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Effect of repaglinide and gliclazide on postprandial control of endogenous glucose production

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Abstract

The effect of repaglinide and gliclazide on postmeal suppression of endogenous glucose production (EGP) has been studied using a variable-rate tracer methodology. Groups of age-, sex-, and weight-matched type 2 diabetic subjects randomized to gliclazide or repaglinide were studied after ingesting a standard mixed meal (550 kcal; 67% carbohydrate, 19% fat, 14% protein). Plasma glucose profiles were similar in each group and markedly different from that of a nondiabetic control group. Endogenous glucose production was similar basally (3.01 ± 0.30 vs 3.06 ± 0.19 mg/kg per minute, gliclazide and repaglinide, respectively). After glucose ingestion, EGP declined rapidly in both the groups until 30 minutes and the greatest suppression was reached earlier in the repaglinide group [0.88 mg/kg per minute at 120 minutes vs 0.77 mg/kg per minute at 210 minutes in gliclazide group ($P < .05$); median time, 85 vs 195 minutes, respectively ($P < .05$)]. The area under the curve (30-150) for EGP was significantly greater in the gliclazide group than in the nondiabetic control group (109 ± 11 vs 198 ± 22 mg/kg per min^2; $P > .02$) but not significantly different in the repaglinide group (153 ± 25 mg/kg per min^2; $P = .17$). Repaglinide has minimal physiological advantage over gliclazide, but both therapies for type 2 diabetes fall far short of correcting the endocrine and metabolic abnormalities.

1. Introduction

The liver plays a primary role in maintaining the fasting plasma glucose concentration within a very narrow range in healthy subjects. After the ingestion of a meal, maintenance of normal glucose homeostasis depends upon suppression of endogenous glucose production (EGP), augmentation of glucose uptake by splanchnic tissues and muscle, and stimulation of glucose oxidation [1]. Endogenous glucose production is incompletely suppressed in diet-controlled type 2 diabetes [2-4]. Conventional therapy with sulfonylurea agents does not normalize the postprandial insulin response or postprandial hyperglycemia, and the practical importance of this has been emphasized by the close link between postprandial hyperglycemia and the vascular complications of diabetes [5-7].

Recently, a new prandial glucose regulator has been introduced for therapy of type 2 diabetes. Repaglinide is said to offer the advantage of normalizing the insulin secretory response and restoring immediate postprandial metabolic control, which is characteristically lost in type 2 diabetes. This paper describes the postprandial changes in EGP assessed by a new technique in groups of type 2 diabetic subjects randomized to treatment with gliclazide or repaglinide.

2. Materials and methods

2.1. Subjects

Type 2 diabetic subjects controlled on sulfonylurea agents were recruited and randomized to receive either gliclazide bid ($n = 6$) or repaglinide tid ($n = 6$). The 2

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groups were matched for age (66.2 ± vs 62 ± 5.5), sex (4M, 2F vs 4M, 2F), body mass index (BMI) (25.8 ± 2.9 vs 25.2 ± 3.5), fasting plasma glucose (6.3 ± 0.4 vs 6.4 ± 0.4), and HbA1c (7.2 ± 0.4 vs 7.5 ± 0.4%) (Table 1). Athletes in training were excluded. No subject was taking any medication, which might affect carbohydrate metabolism. A group of subjects with normal glucose tolerance was also studied (3M, 3F, aged 48.2 ± 2.9 years; BMI, 28.1 ± 1.3). Subjects were studied after 4 weeks of therapy. Drug dose was individually titrated to achieve fasting blood glucose <6 mmol/L. On the day of the study, drug dose was taken 15 minutes before the test meal. The nature, the purpose, and the potential risks of the study were explained to all the subjects, and their informed, voluntary, written consent was obtained before their participation. The study protocol was reviewed and approved by the Joint Ethics Committee, University of Newcastle upon Tyne.

