

Increased Prandial Insulin Secretion After Administration of a Single Preprandial Oral Dose of Repaglinide in Patients With Type 2 Diabetes

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OBJECTIVE — To examine the dose-related pharmacodynamics and pharmacokinetics of a single preprandial oral dose of repaglinide in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 16 Caucasian men with type 2 diabetes participated in two placebo-controlled double-blind randomized cross-over studies. Patients were randomized to receive a single oral dose of repaglinide (0.5, 1.0, and 2.0 mg in study 1 and 4.0 mg in study 2) or placebo (both studies) administered 15 min before the first of two sequential identical standard meals (breakfast and lunch) that were 4 h apart. During each of the study days, which were 1 week apart, blood samples were taken at frequent intervals over a period of ~8 h for measurement of plasma glucose, insulin, C-peptide, and repaglinide concentrations.

RESULTS — During the first meal period (0–240 min), administration of repaglinide reduced significantly the area under the curve (AUC) for glucose concentration and significantly increased the AUC for insulin levels, C-peptide levels, and the insulin secretion rate. These results, compared with those of administering placebo, were dose dependent and log linear. The effect of repaglinide administration on insulin secretion was most pronounced in the early prandial period. Within 30 min, it caused a relative increase in insulin secretion of up to 150%. During the second meal period (240–480 min), there was no difference between repaglinide and placebo administration in the AUC for glucose concentration, C-peptide concentration, and the estimated insulin secretion rate.

CONCLUSIONS — A single dose of repaglinide (0.5–4.0 mg) before breakfast improves insulin secretion and reduces prandial hyperglycemia dose-dependently. Administration of repaglinide had no effect on insulin secretion with the second meal, which was consumed 4 h after breakfast.

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The relative roles of pancreatic β -cell dysfunction and decreased insulin sensitivity in the pathogenesis of type 2 diabetes remain unclear (1–3). Regardless of which is the primary defect, by the time

“frank” type 2 diabetes is established, both defects coexist to varying degrees. The increase in hyperglycemia is paralleled by a decreasing capacity of the β -cell to secrete insulin. By comparison, although insulin

sensitivity in most patients with type 2 diabetes is markedly reduced when plasma glucose exceeds 7.0 mmol/l, there is relatively little further reduction in insulin sensitivity with increasing fasting glycemia (4). This finding supports the view that β -cell dysfunction has a major impact on the progression of established type 2 diabetes.

The U.K. Prospective Diabetes Study confirmed that improving glycemic and blood pressure control in type 2 diabetes decreases the incidence of microvascular complications; however, despite earlier evidence that poor glycemic control is one of many risk factors for macrovascular complications (5–7), the study provided little evidence that this approach reduces the incidence of macrovascular complications (8). One possibility for this apparent contradiction is that the profile of postprandial hyperglycemia in type 2 diabetes, rather than fasting blood glucose levels, contributes significantly to the development of macrovascular complications (9).

Deficient early prandial insulin secretion is a consistent abnormality in patients with type 2 diabetes, in people with impaired glucose tolerance, and in the children of patients with type 2 diabetes (4,10–14). Postprandial hyperglycemia and the delayed hyperinsulinemia in patients with type 2 diabetes are reduced when the early phase of insulin secretion is restored by intravenous insulin infusion (15,16). This effect suggests that postprandial hyperinsulinemia results from the persistent postprandial hyperglycemia that is caused by the absence of an early insulin response to limit prandial glucose excursions. Of the currently available oral hypoglycemic agents, only sulfonylureas act by stimulating insulin secretion (17).

Repaglinide is a novel enantiomeric benzoic acid derivative. It is an insulin secretagogue that acts by closing ATP-sensitive potassium channels in the β -cell membrane. Although sulfonylureas stimulate the same secretory mechanism (18), studies in vitro indicate that repaglinide has a distinct β -cell-binding site and that its effect is

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Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; C_{max} , maximal plasma concentration; CV, coefficient of variation; RIA, radioimmunoassay; T_{max} , time to maximal concentration.

