Comparison of the Effects of Three Insulinotropic Drugs on Plasma Insulin Levels After a Standard Meal

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OBJECTIVE — To compare the effects of repaglinide, glipizide, and glibenclamide on insulin secretion and postprandial glucose after a single standard 500-kcal test meal.

RESEARCH DESIGN AND METHODS — A total of 12 type 2 diabetic patients with early diabetes (mean HbA_{1c} of 6.1%) and 12 matched control subjects were enrolled in this randomized, double-blind, crossover trial. Subjects received placebo, 2 mg repaglinide, 5 mg glipizide, and 5 mg glibenclamide in a random fashion during the trial. Administration of each drug was followed by a single standard 500-kcal test meal. A washout period of 7–12 days existed between the four study visits.

RESULTS — All three drugs were equally effective on the total prandial insulin secretion (area under the curve [AUC] –15 to 240 min). However, clear differences were noted in the early insulin secretion (AUC –15 to 30 min); both repaglinide and glipizide increased secretion in nondiabetic subjects by ~61 and 34%, respectively, compared with placebo. In the diabetic patients, the difference versus placebo was 37 and 47%, respectively. The difference between glipizide and glibenclamide reached significance in both groups of subjects, whereas repaglinide was more effective than glibenclamide only in the healthy nondiabetic subject group. All three drugs were effective in decreasing total glucose AUC in the nondiabetic and diabetic population. In the nondiabetic subjects, however, repaglinide was significantly more effective than glibenclamide. The differences disappeared in the diabetic subjects, probably as a result of increased prevalence of insulin resistance in this group.

CONCLUSIONS — Repaglinide and glipizide but not glibenclamide significantly enhanced the early insulin secretion in both nondiabetic and diabetic subjects with preserved β-cell function after a single standard meal.

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Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in type 2 diabetes (1). The classical risk factors of hypertension, smoking, increased LDL, and reduced HDL with increased triglycerides (2) account for <50% of the excess risk of CVD (3). Dysfunction of the vascular endothelium is present early in the history of diabetes (4) and has been implicated in atherogenesis. Insulin resistance and its associated features are a major determinant of the abnormal endothelial function in the prediabetic stages (5). However, both chronic (6) and acute hyperglycemia (7) have been shown to worsen the function of the endothelium.

Recent prospective studies have attempted to assess the effects of fasting and postprandial hyperglycemia independent of each other. Postprandial hyperglycemia might be more important than fasting hyperglycemia in predicting CVD (8). However, despite indisputable evidence that better diabetes control reduces the incidence of microvascular complications, a reduction in the risk of developing CVD has not been proven convincingly.

Hemoglobin glycosylation is influenced by both fasting and postprandial glucose; the latter is more strongly correlated with HbA_{1c} values (9). Therefore, targeting the postprandial glucose level when elevated seems logical and has been shown to achieve better control than focusing on the fasting glucose level alone (10).

Postprandial hyperglycemia is generated by a combination of impaired pancreatic insulin secretion, unsuppressed hepatic glucose production, and reduced glucose uptake in the periphery (11). Insulin secretion in normal subjects has a characteristic biphasic pattern, with an early phase lasting <10 min after food ingestion followed by a more sustained later phase of insulin release, which parallels the glucose absorption from the gut (12). In type 2 diabetes, there is a loss of the early phase and a delayed, blunted, and consequently more prolonged late phase (13). These changes occur very early in the natural history of this syndrome, and the degree of blunting relates to the fasting plasma glucose, the so-called "Starling curve" of the pancreas (14). The early-phase loss contributes to a lack of early suppression of the glucagon secretion after ingestion of carbohydrates (15), which in turn leads to continuing hepatic glucose production and an accentuation of the hyperglycemia (16). A loss of the early phase of secretion has been shown to cause postprandial glucose intolerance in nondiabetic subjects (17). In

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Abbreviations: AUC, area under the curve; CVD, cardiovascular disease; KATP, ATP-sensitive potassium.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial on p. 1472.