3. Experimental protocol

Subjects were studied in the semirecumbent position after a 12-hour overnight fast. At 7 AM, an intravenous cannula for infusion was sited in an antecubital vein, and a second cannula was sited in a distal forearm vein in a retrograde fashion, this hand being placed in a heated box at 50°C to allow sampling of arterialized blood. At time −180 minutes, a prime-continuous (0.40 μCi/min) infusion of [3-^{3}H] glucose was started. The prime was adjusted according to fasting plasma glucose in both the groups to avoid delay in achieving steady-state plasma glucose-specific activity [8]. The prime in 10-mL normal saline was flushed through the cannula followed by 5-mL saline. A period of 180 minutes was allowed for equilibrium of tritiated glucose; the end of this equilibrium was taken to be time 0. A liquid meal (550 kcal; 67.3% carbohydrate, 18.5% fat, 14.2% protein) including 2 g of [2-^{2}H]glucose was consumed within 10 minutes starting at time zero. After the meal, the rate of infusion of tritiated glucose was adjusted to reproduce the pattern of endogenous glucose release anticipated from our previous observations [4]. Subjects voided just before ingestion of the glucose load, and urine was collected at 210 minutes and at the end of the experiment for determination of urinary glucose loss. Glucose oxidation rates were calculated from indirect calorimetry data derived by use of a constant flow hood calorimeter (Deltatrac) [9]. Measurements were made over 20-minute periods in the fasting state and at regular intervals after the meal. Fuel oxidation data were calculated using equations of Lusk [10]. Frequent blood samples were taken for the determination of plasma glucose, [2-^{2}H]glucose, [3-^{3}H]glucose, lactate, free fatty acid (FFA), insulin, and glucagon.

Table 1
Clinical and metabolic characteristics of subjects

	Gliclazide	Repaglinide	Nondiabetic
Sex (M/F)	4/2	4/2	3/3
BMI	25.8 ± 2.9	25.2 ± 3.5	28.1 ± 1.3
Age (y)	66.2 ± 4.1	62 ± 5.5	48.2 ± 2.9
Fasting glucose (mmol/L)	6.3 ± 0.4	6.4 ± 0.4	4.9 ± 0.1
HbA1C (%)	7.2 ± 0.4	7.5 ± 0.4	5.0 ± 0.1
Duration (y)	3.5 ± 1.1	4.5 ± 1.1	N/A

4. Variable tracer infusion rate

The [3-^{3}H]glucose infusion rate was varied in a stepwise fashion to anticipate the decrease and subsequent increase in EGP after the meal. The protocol was determined iteratively in preliminary studies. The variable infusion protocol remained the same for both the groups to avoid potential complicating factors because the main aim of the study was to compare the pattern of postprandial EGP between the 2 groups. It was as follows: basal period: 100% of basal infusion rate; 0 to 5 minutes: 100%; 5 to 10 minutes: 90%; 10 to 15 minutes: 75%; 15 to 20 minutes: 55%; 20 to 25 minutes: 40%; 25 to 30 minutes: 30%; 30 to 220 minutes: 20%; 220 to 240 minutes: 30%; 240 to 260 minutes: 35%; 260 to 280 minutes: 40%; 280 to 300 minutes: 45%. To ensure that any differences among groups were genuine and not affected by the protocol itself, identical infusion protocols were used for both diabetic and control subjects.

5. Calculation of EGP

The profile of exogenous glucose concentration, that is, the component of total glucose concentration due to exogenous glucose ingestion, was initially calculated. Because this is proportional to the concentration of [2-^{2}H]glucose, its calculation is straightforward and model independent [11]. We then calculated the time course of endogenous glucose concentration, that is, the component of total glucose concentration due to EGP only, by subtracting the calculated exogenous component from the measured total glucose concentration. The steady-state values of plasma clearance rate (PCR) and basal EGP (basal EGP = PCR × basal glucose concentration) were estimated from the [3-^{3}H]glucose decay curve after the primed continuous infusion of [3-^{3}H]glucose given 3 hours before the administration of the meal [12]. Subsequently, the time course of EGP was calculated from the endogenous glucose concentration and [3-^{3}H]glucose data. Because 3-^{3}H]glucose had been infused mimicking the expected behavior of EGP, the specific activity given by the ratio [3-^{3}H]glucose/endogenous glucose was steady, thus allowing a more reliable estimation of EGP. Endogenous glucose production was calculated using the 2-compartment model of Radziuk et al [13]. The concentration of [3-^{3}H]glucose and the ratio between [3-^{3}H]glucose and endogenous glucose concentration were smoothed