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

Table 1—Baseline characteristics of the study subjects

	Total group	Study 1	Study 2
Age (years)	58.3 ± 9.0	55.6 ± 8.6	61.7 ± 9.5
Weight (kg)	86.7 ± 7.7	89.4 ± 9.0	83.3 ± 5.2
BMI (kg/m ²)	28.2 ± 2.6	29.6 ± 2.1	26.4 ± 1.9
Time from diagnosis (months)	67.8 ± 29.4	71.1 ± 27.9	63.6 ± 35.1
Fasting plasma glucose (mmol/l)	10.0 ± 3.6	9.7 ± 3.2	10.5 ± 4.6
HbA _{1c} (%)	8.66 ± 1.68	8.21 ± 1.71	0.24 ± 1.70

Data are means ± SD.

likely to be mediated through this site; blockage of a common repaglinide-glibenclamide-binding site abolishes the effect of glibenclamide, leaving the effect of repaglinide unaltered. This may explain the differences in the cellular mechanism of action of the two drugs (19). Repaglinide, unlike glibenclamide, does not stimulate insulin secretion in the absence of glucose *in vitro* (19). Furthermore, repaglinide, unlike sulfonylureas (20), does not inhibit glucose-stimulated insulin biosynthesis in pancreatic islets. The potential clinical significance of this requires further examination.

These findings suggest that repaglinide is suitable for preprandial administration in type 2 diabetic patients with a view to improving prandial insulin secretion and hyperglycemia. We report here the results of studies investigating the dose-response relationship between single preprandial doses of repaglinide and the ensuing plasma concentration profiles of glucose, insulin, and C-peptide and the derived insulin secretion rates in patients with type 2 diabetes.

RESEARCH DESIGN AND

METHODS—A cohort of 16 Caucasian men with type 2 diabetes, who had been treated with diet only, took part in one of two placebo-controlled double-blind block-randomized cross-over studies. Patients who had severe late complications of diabetes, severe concurrent diseases, or who were taking concomitant medications were excluded.

In study 1 (n = 9), patients were randomized to receive different sequences of three single oral doses of repaglinide (0.5, 1.0, and 2.0 mg) and placebo each on 4 study days that were 1 week apart. In study 2, patients (n = 7) were randomized to two "sequences": a single oral dose of repaglinide 4.0 mg or placebo. Each of the 6 study days was 1 week apart.

Smoking was not permitted during any study day. All participants gave informed

consent, and both studies had the approval of local research ethics committees and were performed in accordance with the Declaration of Helsinki.

After a 10-h overnight fast, each patient was cannulated, and a baseline venous blood sample was taken. Patients received their study medication orally 15 min after cannulation (t = -15 min). Patients began a standard test meal (55% carbohydrate, 30% fat, and 15% protein with a calorific value of 500 kcal) 15 min later (t = 0). A second identical meal was commenced 4 h later (t = +240 min). Venous blood samples were taken at frequent intervals (-30, -15, 0, 15, 30, 45, 60, 75, 90, 105, 120, 165, 225, 240, 270, 300, 360, 420, and 480 min) after dosing for measurement of plasma glucose, insulin, C-peptide, and repaglinide concentrations.

Plasma was separated from blood samples by centrifugation and stored at -20°C before analysis. Glucose concentrations were measured with an autoanalyzer (Chemlab Instruments, Hornchurch, Essex, U.K.) by using an enzymatic colorimetric method with intra- and interassay coefficients of variation (CVs) of <2%. Immunoreactive insulin levels were measured with a modification of the radioimmunoassay (RIA) method of Heding (21) by using a second antibody to separate the

free and antibody-bound ¹²⁵I-insulin (intra- and interassay CVs: 4.6 and 7.3%, respectively). C-peptide concentrations were determined with the RIA method of Heding (22), which was modified by polyethylene glycol-assisted precipitation by using a second antibody to separate bound and free ¹²⁵I-labeled synthetic Tyr-C-peptide (intra- and interassay CVs: 5.4 and 8.8%, respectively). Plasma repaglinide concentrations were determined with a stereoselective enzyme-linked immunosorbent assay with values interpolated from a calibration curve. The limit of detection of the assay was 1 ng/ml with a CV of 3.8–6.3% for the concentration range 0.5–50 ng/ml.