Table 1—*Baseline characteristics*

	Type 2 diabetic subjects	Nondiabetic subjects
n	12	12
Age (years)	57.0 ± 8.7	56.3 ± 9.3
Men/women (*n*)	7 (58) / 5 (42)	7 (58) / 5 (42)
BMI	29.5 ± 3.2	29 ± 1.9
HbA_{1c} baseline	6.1 ± 1.2*	4.6 ± 0.4 (*n* = 11)*
Duration of diabetes (years min–max)	2.6 (0.5–6.6)	N/A
Fasting glucose baseline (mmol/l)	7.83 ± 0.7*	4.84 ± 0.2*

Data are means ± SD and *n* (%). *$P < 0.05$.

type 2 diabetes, restoration of the early phase using short-acting insulin analogs significantly improves the glucose tolerance by reducing the endogenous glucose output (18). However, despite the inhibitory effects on the hepatic glucose production, the impaired glucose utilization by the insulin-resistant tissues remains unchanged.

Among the agents available for management of type 2 diabetes, only α-glycosidase inhibitors (19) and short-acting insulinotropic agents such as repaglinide (20) and nateglinide (21) have definitely been shown to impact the postprandial glucose levels.

The purpose of this study was to compare the effects on the β-cell function of three insulinotropic agents available for the treatment of patients with type 2 diabetes: repaglinide, glipizide, and glibenclamide.

RESEARCH DESIGN AND METHODS

Study design

This study was a randomized, double-blind, crossover trial performed at two centers, one in the U.K. and the second in Austria. A total of 12 diet-treated type 2 diabetic patients and 12 nondiabetic control subjects matched for age, sex, and weight were enrolled in the study. The Austrian center recruited four diabetic subjects. All healthy control subjects and eight diabetic patients were recruited in the U.K. center. All subjects gave written informed consent to participate in the trial. The study received approval of the local ethics committee and was conducted in accordance with the Declaration of Helsinki. The diabetic population recruited in our study had early type 2 diabetes with a mean HbA_{1c} of 6.1% (laboratory normal range ≤6.4%). Eight patients had good control with HbA_{1c} ≤6.5%, two had borderline control with HbA_{1c} between 6.5 and 7.5%, and two had poor control with HbA_{1c} >7.5%.

The treatment period started within 30 days after the screening visit and consisted of four visits with washout periods of 7–12 days between them. A follow-up visit was conducted 7–12 days after the last treatment day. The maximum duration of participation for each subject was 77 days from the first visit to the last visit.

After a 10-h overnight fast, an intravenous cannula was inserted and saline infusion was started. Each subject received placebo, 2 mg repaglinide, 5 mg glipizide, and 5 mg glibenclamide in a random fashion. Administration of the drug was followed 15 min later by a standard 500-kcal meal tolerance test (55% carbohydrate, 30% fat, and 15% protein). Blood sampling for glucose, insulin, and C-peptide was performed at –30, –20, –15, and 0 min before the meal. Postmeal samples were collected every 10 min during the first hour, every 15 min during the second hour, and hourly thereafter for a total of 4 h.

Analytical methods

All specimens were centralized and processed in a single laboratory in the U.K. The samples were taken into fluoride-oxalate for assay of blood glucose (YSI 2300; YSI, Aldershot, Hants, U.K.). Blood samples for assay of insulin and C-peptide were taken into lithium heparin and centrifuged, and the plasma was stored at –20°C before assay. Insulin was measured by a specific immunoassay (MLT Research, Cardiff, S. Glam, U.K.) and the cross-reactivity of proinsulin in the insulin assay was <2%. C-peptide was measured by immunoassay (Dako Diagnostics, Ely, Cambs, U.K.), which cross-reacted <2% with insulin and ~100% with proinsulin.

