

Optimizing Insulin Secretagogue Therapy in Patients With Type 2 Diabetes

A randomized double-blind study with repaglinide

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OBJECTIVE — Repaglinide, a novel antidiabetic agent that has a rapid onset and short duration of action, was developed for mealtime dosing. The purpose of this pharmacodynamic study was to validate a prandial regimen of repaglinide by comparing meal-related dosing with a regimen in which the same total daily dose was divided into only two doses at morning and evening meals.

RESEARCH DESIGN AND METHODS — The study was a double-blind, randomized, parallel-group trial in 19 antidiabetic agent-naïve subjects with type 2 diabetes (mean age 58 years, known duration of diabetes 3.5 years, HbA_{1c} 7.3%, and BMI 32 kg/m²). Patients were randomly assigned to receive repaglinide either before each of the three main meals or before breakfast and before the evening meal. Patients in both groups received the same total daily dose of repaglinide. Twenty-four hour profiles of blood glucose, plasma insulin, and plasma C-peptide concentrations were measured at baseline and after 4 weeks of treatment.

RESULTS — Repaglinide increased postprandial insulin levels and markedly reduced postprandial glucose levels relative to baseline in both groups. Significant reductions were also recorded in fasting blood glucose and HbA_{1c} levels. The repaglinide regimen, in which a dose was taken before each main meal, was more effective in improving glycemic control (including postprandial glucose and HbA_{1c} levels) than the same total dose of repaglinide divided into morning and evening mealtime doses.

CONCLUSIONS — These data support the strategy of mealtime dosing with repaglinide. The improvements in glycemic control observed in these patients are encouraging. In addition to classic parameters of glycemic control, improvements in postprandial glucose excursions may prove to be important because postprandial hyperglycemia has been suggested to be an independent risk factor for cardiovascular disease in diabetes.

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Type 2 diabetes is characterized by impaired insulin secretion, usually with concomitant impaired insulin sensitivity (1,2). Insulin secretagogue therapy is therefore a logical part of therapy of type 2 diabetes when diet and lifestyle modifications fail. Secretagogue therapy is the appropriate means to augment circulating insulin levels in patients

with a moderate degree of β -cell dysfunction; in individuals with more advanced β -cell dysfunction, exogenous insulin therapy may be necessary.

Sulfonylureas have been used for almost five decades as insulin secretagogues in the management of type 2 diabetes. Sulfonylureas stimulate insulin secretion and thereby reduce hyperglycemia, with

few side effects. Nevertheless, the long plasma half-life and the long-lasting effect of some sulfonylureas increase the risk of hypoglycemia, especially in elderly patients and in patients with renal insufficiency (3–5). As the need to achieve near-normal glycemia becomes recognized in the light of the findings of large prospective studies, hypoglycemia is likely to become an increasingly common feature of type 2 diabetes (6,7). In addition, sulfonylurea therapy may introduce restrictions in patients' daily lives because of the increased hypoglycemic risk associated with missed or delayed meals (8).

Repaglinide, a carbamoylmethyl benzoic acid derivative, is a novel antidiabetic agent that differs from sulfonylureas in molecular structure, profile of action, and mode of excretion. In contrast to available sulfonylureas, repaglinide binds to a specific and distinct site on the pancreatic β -cell, blocking ATP-dependent potassium channels to stimulate insulin release only in the presence of nutrient and without suppressing cellular protein synthesis (9). Furthermore, this compound has no direct effects on the insulin release process apart from those mediated by its specific binding to the β -cell (10). The drug has a rapid absorption and fast elimination profile, with a plasma half-life of <1 h in healthy volunteers (11).

Repaglinide is recommended for use in a prandial dosing regimen, with a dose being taken before each main meal. In contrast to those receiving longer-acting insulin secretagogues such as sulfonylureas, patients treated with repaglinide are free to vary their meal pattern from two to four main meals daily and are also able to vary the timing of meals without impairing efficacy or augmenting the risk of hypoglycemia (12). Previously reported studies involving placebo or sulfonylureas as comparators have established the efficacy of repaglinide in improving glycemic control as being at least equivalent to that of conventional oral hypoglycemic agents (13,14).

The purpose of this pharmacody-

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Abbreviations: AUC, area under the curve.