Data from both studies were combined because the study designs were identical, except for the doses of repaglinide, and the baseline characteristics of both groups, including their metabolic profiles, were similar. There was no systematic difference between the two study groups for the placebo period. Data were analyzed separately for the first (t = 0–240 min) and second (t = 240–480 min) meal periods. The effects of repaglinide and placebo on glucose, insulin, and C-peptide plasma concentration profiles were compared by performing an analysis of covariance (ANCOVA) on the areas under the plasma concentration-time curve during period 1 (AUC_{0–240min}) and period 2 (AUC_{240–480min}). The plasma concentration of each parameter at the beginning of each analysis period was used as a covariate for the ANCOVA. The dose-relationship of these pharmacodynamic responses was examined by estimating the population means of each parameter for each repaglinide dose and for placebo during period 1 (i.e., an average of all values during that period) by use of the method of least-square means. The insulin secretion rates were estimated from C-peptide concentrations and demographic infor-

Table 2—Comparison of the C_{max} and T_{max} of pharmacodynamic parameters during the first 4 h after receiving a single dose of either oral repaglinide (0.5, 1.0, 2.0, and 4.0 mg) or placebo

Treatment	Glucose (mmol/l)		Insulin (pmol/l)		C-peptide (nmol/l)	
	C _{max}	T _{max}	C _{max}	T _{max}	C _{max}	T _{max}
Placebo	14.5 ± 4.1	86.3 ± 20.1	423.4 ± 213.2	102.2 ± 22.7	2.6 ± 0.9	119.1 ± 15.9
Repaglinide						
0.5 mg	13.3 ± 3.0	70.0 ± 10.6	579.3 ± 263.8	101.7 ± 18.0	3.0 ± 1.0	120.0 ± 18.4
1.0 mg	12.9 ± 3.9	70.0 ± 10.6	614.9 ± 259.2	105.0 ± 16.8	3.2 ± 1.1	121.7 ± 13.9
2.0 mg	13.1 ± 3.7	75.0 ± 15.0	694.7 ± 284.9	93.3 ± 27.8	3.2 ± 1.1	113.3 ± 30.1
4.0 mg	12.0 ± 3.3	62.1 ± 10.4	654.0 ± 426.8	100.7 ± 25.6	3.9 ± 1.0	137.1 ± 36.2

Data are means ± SD.

