. Insulin administration was then stopped. This euglycaemic phase lasted 45 min and enabled an identical glucose stimulus in all patients. During this phase, the 'morning dose' of either glibenclamide or repaglinide was administered orally with 150 mL of water; glibenclamide 30 min and repaglinide 5 min before the start of the hyperglycaemic clamp.

Subsequently, a hyperglycaemic clamp [8] was started by an intravenous bolus of 0.8-mL glucose 20% solution per kilogram of body weight, followed by a continuous glucose 20% infusion in order to maintain a blood glucose level of 12 mmol L^{-1} for a total duration of 60 min (start of the clamp is $t = 0$ min). Blood glucose levels were measured every 2.5 min to allow precise adjustment of the glucose infusion rate. Blood samples were taken at $t = 0$, 2.5, 5, 7.5, 10, 15, 20, 30, 45 and 60 min for assessment of insulin, proinsulin and C-peptide concentration.

Following the 60 min of hyperglycaemia, glucose infusion was discontinued, and, during an observation period of 4 h ($t = 60$ to $t = 300$ min), further blood samples were taken every 15 min for assessment of glucose, insulin, proinsulin and C-peptide concentrations. Glucose infusion was restarted if blood glucose levels decreased below 5.0 mmol L^{-1}.

Analytical methods

Blood glucose levels were measured in plasma using the glucose oxidation method (Beckman Glucose Analyzer 2, Beckman Instruments, Fullerton, CA, USA). HbA_{1c} was measured using a HPLC technique (Hi-AUTO A1c analyser HA 8140, Menarini Diagnostics Benelux NV, Valkenswaard, The Netherlands), with reference values of 4.2 to 6.3%. Total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride concentrations were determined using commercially available enzymatic reagents (Hitachi 747, Roche, Almere, The Netherlands; reference values 4.7–6.5, 0.95–1.50 (male)/1.10–1.70 (female), <4.7 and 0.8–2.0 mmol L^{-1}, respectively). Plasma insulin and plasma C-peptide concentrations were assessed by means of radioimmunoassay [9]. Proinsulin was measured using a commercially available kit (Dako A-S, Glostrup, Denmark, K642).

Drugs

Insulin (Actrapid, NovoNordisk, Denmark) was diluted in NaCl 0.9% to a concentration of 1 U mL^{-1}. Glibenclamide tablets of 2.5 mg were obtained from Centra-Farm BV, Etten-Leur, The Netherlands, and repaglinide (Novonorm) tablets of 1.0 mg were manufactured by Novo Nordisk A/S.

Calculations and statistics

Power calculations, based on a pilot study, revealed that 12 patients with type 2 diabetes mellitus in this randomized crossover study should provide an 80% statistical power to detect a 20% difference in the time needed for the glucose concentration to fall below 5 mmol L^{-1} after the hyperglycaemia in repaglinide versus glibenclamide treatment.

Each individual's three-weekly glucose day profiles, measured during each treatment period, were averaged to one representative curve. With respect to the hyperglycaemic clamp, weighted mean levels of glucose concentration and beta-cell products were calculated over the intervals (1) 0 to 60, (2) 61 to 120, (3) 121 to 180, (4) 181 to 240 (5) and 241 to 300 min.

Glucose day profiles after repaglinide and glibenclamide treatment were compared using a two-factor repeated measures analysis of variance (ANOVA). Mean levels of glucose concentration at each time interval during the experiments were analysed using a paired samples t-test. As insulin, proinsulin and C-peptide were not normally distributed, non-parametric tests (Wilcoxon for paired observations) were applied. The SPSS PC + 9.0.1 program (Statistical Package for Social Sciences) was used. Data are presented as mean ± SEM. A value of $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

The study population consisted of 12 patients (9 males) with type 2 diabetes mellitus, mean age 62 ± 2 years, BMI 28.3 ± 1.3 kg m^{-2}. HbA_{1c}, before entering the study, was 6.7 ± 0.2%, office systolic and diastolic blood pressures were 145 ± 6 and 82 ± 3 mmHg (sphygmomanometer). Before entering the study, seven patients were treated with tolbutamide, three with gliclazide, one with glimepiride and one with metformin. Mean diabetes duration was 3.6 ± 0.7 years (range 6 months–9.5 years).

The concomitant medication consisted of ACE inhibitor (5 patients), calcium antagonist (3), beta blocker (4), thiazide diuretic (2), statin (3), acetylsalicyl acid (3), proton pump blocker (2), NSAID (1), hormone replacement therapy (1), sildenafil (1), selective α_1 receptor blocker (1), parasympaticomimetical eye drops (1; glaucoma), benzodiazepine (1) and selective serotonin reuptake blocker (1).