Statistical analysis

Data were analyzed using SAS 6.11 software on a UNIX platform. Metabolic parameters with a normal distribution are presented as means with SD or 95% CI. Nonnormally distributed data parameters are shown as median with minimum and maximum also given. Area under the curve (AUC) was calculated using the trapezoidal rule. Fasting levels for glucose, insulin, and C-peptide were calculated by averaging premeal values (−30, −20, −15, and 0 min). Insulin secretion was analyzed as early phase, terminal phase, and total insulin secretion by calculating insulin AUCs for the first 30 min, the last 120 min, and the total 240 min, respectively. AUC and the maximal plasma concentration (*Cmax)* were logarithmically transformed to obtain normally distributed data. The transformed end points were compared across groups using ANOVA for a crossover design accounting for sequence of treatment, subject (within a treatment sequence), visit (period), and treatment. Wilcoxon's signed-rank test was used to compare the individual groups. To account for multiple comparisons, the Bonferroni method was applied. Using an overall level of significance of 0.05, the nominal level of significance was 0.05/3 = 0.02 with three comparisons.

RESULTS — All 24 subjects who were recruited completed the study. Demographic and glycemic parameters of the study population are shown in Table 1. The only significant differences between the diabetic population and the control group were in the fasting glucose and the HbA_{1c} levels.

Glucose, insulin, and C-peptide AUCs in the diabetic and nondiabetic control subjects are shown in Table 2. Mean *Cmax* and the time to maximal concentrations (T*max*) are shown in Table 3.

The AUC –15 to 240 min for glucose, insulin, and C-peptide was significantly different with all three secretagogues versus placebo in both groups of subjects. Maximum insulin and C-peptide concentrations (*Cmax*) were significantly higher with all active drugs compared with placebo. Glucose *Cmax*, however, was decreased significantly only by repaglinide and glipizide. In addition, in nondiabetic

Table 2—*Comparison of the glucose, insulin and C-peptide AUCs in type 2 diabetic and nondiabetic subjects*

	Glucose AUC (mmo/l × h^{-1}) (−15 to 240 min)	Insulin AUC* (mU/l × h^{-1}) (−15 to 30 min)	Insulin AUC* (mU/l × h^{-1}) (120 to 240 min)	Insulin AUC* (mU/l × h^{-1}) (−15 to 240 min)	C-peptide AUC (pmol/1/× h^{-1}) (−15 to 240 min)
Type 2 diabetic subjects					
Placebo	34.0 (28.0–41.4)	13.0 (8.5–19.9)	58.1 (41.3–82.0)	158.5 (113.3–221.7)	6.2 (5.3–7.4)
Repaglinide	27.6 (22.7–33.5)†	17.8 (11.7–27.2)†	91.2 (64.7–128.5)†	244.4 (174.8–341.9)†	9.1 (7.7–10.8)†
Glipizide	27.0 (22.2–32.8)†	19.2 (12.6–29.3)†‡	88.4 (62.7–124.6)†	233.9 (167.3–327.1)†	8.7 (7.4–10.3)†
Glibenclamide	27.8 (22.9–33.9)†	14.0 (9.2–21.4)	112.2 (79.6–158.1)†	254.5 (182.0–355.9)†	8.9 (7.5–10.5)†
Nondiabetic subjects					
Placebo	21.3 (20.1–22.6)	16.8 (12.7–22.3)	31.4 (24.1–41.0)	137.3 (110.6–170.3)	5.9 (5.0–7.0)
Repaglinide	15.7 (14.8–16.6)†‡	27.2 (20.5–36.0)†‡	52.4 (40.3–68.6)‡	236.5 (190.6–293.4)†	8.8 (7.4–10.3)†
Glipizide	16.6 (15.6–17.6)†	22.5 (17.0–29.8)‡	62.3 (47.8–81.3)	247.4 (199.4–307.0)†	8.4 (7.1–9.9)†
Glibenclamide	17.5 (16.5–18.6)†	17.3 (13.1–22.9)	76.2 (58.4–99.5)†	238.6 (192.2–296.0)†	8.5 (7.3–10.0)†

Data are mean (95% CI). *ANOVA significance level at $P < 0.02$ across both nondiabetic and type 2 diabetic groups; †significant difference against placebo ($P < 0.02$); ‡ significant difference against glibenclamide ($P < 0.02$).

subjects, the AUC –15 to 240 min for glucose was smaller, and glucose C*max* was significantly lower with repaglinide compared with glibenclamide. The mean concentration-time profiles for glucose and insulin are shown in Figs. 1 and 2.