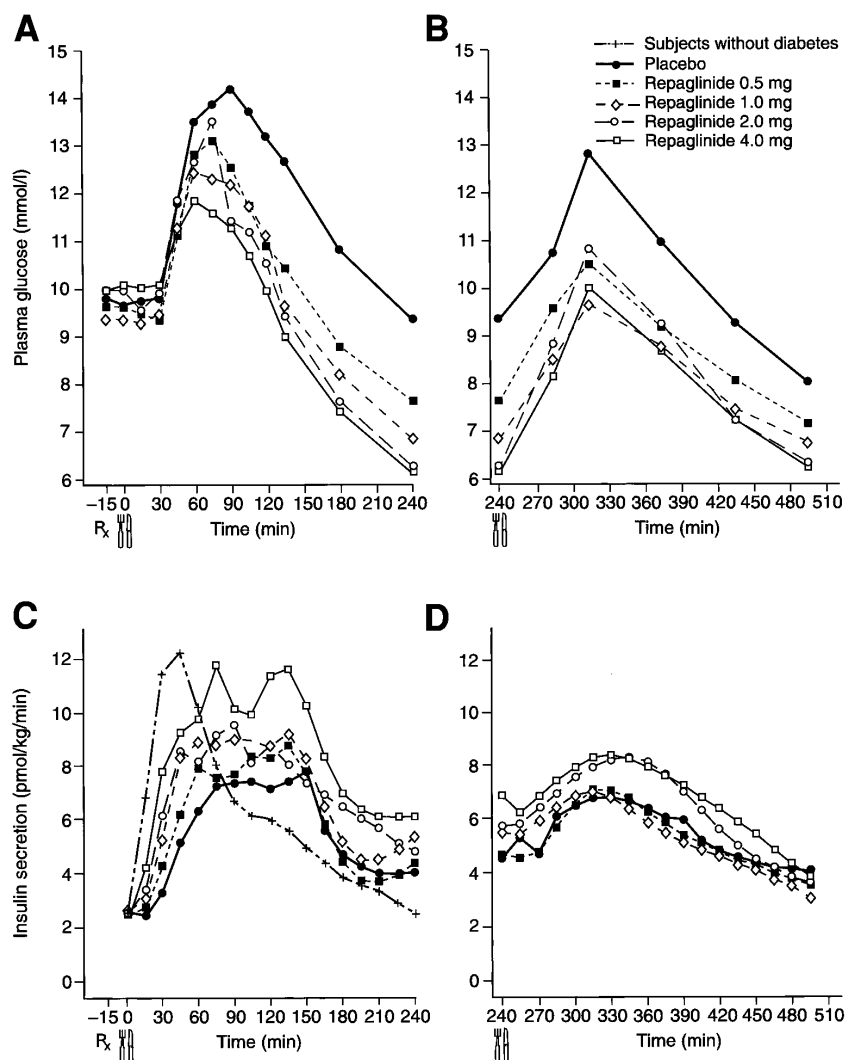


Figure 1—The mean plasma concentration–time profiles of glucose during periods 1 (A) and 2 (B) and the mean estimated insulin secretion profile during periods 1 (C) and 2 (D) after receiving single oral doses of repaglinide 0.5, 1.0, 2.0, 4.0 mg or placebo, followed by two test meals. Data for insulin secretion from healthy control subjects are shown for comparison with period 1.

mation by using the ISEC (Insulin SEcretion) program developed by Hovorka et al. (23). The responses to repaglinide and placebo on insulin secretion rates were then estimated and compared by using ANCOVA with mean blood glucose as a covariate. This adjustment for blood glucose is important because prandial insulin secretion in patients with type 2 diabetes deteriorates as fasting hyperglycemia worsens (4) and the insulin-secretory effect of most insulin secretagogues varies with plasma glucose concentrations (24). Dose-response relationships were fitted as polynomials; however, all fits could be reduced to linear relationships.

The relative contribution of repaglinide to insulin secretion was evaluated by calculating the percentage of the insulin secretion rate and the C-peptide concentration relative to placebo for each dose of repaglinide. Finally, the dose-response relationship of plasma repaglinide concentrations was examined using regression analysis of log-log plots of $AUC_{0-240 \text{ min}}$ and the maximal plasma concentration (C_{max}). Plasma levels of repaglinide after 4 h were negligible and were therefore ignored for the purposes of the AUC calculation.

RESULTS — Baseline characteristics for both study groups are shown in Table 1.

There were no significant differences between groups; notably, their metabolic profiles (plasma glucose, C-peptide, and insulin concentrations) were very similar.

Mean C_{max} and time to maximal concentration (T_{max}) are shown in Table 2. Administration of repaglinide at all doses (0.5–4.0 mg) reduced both the mean plasma glucose C_{max} and T_{max} compared with administration of placebo during period 1; this effect was reflected in an increase in the C_{max} of both insulin and C-peptide compared with placebo. For patients treated with repaglinide, as compared with those patients who received placebo, the AUC_{0-240} for glucose was significantly smaller ($P = 0.0001$), whereas the AUC_{0-240} for insulin and C-peptide was significantly larger ($P = 0.0001$). The C_{max} after receiving placebo during period 2 was notably smaller than that during period 1.