Clinical parameters

Mean 7-point glucose day profiles, HbA_{1c} and lipid levels were similar during both treatments (repaglinide vs glibenclamide: HbA_{1c} 6.3 ± 0.2 vs 6.3 ± 0.2%, total cholesterol 5.3 ± 0.2 vs 5.1 ± 0.3 mmol L^{-1}, HDL-cholesterol 1.0 ± 0.1 vs 0.9 ± 0.1 mmol L^{-1}, LDL-cholesterol 3.2 ± 0.2 vs 3.3 ± 0.2 mmol L^{-1} and triglycerides 1.9 ± 0.5 vs 2.2 ± 0.6 mmol L^{-1}, P = NS, for all comparisons). Minor hypoglycaemic symptoms were reported by five patients during glibenclamide treatment and by three patients during repaglinide treatment.

Hyperglycaemic clamp

Glucose concentration increased rapidly after the intravenous bolus of glucose 20% and after approximately 15 min, the glucose concentration in all patients reached a value of around 12 mmol L^{-1} (Figure 1A). Glucose infusion rates to maintain plasma glucose levels at this hyperglycaemic plateau were equal after repaglinide and glibenclamide. In response to the raised glucose concentration, insulin (Figure 1C), proinsulin (Figure 1E) and C-peptide (Figure 1G) concentrations increased. The increases in glucose, insulin, proinsulin and C-peptide concentrations were similar after repaglinide and glibenclamide treatment.

After discontinuation of glycaemic stimulation, plasma glucose levels gradually decreased. The mean glucose concentration fell to a level of 5 mmol L^{-1} approximately 150 min after the end of hyperglycaemia with repaglinide treatment, compared to approximately 190 min with glibenclamide treatment. During the first and second hour of the observation period, mean glucose concentration