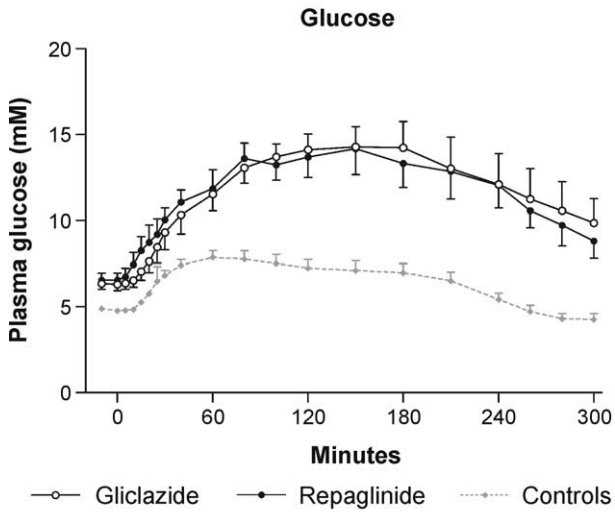

Fig. 1. Change in plasma glucose concentration after the test meal in the gliclazide group (open circles) and the matched repaglinide group (closed circles). Change in plasma glucose in a group of metabolically healthy subjects is shown (gray line, triangles). Data are shown as mean ± SEM.

using an algorithm on the basis of stochastic nonparametric deconvolution [14].

6. Analytical procedures

Plasma glucose concentration was measured by the glucose oxidase method using a Beckman Glucose Analyzer. Plasma insulin concentration was measured using an enzyme-linked immunosorbent assay kit (Dako) and a plasma glucagon by radioimmunoassay [15]. Plasma lactate was measured on perchloric acid extracts on a Cobas Bio centrifugal analyzer (Roche, Welwyn Garden city, UK) [16]. Plasma FFA was measured by centrifugal enzymatic analysis [17]. Atom percent enrichment of plasma [2-^{2}H]glucose was determined by gas chromatography–mass spectrometry [18]. Plasma [3-^{3}H]glucose radioactivity was determined after deproteinization of plasma with $ZnS0_4$ and $Ba(OH)_2$ as described [19].

7. Results

7.1. Plasma glucose

Fasting plasma glucose was similar in each treatment group (6.3 ± 0.4 vs 6.4 ± 0.4 mmol/L, gliclazide and repaglinide, respectively. HbA1c was 7.2 ± 0.4 vs 7.5 ± 0.4). After meal ingestion, the rate of increase was similar and peak concentrations were achieved in both groups at 150 minutes (14.2 ± 1.1 vs 14.1 ± 1.1 mmol/L). Neither group had returned to fasting levels by 300 minutes (Fig. 1). The profiles were markedly different from that of the nondiabetic control subjects that increased from a basal level of 4.8 ± 0.1 mmol/L to peak concentration of 7.8 ± 0.4 mmol/L at 60 minutes and returned to basal values between 180 and 240 minutes.