There was no difference between the active treatment groups in the total insulin (AUC –15 to 240 min) secreted over 4 h after the meal, confirming the equivalence between the doses used in the study with respect to overall prandial insulin secretion. There were nonsignificant differences in the T*max* for insulin between the active treatment and placebo in both groups. The difference between glibenclamide and repaglinide in the control group became significant, suggesting that glibenclamide has a delayed effect on the pancreatic secretion. T*max* for C-peptide was increased by all secretagogues compared with placebo, but the only significant difference was noted with glibenclamide in nondiabetic subjects. The difference between glipizide and glibenclamide was also significant in these subjects, suggesting that the latter has a more protracted action on the β-cell than glipizide.

Separate analysis of the insulin secretion over the first 30 min (AUC –15 to 30 min) and the last 120 min (AUC 120–240 min) after the meal is shown in Table 2.

There were clear interdrug differences in the early-phase insulin output (AUC –15 to 30 min). Therefore, in the diabetic subjects, insulin AUC –15 to 30 min was significantly higher with both repaglinide (+37%) and glipizide (+47%) compared with placebo. In addition, glipizide reached significance against glibenclamide. Glibenclamide had only a minor effect on this phase of secretion (3% increase versus placebo).

In the nondiabetic group, repaglinide increased the early-phase β-cell secretion by ~61% compared with placebo ($P < 0.02$) and reached significance against glibenclamide. Glipizide increased the secretion by ~34% (not significant versus placebo) but reached significance compared with glibenclamide.

Glibenclamide, but not the other two drugs, significantly increased the insulin output in the late phase in nondiabetic subjects (142% increase relative to placebo). These effects were notably higher compared with repaglinide in this group of subjects. In type 2 diabetic subjects, all three drugs significantly increased the insulin secretion in the late phase compared with placebo: glipizide by ~52%, repaglinide by 57%, and glibenclamide by 93%.

The rates of insulin secretion (ISR) were reconstructed from plasma C-

Table 3—*Comparison of the C*max *and T*max *in type 2 diabetic and nondiabetic subjects*

	Glucose (mmol/l) C*max*	Glucose* (mmol/l) (T*max*)	Insulin (mU/l) (C*max*)	Insulin* (mU/l) (T*max*)	C-peptide (pmol/l) (C*max*)	C-peptide* (pmol/l) (T*max*)
Type 2 diabetic subjects						
Placebo	11.1 (9.3–13.2)	50.0 (30.0–75.0)	73.8 (51.5–105.7)	75.0 (30.0–120)	2.1 (1.8–2.6)	97.5 (75.0–120)
Repaglinide	10.0 (8.4–11.9)†	40.0 (30.0–90.0)	108.6 (75.8–155.6)†	82.5 (50.0–120)	3.2 (2.7–3.8)†	120 (75.0–120)
Glipizide	9.8 (8.2–11.7)†	50.0 (0.0–90.0)	111.0 (77.4–59.0)†	82.5 (30.0–120)	3.1 (2.5–3.7)†	105 (50.0–180)
Glibenclamide	10.3 (8.6–12.3)	50.0 (30.0–75.0)	111.4 (77.8–159.7)†	90.0 (40.0–120)	3.0 (2.5–3.6)†	113 (60.0–240)
Nondiabetic subjects						
Placebo	7.5 (6.9–8.2)	30.0 (30.0–50.0)	92.8 (73.4–117.4)	50.0 (30.0–90.0)	2.6 (2.2–3.0)	55.0 (50.0–120)
Repaglinide	6.4 (5.9–7.0)†‡	30.0 (0.0–40.0)	149.2 (118.0–188.7)†	50.0 (30.0–75.0)‡	3.9 (3.3–4.6)†	60.0 (50.0–105)
Glipizide	6.7 (6.2–7.3)†	30.0 (20.0–40.0)	158.5 (125.3–200.5)†	40.0 (30–120)	3.6 (3.0–4.2)†	60.0 (50.0–120)‡
Glibenclamide	7.2 (6.6–7.8)	40.0 (20.0–50.0)	125.1 (98.9–158.2)†	55.0 (30.0–90.0)	3.3 (2.8–3.9)†	75.0 (50.0–180)†

Data are means (95% CI). *Median with minimum-maximum interval (brackets); †significant difference against placebo ($P < 0.02$); ‡significant difference against glibenclamide ($P < 0.02$).