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

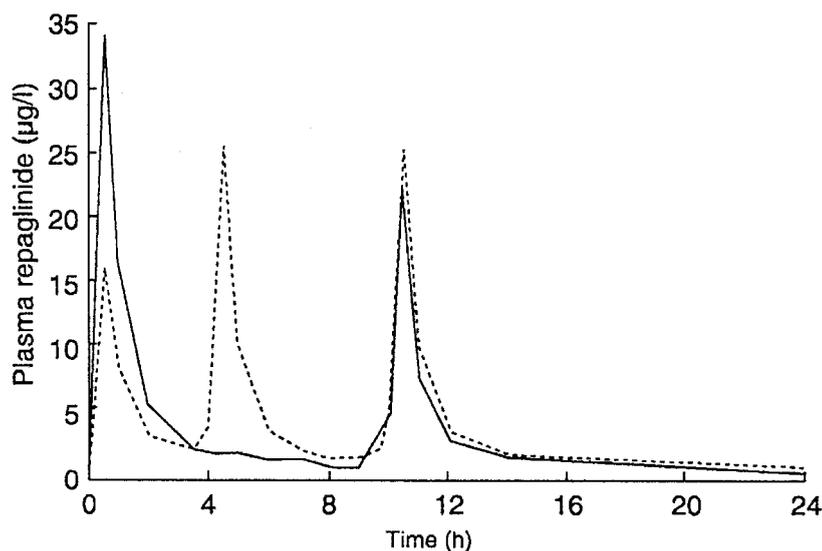


Figure 1—Plasma repaglinide levels after 4 weeks of treatment with three mealtime doses (---) or two doses at morning and evening meals (—).

dynamic study was to validate the prandial regimen of repaglinide by comparing meal-related dosing with a regimen in which the same total daily dose was divided into only two doses before morning and evening meals.

RESEARCH DESIGN AND METHODS

This 4-week study was a double-blind, randomized, parallel-group trial in subjects with type 2 diabetes. The study was performed according to the Declaration of Helsinki, and informed consent was obtained from all participants.

A total of 20 patients entered the study, 19 of whom were randomized to treatment groups. Patients entering the study had not previously received drug treatment for type 2 diabetes and had been diagnosed with the disease for at least 1 year. Patients were randomly assigned to receive repaglinide, 0.75 mg daily, in one of two treatment regimens. The group assigned to receive repaglinide with each meal received a 0.25-mg dose before each of the three main meals; the group assigned to receive two daily doses received 0.5 mg repaglinide before breakfast and 0.25 mg before the evening meal, with a placebo tablet taken with lunch. Mealtime dosages were doubled in all patients after 2 weeks (i.e., to a total daily dose of 1.5 mg repaglinide in both groups). Of note, in a group of drug-naive and previously sulfonylurea-treated type 2 diabetic patients, 0.5 mg repaglinide

three times a day has been demonstrated to lead to ~70% of the maximal glucose-lowering effect (15). Two patients withdrew due to adverse events (one patient with influenza and one with mild hypoglycemia), and one patient was excluded from analysis due to noncompliance with study criteria. The 16 remaining patients had a mean age 58 ± 6 years (\pm SD), BMI 32 ± 5 kg/m², and known duration of diabetes 3.5 ± 4.0 years. Mean baseline fasting blood glucose was 11.2 mmol/l and HbA_{1c} was 7.3%.

Twenty-four-hour profiles for blood glucose, plasma insulin, and plasma C-peptide were measured at baseline and after 4 weeks. These profiles were each based on 43 measurements. In addition, a 24-h profile for plasma repaglinide was also obtained after 4 weeks. On both occasions, patients received a standard breakfast (2,213 kJ) at 8:00 A.M., followed by lunch at noon and an evening meal at 6:00 P.M. Lunch and the evening meal were individualized according to weight and were identical for each patient at baseline and the 4-week visit.

Plasma glucose measurements were immediately performed using a Beckman glucose analyzer, HbA_{1c} was measured by high-performance liquid chromatography (normal range <6.2%), and immunometric plasma insulin and C-peptide measurements were performed at a central laboratory. The insulin assay exhibited no cross-reactivity with proinsulin and proinsulin fragments. Insulin secre-

tion rates were calculated according to the combined model from the measurements of insulin and C-peptide (16).

Statistical methods

The changes from baseline to 4 weeks in fasting blood glucose, 2-h postprandial levels, and HbA_{1c} were analyzed by standard statistical methods for paired and nonpaired data. The area under the glucose curve, calculated by the trapezoidal method, as well as the maximal postprandial levels and the times of maximum were compared for the two treatment regimens. The slope of the initial rise in insulin concentration during the first 30 min after each meal was calculated by regression analysis, and the changes from baseline to 4 weeks were analyzed for the two treatments.