7.2. Plasma metabolites and hormones

The fasting insulin concentrations were similar in the 2 groups (60.5 ± 16.8 vs 44 ± 10.3 pmol/L, gliclazide and repaglinide, respectively; Fig. 2). At 40 minutes after meal ingestion, there was a modest but nonsignificantly higher plasma insulin concentration in the repaglinide group (141 ± 24.2 vs 171.2 ± 34.8 pmol/L, respectively). Plasma insulin increased to a peak concentration in the gliclazide group by 260 minutes (424.6 ± 107.0 pmol/L) whereas the peak concentration was achieved by 150 minutes in the repaglinide group (336 ± 86.0 pmol/L). The time to peak concentration was not significantly different between the 2 groups (187 ± 39 vs 127 ± 22 minutes, respectively, P = NS). Plasma insulin levels had not returned to basal values in either treatment group 5 hours after glucose ingestion (Fig. 1). The figure demonstrates the considerable abnormality in both of the diabetic groups and the normal control group. Fasting plasma insulin was 44.4 ± 10 pmol/L in the control group and peaked at 80 minutes (518 ± 179 pmol/L, P = .09 vs all diabetic subjects) compared with 260 and 150 minutes in the gliclazide and repaglinide groups. It declined steadily to reach fasting levels by 260 minutes in the control subjects. Time to peak concentration was

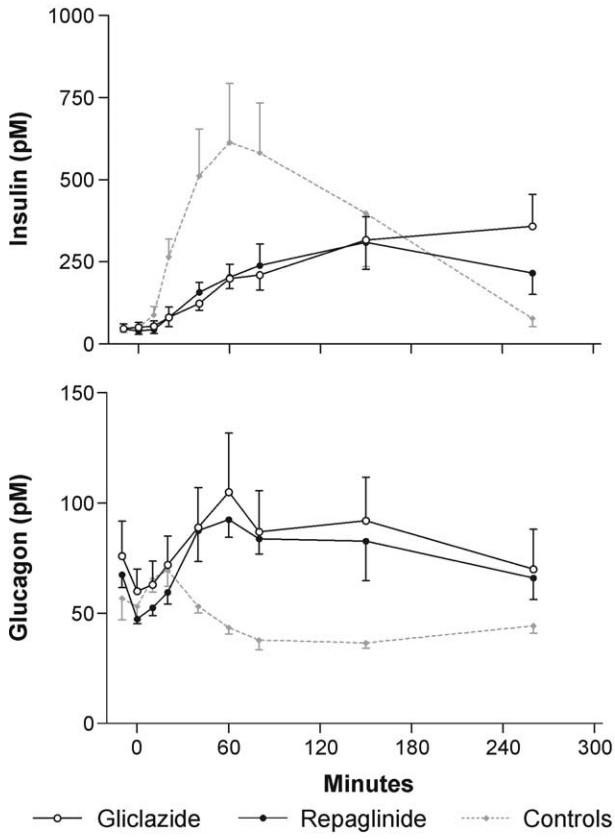

Fig. 2. Change in plasma insulin and glucagon concentrations after the test meal in gliclazide group (open circles) and the matched repaglinide group (closed circles). Change in plasma glucose in a group of metabolically healthy subjects is shown (gray line, triangles). Data are shown as mean ± SEM.

significantly different between controls and all diabetic subjects, $P < .05$.

Plasma glucagon concentrations exhibited the paradoxical postprandial stimulation of type 2 diabetes and were not significantly different between the 2 diabetic groups at any point. In contrast, plasma glucagon levels decreased in the control group from fasting of 56.7 ± 7.6 ($P = .8$ vs all diabetic subjects) to 38.2 ± 2.5 ng/L at 150 minutes ($P < .05$ vs all diabetic subjects) and remained suppressed thereafter (Fig. 2).

7.3. Plasma FFA

Fasting FFA concentration was not significantly different between the 2 groups (0.64 ± 0.07 and 0.57 ± 0.08 mmol/L, respectively) and fell similarly in the 2 groups reaching a nadir at 150 minutes and remaining suppressed (Fig. 3). In the control group, fasting FFA was 0.48 ± 0.03 and 0.09 ± 0.05 mmol/L at 80 minutes ($P = .007$ to that of the diabetic groups), but the rate of postprandial fall in plasma FFA was strikingly similar (Fig. 3).