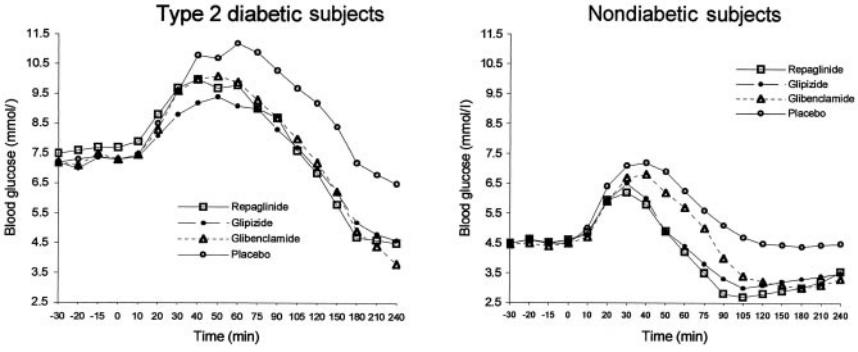

Figure 1—*Mean concentration-time profiles of glucose in type 2 diabetic and nondiabetic subjects.*

peptide concentration and demographic data, using ISEC (Insulin SECretion) software developed by Hovorka et al. (version 3.4a, 1994). This software package allows an estimation of the pancreatic insulin secretion (before hepatic extraction) by using the point-area deconvolution method in a mathematical model. The temporal profiles relative to placebo in both groups of subjects are presented in Fig. 3.

Secretion rates in the diabetic group were significantly higher with repaglinide and glipizide compared with placebo at any time point beginning with 10 min after consuming the meal (repaglinide from 0 min). Glibenclamide, however, became significant only 30 min after the meal. Moreover, both repaglinide and glipizide were significantly more potent than glibenclamide at the 20- and 30-min time points; glipizide was higher than glibenclamide, even at the 40-min point.

In the nondiabetic subjects, the secretion rates with repaglinide became significant against placebo after the 0-min time point. Glipizide reached significance versus placebo slightly later than repaglinide (after 20 min). Furthermore, both drugs were significantly more potent than glibenclamide between 30 and 50 min after the meal; repaglinide was still notably higher than glibenclamide at the 60-min time point.

CONCLUSIONS — Insulin secretagogues have different effects on the insulin secretion, largely conditioned by their individual pharmacokinetic profiles and their actions on the pancreatic ATP-sensitive potassium channels (KATP). For instance, repaglinide is rapidly absorbed from the gut and the time to peak (T*max*) plasma concentration in humans is 30–50 min (22). By contrast, glibenclamide and glipizide have a much slower absorption with T*max* over 120 min (23,24). Although all secretagogues lead to inhibition of the KATP channel and depolarization of the β-cell with subsequent insulin exocytosis, the duration and magnitude of this effect are variable among the antidiabetic agents. Therefore, repaglinide has been shown to inhibit the KATP channels more potently than glibenclamide in animal models (25), with a higher stimulation of the insulin release in vitro and in vivo (26).

We have previously shown that repaglinide increased the insulin secretion rate within 30 min after a solid meal and improved the early phase of secretion in diabetic subjects (20). Similarly, nateglinide, another member of the meglitinide family, improved the early insulin secretion and reduced the prandial glucose excursions after a liquid meal (21) and after an intravenous glucose challenge (27). The effects of the sulfonylureas on the early insulin secretion have been studied less. Gliclazide has been shown to increase the early insulin response after an intravenous glucose tolerance test in both nondiabetic and diabetic subjects (28). In a study using hyperglycemic clamp technique in nondiabetic volunteers, glibenclamide had no effect on the first phase of insulin secretion (29). Glibenclamide was also less effective than nateglinide in reducing the incremental glucose AUC after a liquid meal (30).