The mean plasma concentration–time profiles for glucose and the mean estimated insulin secretion rate profile for each treatment for periods 1 and 2 are shown in Fig. 1. During period 1, total insulin secretion in patients treated with repaglinide was significantly greater than in subjects treated with placebo ($P = 0.0001$). In addition to the overall increase in the insulin secretion rate, administration of repaglinide greatly increased the insulin secretion rate during the first 30 min after the first test meal. Higher doses of repaglinide caused a more rapid and steeper rate of insulin secretion that more closely mimicked the profile of healthy subjects without diabetes. In the period after the second test meal, when no repaglinide was given, there was no residual effect on the insulin secretion from the dose given with the first meal.

During period 1, there was a log-linear reduction in mean plasma glucose concentration with increasing repaglinide dose, and this occurrence was reflected by a log-linear increase in the mean insulin, C-peptide, and derived total insulin secretion with increasing repaglinide concentration. The dose-response relationships of the estimated mean plasma concentrations for mean glucose and total insulin secretion during periods 1 and 2 are shown in Fig. 2. During period 2, there were no significant differences between the repaglinide and placebo treatment groups for mean glucose concentration. The difference between repaglinide at all doses overall and placebo was significantly higher for the mean insulin concentration ($P = 0.04$) during this period. However, the difference was

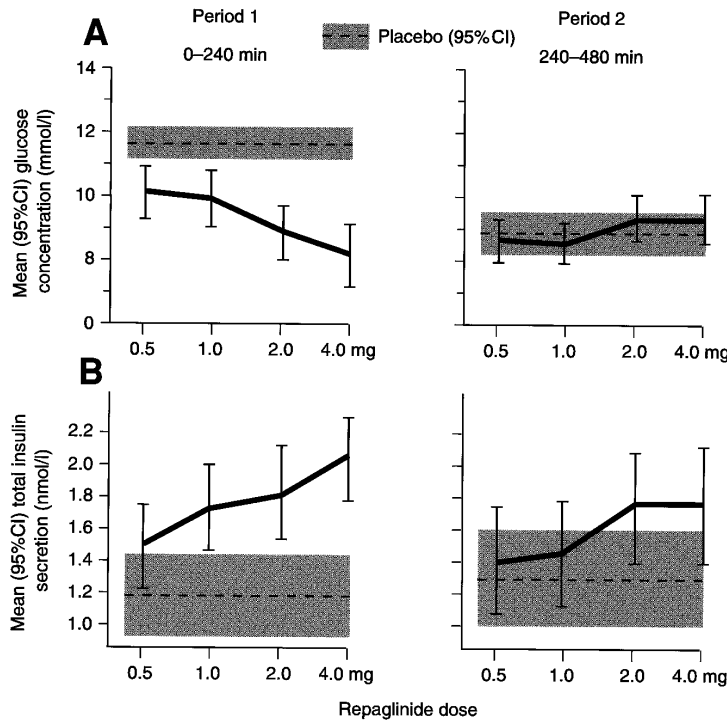


Figure 2—Mean plasma concentrations of **A** glucose and **B** estimated insulin secretion after receiving single oral doses of repaglinide (0.5, 1.0, 2.0, 4.0 mg) or placebo for periods 1 and 2.