RESULTS— Plasma repaglinide profiles confirmed the rapid pharmacokinetics of this agent (Fig. 1), with peaks following each mealtime dose consistent with its very rapid absorption and stated half-life of ~1 h. As a result, both repaglinide regimens markedly increased ($P \leq 0.020$) postprandial plasma insulin levels relative to baseline (Fig. 2). Blood glucose levels throughout the day were reduced by both regimens relative to baseline ($P < 0.01$) (Fig. 2). Significant reductions were recorded in postprandial glucose, fasting glucose, and HbA_{1c} levels (Table 1).

Comparing the two repaglinide regimens, area under the curve (AUC) of prandial (0–16 h) plasma insulin levels tended to be higher in patients receiving doses before all meals (0.233 ± 0.053 nmol/l) than in those receiving doses with only two of three meals (0.197 ± 0.041), though the difference was barely statistically significant ($P = 0.06$) (Fig. 1). This effect would be expected in the lunchtime period (when no repaglinide was taken in the two-dose group) but was also seen after breakfast and the evening meal. As a result, it was evident that despite identical total daily repaglinide doses in each group, three daily repaglinide doses were more effective than two in controlling blood glucose (Table 1). Postprandial glucose levels after each meal were 2.3–2.8 mmol/l lower in patients receiving three doses compared with those receiving two, and fasting glucose levels were 1.9 mmol/l lower. Reductions in HbA_{1c} were also significantly greater with three repaglinide

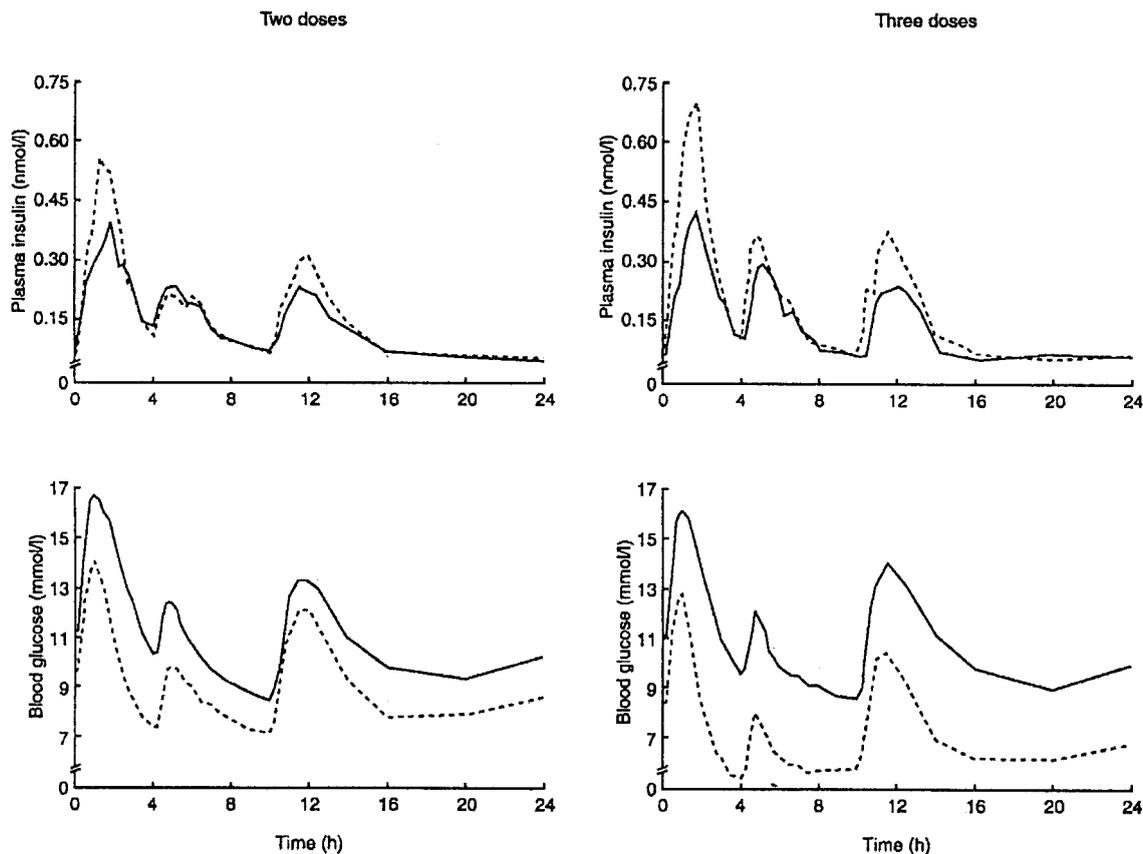


Figure 2—Plasma insulin and blood glucose levels at baseline (—) and after 4 weeks of treatment (- - -).

doses than with two, despite the relatively short treatment period (difference between groups in HbA_{1c} change 0.72%, $P = 0.028$). Total glucose exposure, measured as AUC for glucose, was reduced to a significantly greater extent in the three-dose group than in the two-dose group (Table 1). Similarly, plasma glucose maxima (C_{max}) and nadirs (C_{min}) were numerically lower in the three-dose group than the two-dose group, with differences reaching statistical significance in the 10- to 16-h and 4- to 10-h intervals, respectively (Table 1).