Our study confirmed that the three test drugs—repaglinide, glipizide, and glibenclamide—were all powerful insulin secretagogues. An increase of >47% (47% glipizide, 54% repaglinide, and 61% glibenclamide) in the total insulin (AUC –15 to 240 min) secretion was noted in diabetic patients when compared with placebo. The diabetic subjects in our study had relatively preserved β-cell function, and therefore, a good secretory response was expected. In a real clinical context, however, this group of patients represents a minority of the type 2 diabetic population requiring pharmacological intervention. An extrapolation of these results to all diabetic populations requiring drug treatment should be undertaken with care.

We found that repaglinide, as previously reported (20), significantly increased the insulin secretion in the early phase both in diabetic and nondiabetic subjects. Interestingly, glipizide was very similar to repaglinide with respect to the effects on the early phase. Moreover, glipizide reached significance against glibenclamide in both groups of subjects, whereas repaglinide was significantly more effective than glibenclamide only in the nondiabetic group.

Due to its pharmacokinetic properties, the effects of repaglinide become apparent within 30 min after intake (22).

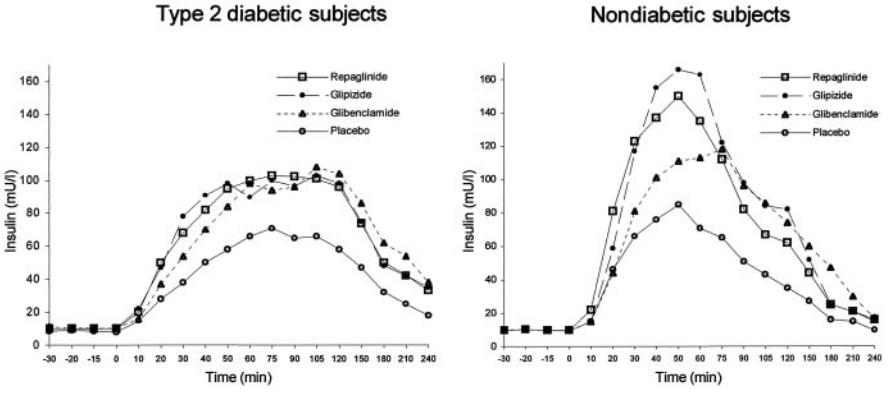

Figure 2—*Mean concentration-time profiles of insulin in type 2 diabetic and nondiabetic subjects.*

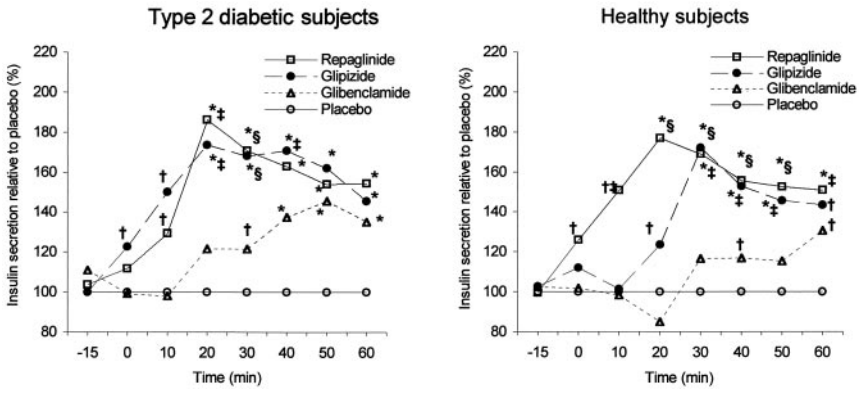

Figure 3—*Mean estimated insulin secretion rates relative to placebo for the first 60 min after the meal. Significant difference against placebo:* $P < 0.05$ (†), $P < 0.01$ (*). *Significant difference against glibenclamide:* $P < 0.05$ (‡), $P < 0.01$ (§).