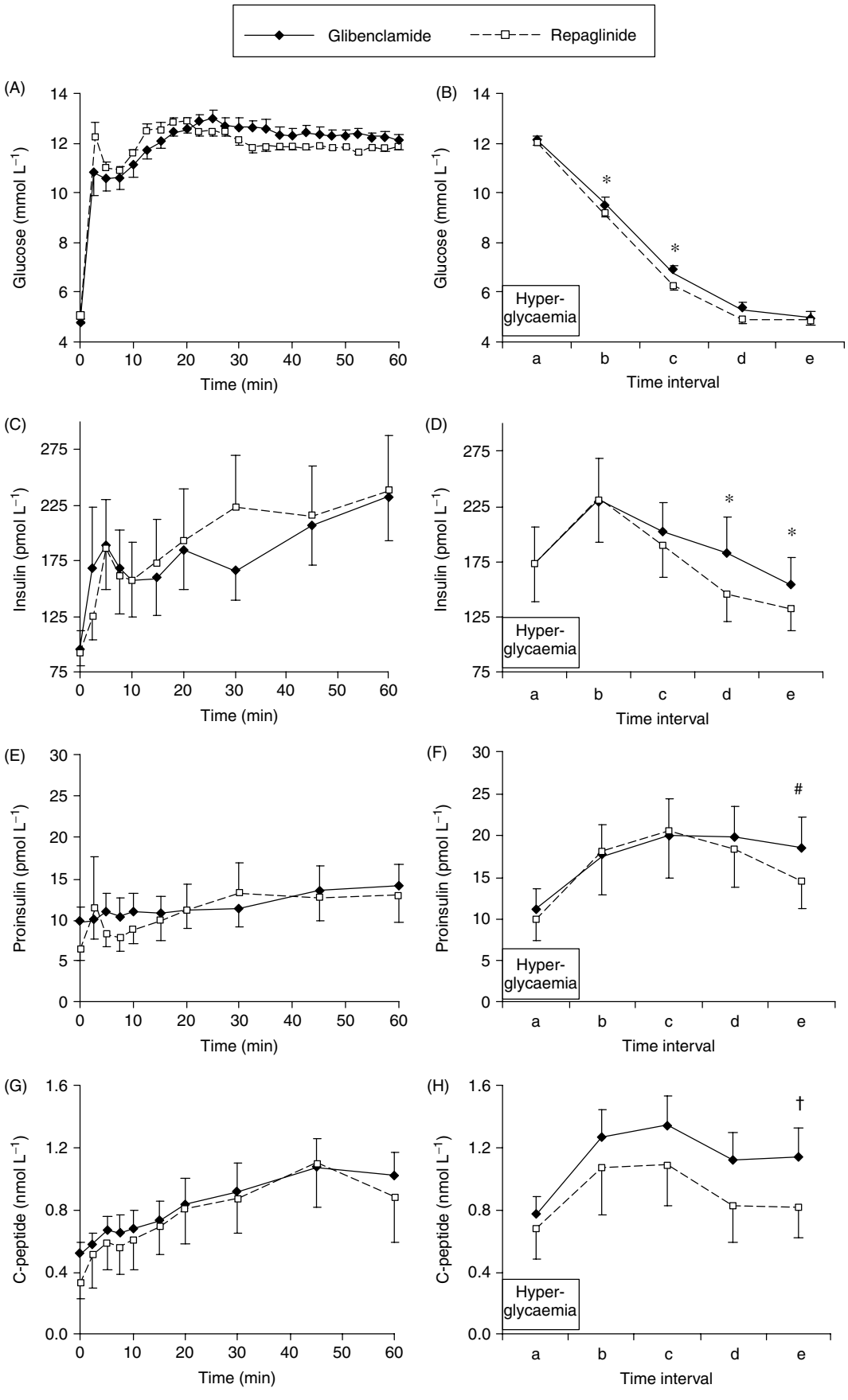

Figure 1. Glucose, insulin, proinsulin and C-peptide concentrations ± SEM during the hyperglycaemic clamp (Figure 1A, 1C, 1E and 1G respectively) and during a 4-h observation period following the clamp (Figure 1B, 1D, 1F and 1H respectively) after glibenclamide as compared with repaglinide treatment. Time intervals a, 0 to 60; b, 61 to 120; c, 121 to 180; d, 181 to 240; e, 241 to 300 min. *$P < 0.05$, #$P = 0.06$, †$P = 0.05$

was slightly but significantly lower after repaglinide than after glibenclamide (Figure 1B).

During the observation period, plasma insulin concentrations decreased after both treatment strategies, but in the third and fourth hour of this period, insulin levels were significantly lower after repaglinide treatment (Figure 1D). Proinsulin levels also initially increased, followed by a decrease during the observation period. During the last hour, proinsulin concentrations tended to be lower after repaglinide ($P = 0.06$; Figure 1F). The plasma concentration of C-peptide increased during the first and second hour following hyperglycaemia and decreased in the third and fourth hour after both treatment strategies. During the last hour, C-peptide concentrations tended to be lower after repaglinide ($P = 0.05$; Figure 1H).

Discussion

The main results of the present study are that, compared to glibenclamide, repaglinide treatment resulted in a more rapid fall in glucose concentration and an earlier decline in the insulin secretion following a 60 min hyperglycaemic stimulus. In addition, plasma proinsulin and C-peptide concentrations tended to be lower after repaglinide. These results are in agreement with a more acute onset of action and a shorter induction of insulin secretion with repaglinide, and thus reflect the difference in pharmacokinetic properties of repaglinide compared to glibenclamide.

While these results provide proof of concept for the notion that repaglinide has favourable pharmacodynamic characteristics after a controlled glucose load, the study does not prove that these characteristics translate into a clinically meaningful improvement of post-prandial glucose control or a lower risk of hypoglycaemia. In fact, post-prandial glucose concentrations, as measured by blood glucose self-monitoring, did not differ between the two treatment periods in our study. However, it should be noted that this small-scale study of relatively short duration (3 weeks on either drug) was not designed to investigate post-prandial glucose control, and other studies have reported improved post-prandial glucose control with repaglinide [5], neither can differences in the incidence of hypoglycaemia be derived from our study, as only a few minor hypoglycaemic symptoms were reported. Some [6], but not all [4,10], studies did observe a reduced risk for hypoglycaemia associated with repaglinide treatment.

Clearly, more comparative studies are needed to determine whether the pharmacokinetic and -dynamic properties of repaglinide result in long-term, clinically relevant, benefits.

In subjects with impaired glucose tolerance, hyperproinsulinaemia predicts progression to type 2 diabetes mellitus [11]. SU treatment stimulates proinsulin secretion [12–14], and, as such, prolonged pharmacological stimulation may accelerate beta-cell exhaustion and cause a more rapid beta-cell failure [15]. In our study, plasma proinsulin levels tended to be lower during the last hours of the test after repaglinide treatment (Figure 1F), which is in line with previous experiments using a similar setup, demonstrating that the long-acting secretagogues glibenclamide and glimepiride induce significantly increased proinsulin secretion at 3 to 4 h after a hyperglycaemic stimulus [13,14]. While the lower proinsulin levels after repaglinide can be explained by the pharmacokinetic properties of repaglinide, our study cannot determine whether the shorter pharmacological action will eventually postpone beta-cell failure. This would require long-term studies, comparing secondary failure rates of the different drugs.

Although the study was randomized and controlled, the treatments were not blinded. This design was chosen to allow administration of the drugs at appropriate time intervals before the test and meals. As the main outcome parameters are insulin concentrations, and analyses were performed completely blinded, we do not think that our study results have been affected by the design of the study.

In summary, this study shows that repaglinide treatment results in a more rapid fall in glucose levels and a more rapid decrease in insulin secretion after glucose stimulation compared to glibenclamide and tended to induce a more rapid decline in proinsulin and C-peptide secretion. These findings are consistent with a faster onset and shorter duration of action of repaglinide. Whether these pharmacodynamic characteristics translate into a clinically relevant improvement of post-prandial glucose control, a decrease in the incidence of hypoglycaemia and a reduced potential to develop secondary failure remains to be determined.

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