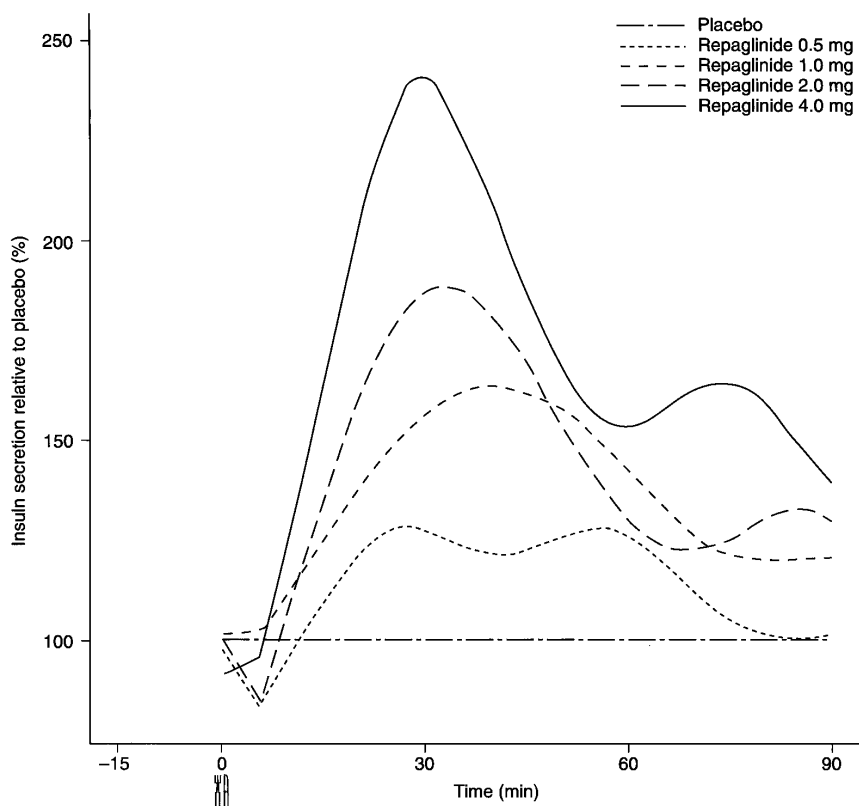


Figure 3—Mean estimated insulin secretion rates relative to placebo after receiving single oral doses of repaglinide (0.5, 1.0, 2.0, 4.0 mg) or placebo for the first 90 min after consuming a meal.

smaller than that during period 1, and there were no significant differences between the repaglinide and placebo treatment groups for C-peptide concentrations or derived insulin secretion.

Figure 3 shows the percentage of the increase in insulin secretion relative to placebo for the first 90 min after treatment. The highest dose of repaglinide (4.0 mg) resulted in an almost 150% relative increase in insulin secretion rate in the early postprandial period (~30 min). Figures 2 and 3 confirm the dose-dependent effect of repaglinide.

The mean plasma concentration–time profiles for each dose of repaglinide are shown in Fig. 4. The T_{max} was similar for all doses of repaglinide at ~30 min. By the end of the first meal period (240 min), plasma levels of repaglinide were below the level of detection. The log-log plots of $AUC_{0-240 \text{ min}}$ and C_{max} for plasma repaglinide concentrations by dose were linear. C_{max} showed dose proportionality (95% CI 0.95–1.37), whereas the AUC was close to dose proportionality (95% CI 1.11–1.36).

No clinically significant adverse events or laboratory abnormalities were observed.

CONCLUSIONS — We have shown that a single preprandial dose of repaglinide (0.5, 1.0, 2.0, or 4.0 mg) increased plasma insulin and C-peptide concentrations within 30 min of a meal in patients with type 2 diabetes, particularly at the higher doses (2 and 4 mg). Furthermore, insulin secretion in the first meal period increased dose-dependently and was significantly greater than placebo at all dose levels. The early phase of insulin secretion in particular was significantly improved by repaglinide. The drug effect could be seen within 10 min after the first meal with the peak response at ~30 min, which caused the overall insulin secretion profile of these patients to resemble more closely that of subjects without diabetes. These effects were associated with a blunting of prandial hyperglycemia and an overall reduction in the plasma glucose concentration in the first meal period.