Calculated insulin secretion rates in our study confirmed these observations. Repaglinide boosted the secretion significantly more than placebo, as early as 15 min after drug ingestion (0 min on the ISEC profiles). Glipizide, on the other hand, increased the secretion rates slightly later (after the 10-min point in diabetics and after the 20-min point in nondiabetic control subjects) but well before glibenclamide had any significant effect. Our findings were confirmed by a recent study done in rats (31). Repaglinide and nateglinide stimulated an early increase in the insulin secretion with a subsequent decrease of the prandial glucose excursions after the meal (powdered rodent diet), whereas glibenclamide had no significant effect. Glipizide, on the other hand, had intermediate effects, with less early insulin secretion than repaglinide and nateglinide but still significant decreasing the glucose excursions compared with the vehicle (control).

The differences in the insulin secretion were partly associated with corresponding effects on blood glucose in the nondiabetic subjects. Therefore, repaglinide was more effective than glibenclamide in reducing postmeal glucose peaks (glucose *Cmax*). Furthermore, whereas both repaglinide and glipizide significantly lowered the peaks compared with placebo (mean reduction 1.1 mmol/l with repaglinide and 0.8 mmol/l with glipizide), glibenclamide had no significant effect. The clinical significance of a decrease in the glucose *Cmax* of the magnitude shown in our study is unclear. On the other hand, total postprandial glucose exposure may be at least as important as the acute exposure (glucose *Cmax*) with respect to harmful consequences. Glibenclamide was significantly less effective than repaglinide in decreasing the total glucose AUC in this group of subjects. Glipizide also seemed to have greater effects than glibenclamide on the total glucose AUC, although it did not reach statistical significance on direct comparison. Interestingly, these differences were noted despite significantly more insulin being secreted by glibenclamide in the late phase (AUC –120 to 240 min).

Insulin resistance and reduced β-cell insulin secretory capacity are important factors in the pathogenesis of type 2 diabetes. Glucose toxicity accentuates and compounds the secretory defect and also enhances the insulin resistance (32). The effects of various insulin secretagogues are expected, therefore, to be less evident in the diabetic patients compared with the normal subjects. Our study showed that both repaglinide and glipizide maintained their efficacy on decreasing the postprandial glucose peaks (glucose *Cmax*) in type 2 diabetic patients with preserved β-cell function compared with placebo (mean reduction 1.1 mmol/l with repaglinide and 1.3 mmol/l with glipizide). Again, similar to the effects in nondiabetic subjects, glibenclamide did not significantly impact the peak postprandial glucose. All study drugs, on the other hand, similarly reduced total glucose AUC (AUC –15 to 240 min). The latter contrasts with the observations in nondiabetic population, in which significant differences were noted between repaglinide and glibenclamide. Also, the magnitude of the reduction in the total glucose AUC (AUC –15 to 240 min) versus placebo was smaller in the diabetic population compared with their nondiabetic peers. These data suggest a reduction in the insulin action with an effacement of the interdrug differences in the diabetic subjects, most likely due to increased resistance to insulin in this population.

Our study compared the effects of a single dose of each of the three drugs on the insulin and glucose profiles after a single meal. This scenario, however, could be different in the clinical practice situation. Therefore, whereas repaglinide has a short half-life and the effects of one dose would have entirely disappeared before the next meal, the other two drugs have a long duration of action. The effects of glipizide and glibenclamide on subsequent meals during a 24-h period cannot be assumed to be identical to the observations after a single meal.

In summary, our data show that repaglinide significantly enhanced the early phase of insulin secretion in both nondiabetic and diabetic subjects. This resulted in a significant reduction in the postprandial glucose peaks compared with placebo.

We also showed that glipizide, a second-generation sulfonylurea, has similar effects to repaglinide on the early phase of insulin secretion. Therefore, in both groups of subjects, insulin levels were significantly higher than with glibenclamide. Postprandial glucose peaks were significantly lower compared with placebo.

Glibenclamide had no significant effect on the early phase of insulin secretion and consequently failed to significantly change the postprandial glucose peaks. Its action became evident only on the late phase of insulin secretion. However, total postprandial glucose-lowering effect (AUC –15 to 240 min) was similar to the other two drugs in the diabetic patients.

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