7.4. Endogenous glucose production

Fasting EGP was almost identical in the 2 diabetic groups (3.06 ± 0.19 vs 3.01 ± 0.30 mg/kg per minute, gliclazide and repaglinide, respectively, from the tritiated glucose decay curve, and 3.20 ± 0.19 vs 3.01 ± 0.28 mg/kg per minute, respectively, from the steady-state calculations). After glucose ingestion, EGP declined rapidly in both the groups until 30 minutes, and the greatest suppression of EGP was reached earlier in the repaglinide group (0.88 mg/kg per minute at 120 minutes vs 0.77 mg/kg per minute at 210 minutes in gliclazide group, $P < .05$) (Fig. 4). The median time to maximum suppression of EGP was 85 vs 195 minutes for repaglinide and gliclazide, respectively ($P < .05$). Fasting EGP was 2.65 ± 0.12 mg/kg per minute in control subjects and declined steadily to a nadir at 60 minutes (0.79 ± 0.1 mg/kg per minute, $P < .005$ compared to all diabetic subjects),

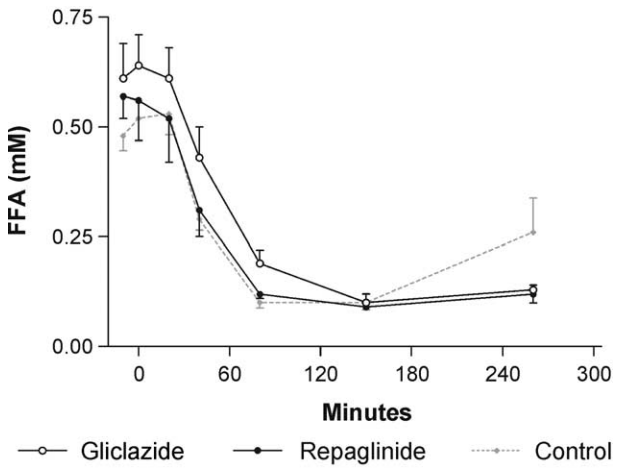

Fig. 3. Change in plasma FFA concentration after the test meal in gliclazide group and the matched repaglinide group, and healthy subjects (symbols same as that of Fig. 1). Data are shown as mean ± SEM.

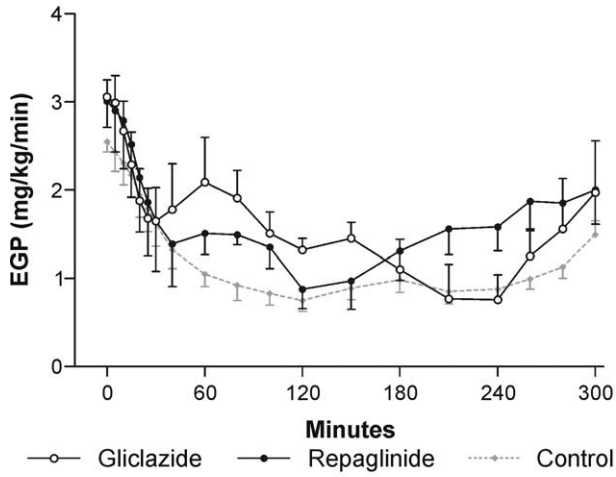

Fig. 4. Change in EGP concentration after the test meal in gliclazide group (open circles), the matched repaglinide group (closed circles), and healthy subjects (symbols same as that of Fig. 1). Data are shown as mean ± SEM.

remaining less than 1 mg/kg per minute until 240 minutes (Fig. 4). Endogenous glucose production appeared modestly but not significantly lower in the repaglinide group from 30 to 150 minutes compared to the gliclazide group [area under the curve (AUC) 153 ± 25 vs 198 ± 22 mg/kg per min^2, $P = .17$]. However, the $AUC_{30\text{-}150}$ was significantly greater than control in the gliclazide group (109 ± 11 vs 198 ± 22 mg/kg per min^2; $P > .02$) and there was no significant difference in $AUC_{30\text{-}150}$ between the control and the repaglinide group ($P = .17$).