For the second meal period, the difference in the mean glucose and C-peptide concentrations between repaglinide and placebo was not significant. For plasma insulin, the difference between repaglinide and placebo was significant, but the difference was smaller than that of period 1. Furthermore, the difference in insulin secretion between repaglinide and placebo was not significant. These pharmacodynamic

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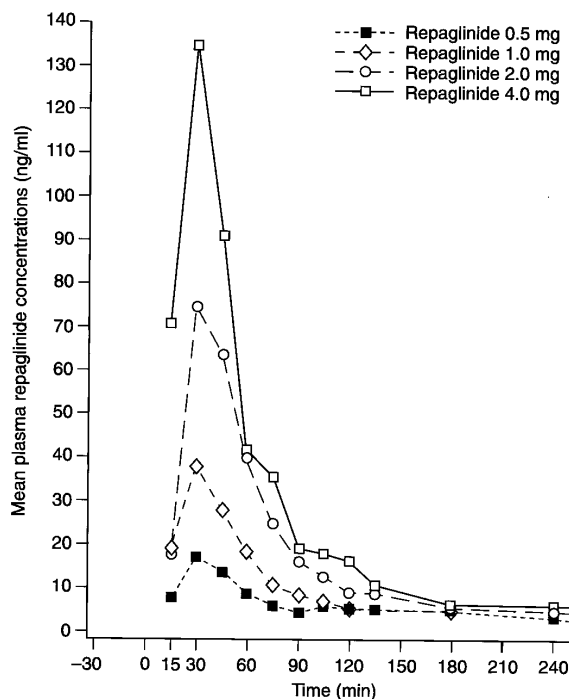


Figure 4—Mean plasma concentration–time profiles of repaglinide after receiving single oral doses of repaglinide 0.5, 1.0, 2.0, or 4.0 mg for period 1.

findings are consistent with the pharmacokinetic properties of repaglinide (i.e., rapid absorption and elimination) (25,26). Our present results show that plasma concentrations of repaglinide, even at the highest dose, were negligible within 4 h of administration. In addition to its rapid absorption and short plasma half-life, a decline in the effectiveness of repaglinide as an insulin secretagogue at low plasma glucose concentrations in vitro has been found (19). Our findings confirm that the insulin secretion properties of repaglinide are short lived and that repaglinide has the added characteristics of a prandial insulin secretagogue.

Although the pharmacodynamics and pharmacokinetics of repaglinide show that its action is brief, we also found that prandial hyperglycemia was blunted after the second meal. This finding suggests that, in addition to its acute antihyperglycemic effect, repaglinide may improve overall glycemic control. The reduction in plasma glucose levels by repaglinide after the first meal may, by lowering the plasma glucose concentration, have reduced glucose toxicity and thus improved β -cell function by the time of the second meal. In a previous study, patients with type 2 diabetes who were treated preprandially three times daily with repaglinide had even greater glycemic

control than patients treated with the same total daily dose of repaglinide administered preprandially twice daily (27). These results and our results support the concept of prandial glucose regulation as a means of improving prandial insulin secretion and overall glycemic control.

The finding that repaglinide improves acute hyperglycemia and may improve overall glycemic control suggests that repaglinide may reduce the risk of the microvascular and macrovascular complications associated with type 2 diabetes. Intensive blood glucose control decreases the risk of microvascular but not macrovascular complications (5); however, given that acute hyperglycemia is believed to be involved in atherosclerosis (28), an improvement in acute postprandial hyperglycemia may possibly decrease macrovascular complications.

In conclusion, we have shown that a single preprandial dose of repaglinide improves insulin secretion and reduces prandial hyperglycemia dose-dependently. Repaglinide, particularly, improves the early phase of insulin secretion, but it has little or no effect on insulin secretion after a second meal eaten 4 h later. These results confirm that repaglinide is a short-acting prandial insulin secretagogue that reduces

postprandial hyperglycemia, which may improve overall glycemic control in patients with type 2 diabetes.

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