Table 2 shows that 4 weeks of treatment with repaglinide led to significantly steeper initial rises in insulin within the first 30 min after breakfast and dinner ($P < 0.05$) compared with baseline. These data suggest a substantial improvement in early-phase insulin secretion with repaglinide in type 2 diabetes. This is confirmed in the group treated with repaglinide at lunch, who showed markedly higher early-phase postlunch insulin secretion compared with the group who received no dose at lunch (although the

change from baseline did not reach statistical significance). Similar results were obtained by analysis of the corresponding initial rises in C-peptide and insulin secretion rates (data not shown).

No serious adverse events occurred during the study; minor adverse events were confined to mild hypoglycemia.

CONCLUSIONS— The present study demonstrated that improvements in glycemic control with repaglinide are greater when the total daily dose is given with all main meals versus doses at breakfast and dinner and no dose at lunch. This offers support to the recommended dosing regimen for repaglinide, in which a dose is taken with each main meal, the number of which can vary from two to four daily.

As would be expected with a rapid-acting mealtime-dosed insulin secretagogue, repaglinide administration significantly augmented mealtime insulin secretion. In particular, early-phase insulin secretion (0–30 min) was significantly increased by repaglinide compared with baseline. The importance of early-phase

insulin secretion, reaching a peak ~10 min after β -cell stimulation, to normal physiological insulin response has been well demonstrated (17,18). It has also been clearly shown that early-phase insulin release is one of the first defects to appear as type 2 diabetes develops (17,19–24). Although initially compensated for by an increase in late-phase insulin output, this insulin is inappropriately timed to suppress hepatic glucose production and effectively restrain the rise in postprandial glucose levels (25). An ability to pharmacologically restore early-phase insulin secretion in type 2 diabetes is therefore particularly welcome.

The enhanced prandial insulin secretion with repaglinide was reflected in reductions in postprandial glucose levels that are likely to be of clinical relevance, even with the low doses of repaglinide used in this study (0.5 mg/meal). This alone is an important attribute of repaglinide because postprandial hyperglycemia is increasingly suspected of involvement in the pathogenesis of late diabetic complications, especially cardio-

Table 1—Changes in glycemc control during the study and glycemc variables after 4 weeks treatment

	Two doses repaglinide				Three doses repaglinide				
	Baseline	4 weeks	Change from baseline	P for change from baseline	Baseline	4 weeks	Change from baseline	P for change from baseline	P between groups
Glycemc control									
Fasting glucose (mmol/l)	11.3 (2.3)	9.6 (2.1)	-1.7 (1.2)*	0.0021	11.1 (3.3)	8.4 (2.0)	-2.7 (2.6)†	0.0311	0.3724
2-h postprandial glucose (mmol/l)									
Breakfast	15.0 (2.8)	10.7 (2.8)	-4.3 (2.4)*	0.0006	13.7 (4.9)	8.2 (3.0)	-5.5 (3.3)*	0.0047	0.4063
Lunch	10.7 (2.8)	9.0 (2.1)	-1.7 (2.2)†	0.0450	9.8 (3.7)	6.2 (1.6)	-3.7 (2.9)†	0.0151	0.1449
Evening meal	13.3 (2.1)	12.1 (2.2)	-1.2 (1.6)	0.0514	13.6 (3.9)	9.8 (1.8)	-3.8 (2.5)*	0.0073	0.0247
HbA _{1c} (%)	7.1 (0.7)	6.8 (1.0)	-0.3 (0.6)	0.179	7.5 (2.0)	6.5 (1.7)	-1.0 (0.7)*	0.004	0.028‡
Glycemc variables									
Glucose AUC (normed, mmol/l)									
0–24 h			8.91 (1.74)				7.00 (1.50)†		0.036‡
0–16 h			9.38 (1.79)				7.37 (1.75)†		0.041‡
Glucose C _{max} (mmol/l)									
0–4 h			14.41 (2.46)				13.02 (2.36)		0.273
4–10 h			10.07 (2.17)				8.11 (1.33)		0.055‡
10–16 h			12.70 (1.88)				10.48 (2.11)†		0.043‡
Glucose C _{min} (mmol/l)									
0–4 h			7.28 (2.66)				5.04 (1.92)		0.081
4–10 h			6.91 (1.39)				5.30 (1.21)†		0.030‡
10–16 h			7.69 (2.28)				6.06 (1.52)		0.124