7.5. Glucose oxidation

Net glucose oxidation rate in the basal state was identical in the gliclazide and repaglinide groups (1.5 ± 0.3 vs 1.5 ± 0.4 mg/kg per minute, groups, respectively), and peak levels were 2.2 ± 0.6 mg/kg per minute at 180 minute vs 2.0 ± 0.3 mg/kg per minute at 120 minutes, gliclazide and repaglinide, respectively. Net glucose oxidation in the control group was similar in both fasting (1.43 ± 0.14 mg/kg per minute) and at the peak rate (2.22 ± 0.26 mg/kg per minute), which was observed at 180 minutes.

8. Discussion

Although in subjects treated with repaglinide, the time course of suppression of EGP was significantly faster than that of the gliclazide-treated subjects, this did not result in a difference in plasma glucose levels. No evidence for a clinically important advantage of repaglinide was observed. Neither treatment was able to normalize the marked abnormalities in the insulin and glucagon responses to the meal, and the most striking observation was the extent of metabolic abnormality in the diabetic subjects despite either treatment.

Repaglinide stimulates insulin release by closing adenosine triphosphate–sensitive potassium channels by binding to

a different site on the β cell [20]. Repaglinide is formulated for rapid release, and the hypothesis under test was that it would bring about a substantially greater improvement than gliclazide in time course and extent of EGP suppression and control of postprandial glucose levels as earlier studies implied [21,22]. A large multicenter study claimed superior blood glucose control on repaglinide compared to glipizide [23]. However, close examination of the protocol reveals that the glipizide dose was inadequate and the observed difference was due to deterioration in blood glucose control on glipizide rather than any improvement on repaglinide. There was no difference in either fasting plasma glucose or postprandial glucose peaks in our study, which compared 2 drug regimens in widespread clinical use. It is unlikely that the study design would fail to detect a clinically important difference in postprandial glucose levels, although it is possible that larger study groups might identify a small statistically significant difference.

It is possible that the apparent paradox we observed of near-normal initial suppression of EGP in the diabetic subjects despite subnormal insulin secretion may reflect the direct effect of the acute elevation of plasma glucose [24]. Conventionally, hepatic insulin resistance and hence faulty regulation of EGP is believed to exacerbate postprandial hyperglycemia [1,25]. As previously observed [4], the time course of FFA suppression cannot explain EGP suppression given that the former is apparent immediately after the meal whereas the latter exhibits a 15-minute delay. It is of interest that the poor insulin response of the diabetic subjects (Fig. 2) was associated with a normal initial rate of EGP suppression. It may be that only a small increase in portal insulin levels are required to initiate change in EGP in conjunction with the rise in plasma glucose.

Figs. 1 and 2 demonstrate the extent of the abnormalities in plasma glucose, insulin, and glucagon despite therapy in the 2 diabetic groups. In healthy subjects, plasma insulin rose 12-fold in the first 80 minutes after eating, compared with only 5-fold in diabetic subjects treated with insulin secretagogues. This notably subnormal plasma insulin response was accompanied by the paradoxical stimulation of glucagon release previously described as a feature of type 2 diabetes [4,14,26]. It is likely that this stimulation, resulting in peak plasma glucagon levels around 80 minutes after the meal, brings about the observed rebound in EGP between 60 and 120 minutes in the diabetic groups. It is noteworthy that the sluggish plasma insulin response in both diabetic groups was accompanied by normal suppression of plasma FFA levels. The insulin concentration required to suppress adipocyte lipolysis is known to be relatively low in healthy subjects, but an effect of low insulin sensitivity of adipose tissue would have been expected.

Postprandial hyperglycemia is now strongly linked to vascular complications of diabetes particularly cardiovascular deaths. Epidemiological studies suggest that in people with type 2 diabetes, cardiovascular mortality is related to the degree of hyperglycemia [5-7,27]. It is important that agents with the potential to reduce postprandial hyperglycemia should be identified. This study has established that repaglinide has minimal physiological advantage over gliclazide. The data emphasize the extent of the persisting metabolic and hormonal abnormalities during oral agent therapy of type 2 diabetes.

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