Data are means (SD). * $P < 0.01$ for change from baseline; † $P < 0.05$ for change from baseline; ‡ $P < 0.05$ for change between groups. C_{max}, maximum concentration reached; C_{min}, minimum concentration reached (nadir).

vascular morbidity (26). We also found that repaglinide improves fasting (preprandial) glucose levels as well as HbA_{1c} levels despite only 4 weeks of treatment. The findings match those in other studies with repaglinide (27–29). The fact that the reduction in prandial glucose excursions induced by this short-acting compound also leads to a reduction in fasting glycemia clearly underlines the importance of controlling prandial glycemia. Although improvements in all glycemc parameters were observed with both repaglinide regimens, dosing with all meals yielded the greater improvement in each case.

Indeed, it is remarkable that the dif-

ferences between the two dosing regimens in this study were not confined to the lunchtime period, when the repaglinide dose was omitted in the two-dose group, and therefore do not simply represent an “escape from control” that might have been predicted when no dose was given with lunch. Figure 2 shows that glucose levels were lower throughout the day in patients taking the drug with each meal, including the preprandial and fasting states, despite the fact that the same total daily dose was administered in each group. This does not represent a more persistent effect of repaglinide in patients receiving doses with each meal because

Figs. 1 and 2 indicate that the presence of repaglinide and its effects on insulin levels are confined to the prandial period. This is confirmed by the analysis of insulin secretion rate, which showed that repaglinide had no effect on lunchtime insulin secretion when given in a two-dose regimen, confirming that the pharmacological effects of this agent do not extend from one meal period to the next. In principle, the benefit of mealtime dosing with repaglinide may reflect a reduction in glucose toxicity in which a greater reduction in blood glucose levels restores a degree of β -cell responsiveness, allowing an enhanced recovery of the endogenous insu-

Table 2—Effects of repaglinide on early-phase insulin response in terms of initial slopes (means and SD) after intake of meals

Slope of insulin vs. time curve (pmol · l ⁻¹ · min ⁻¹)	Two doses			Three doses		
	Baseline	4 weeks	Change from baseline	Baseline	4 weeks	Change from baseline
Breakfast (0–30 min)	5.6 (3.4)	7.4 (4.3)	1.8 (2.9)*	4.9 (3.2)	8.9 (7.1)	4.0 (4.8)*
Lunch (240–270 min)	2.4 (1.2)	2.6 (2.2)	0.2 (2.0)	4.5 (2.9)	6.9 (6.3)	2.3 (4.3)
Dinner (600–630 min)	1.7 (1.9)	3.2 (2.1)	1.5 (1.5)*	1.7 (2.9)	5.5 (5.3)	3.8 (3.8)*

Data are means (SD). * $P < 0.05$ for change from baseline.

lin response to meals. However, the observed improvements in insulin secretion are unlikely to be solely due to reduced glucotoxicity, given the absence of improvement in lunchtime insulin secretion. On the other hand, improved control of glucose excursions at lunch resulted in enhanced early-phase prandial insulin release at the evening meal, despite lower glucose concentrations (Fig. 2). This observation was absent at lunch in the twice-daily regimen, indicating that the improvement may rely on repaglinide treatment at that time.

Significantly steeper initial rises in postprandial insulin levels versus baseline were seen after 4 weeks of treatment with repaglinide (Table 1 and Fig. 2), despite the reduction in glucose levels that had occurred. Because this effect was also present when C-peptide and prehepatic insulin secretion rates were analyzed, it can be concluded that repaglinide treatment augments early-phase β -cell secretion rather than reduces insulin clearance.

In conclusion, these data support a strategy of mealtime dosing with a rapid-acting insulin secretagogue such as repaglinide. The duration of action of repaglinide is seen to be sufficient to effectively suppress postprandial hyperglycemia but short enough that the effects of each mealtime dose are separate from those of the next dose—a feature that permits the flexible dosing regimen used in clinical practice and contributes to the low risk of hypoglycemia with this agent. It is clear that meal-related dosing in type 2 diabetes, in which a dose of short-acting insulin secretagogue is administered at every main meal, approaches the optimum for this form of therapy.

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