Flexible Meal-Related Dosing With Repaglinide Facilitates Glycemic Control in Therapy-Naive Type 2 Diabetes

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OBJECTIVE — This double-blind randomized placebo-controlled parallel group study assessed the efficacy and safety (with particular regard to body weight and hypoglycemia) of repaglinide when used in a flexible mealtime dosing regimen in a situation close to everyday clinical practice.

RESEARCH DESIGN AND METHODS — A total of 408 patients with type 2 diabetes considered poorly controlled by diet, but without a history of previous antidiabetic medication, were randomized to receive 0.5 mg repaglinide at mealtimes (increased to 1 mg after 4 weeks depending on blood glucose response) or placebo for 16 weeks. Patients were free to choose a flexible meal pattern, adjusting the dosing schedule from two to four preprandial doses per day in accordance with a "one meal, one dose; no meal, no dose" principle. Additional snacks were not a requirement of the treatment schedule.

RESULTS — Treatment with repaglinide significantly improved glycemic control with respect to baseline and placebo, reducing HbA_{1c} by 1.14% from baseline and fasting plasma glucose by 1.8 mmol/l. Improvement in glycemic control was independent of the meal pattern adopted by patients, including those most commonly taking two or four meals daily, with no correlation between meal pattern and risk of hypoglycemia. The improvement in glycemic control was also independent of degree of obesity and age ≤65 or >65 years. There was no significant body weight increase in the repaglinide group.

CONCLUSIONS — Mealtime dosing with repaglinide is effective in improving overall glycemic control in type 2 diabetic patients for which control is suboptimal using diet alone. Patients are able to vary their meal pattern from a conventional regimen of three meals daily without compromising control or increasing the risk of adverse events.

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Repaglinide is a novel insulin secretagogue developed for treating type 2 diabetes with a flexible mealtime dosing regimen (1). When dosed preprandially, repaglinide has been shown to augment insulin secretion within the first 30 min of commencing a meal, with no residual secretagogue activity detectable 4 h later (2). This prandial approach to the management of plasma glucose is a logical one, as it addresses one of the primary physiological defects in type 2 diabetes: the progressive loss of the early-phase prandial insulin response (3,4).

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Abbreviations: FPG, fasting plasma glucose.

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

Previous studies in healthy individuals and people with type 2 diabetes have shown that repaglinide is highly effective in controlling both postprandial and fasting plasma glucose (FPG) levels (5–7), and comparative studies of repaglinide and sulfonylureas have shown repaglinide to have comparable or superior efficacy in terms of postprandial glucose and FPG levels and HbA_{1c} (8–11). However, to reduce the risk of hypoglycemia, these studies used fixed-dose and mealtime regimens in accordance with the requirements of sulfonylureas. Indeed, one study demonstrated that, in contrast to the case with repaglinide, missing a meal during glibenclamide treatment significantly increased the risk of hypoglycemia (12). Comparative studies are therefore unsuitable for investigations of the flexible-dosing principle of repaglinide. In the present study, we sought to assess whether the efficacy and safety of repaglinide determined in fixed-dose fixed-meal studies would be sustained when patients were free to vary their number and timing of meals. This was important to establish given the flexible prandial dosing recommended for repaglinide. Inclusion criteria for the study were intended to reflect the real-life decision to start oral antidiabetic therapy; included were patients who were, in the investigator's opinion, candidates for such therapy, rather than those who met an arbitrary cutoff for glycemic control.

RESEARCH DESIGN AND METHODS

— This double-blind randomized placebo-controlled parallel group study was performed in 61 centers in 13 countries. It was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

Patients recruited to the study had type 2 diabetes, as defined by World Health Organization criteria at the time of the study (13), and were at least 40 years of age. Treatment of type 2 diabetes at entry was by diet alone, but in the investigator's opinion, the glycemic control achieved with this treatment was suboptimal. Patients who had previously received oral antidiabetic agents were excluded, as were patients with

Table 1—*Baseline characteristics of patients in the study (intention-to-treat population)*

	Repaglinide	Placebo
n	260	134
Age (years)	57.5 ± 9.0	57.4 ± 8.6
Female sex (%)	46.5	42.5
Ethnic origin (%)		
African	0.4	0
Caucasian	98.8	98.5
Asian	0	0
Other	0.8	1.5
Weight (kg)	84.0 ± 16.1	86.6 ± 16.7
Height (m)	1.67 ± 0.09	1.67 ± 0.09
BMI (kg/m^2)	30.0 ± 5.0	30.9 ± 5.5
Duration of diagnosed diabetes (years)	2.99 ± 4.58	3.07 ± 4.69
Presence of complications (%)		
Retinopathy	0.4	0.7
Nephropathy	0.8	0
Neuropathy	0	0
Microangiopathy	0	0
HbA_{1c} (%)	7.8 ± 1.8 (4.1–13.4)	7.6 ± 1.5 (4.8–12.1)
FPG (mmol/l)	9.9 ± 3.1 (5.0–22.3)	9.6 ± 2.7 (5.2–19.0)

Data are means ± SD or means ± SE (range) unless otherwise indicated. For FPG, n = 259 and n = 133 in the repaglinide and placebo groups, respectively.

hepatic disease, significant cardiovascular disease (including severe uncontrolled hypertension), or other diabetic complications indicative of a late disease state. Patients whose HbA_{1c} deteriorated by ≥1% during the study were withdrawn.

Of 455 patients screened, 408 entered the study. Patients were randomized in a ratio of 2:1 to receive either repaglinide, 0.5 mg at mealtimes (270 patients), or placebo (138 patients). In each case, one tablet was taken immediately before each main meal, in accordance with the dietary pattern of the individual patient (two to four times daily). If a meal was skipped or postponed, the trial medication for that meal was also skipped or postponed, and if a meal was added, trial medication was also added. Patients on repaglinide initially received a prandial dose of 0.5 mg, with the dose being doubled after 4 weeks if FPG exceeded 7.8 mmol/l. Patients remained on this dose for a further 12 weeks.

Efficacy and safety measures

Glycemic control was assessed by HbA_{1c} and FPG performed at the screening visit, after 4 weeks, and after a further 12 weeks. All tests were performed by a central laboratory, except for the week-4 blood glucose measurement, which used an appropriately calibrated capillary blood glucose meter (One Touch Basic; LifeScan). The HbA_{1c} measurement was made using ion exchange in EDTA anticoagulated whole blood (Bio-Rad DIAMAT) (reference range 4.0–6.0%, coefficient of variation <2.0%).

Weight, blood pressure, and clinical laboratory values were recorded at baseline and after 4 and 12 weeks. Meal frequency was recorded after 4 and 12 weeks, allowing analysis according to daily meal number based on each patient's most frequent behavior. Quality-of-life questionnaires were also issued to patients at three time points during the study; results are described elsewhere (14).

All adverse events occurring during the study were recorded, whether observed by the investigator or reported spontaneously by the patient and whether or not they were considered related to trial medication. Hypoglycemia was to be reported as an adverse event only if it represented a serious event (e.g., one that was life-threatening); however, all hypoglycemic episodes were recorded and are reported below. Hypoglycemia was defined as either minor (the patient experienced symptoms but dealt with the situation alone) or major (third-party help was required).

Statistical analysis

All calculations of efficacy were performed on an intention-to-treat population, defined as all patients who were randomized and exposed to at least one dose of trial medication and who yielded data from at least one visit after treatment initiation. Safety analyses were based on the population of patients randomized and exposed to at least one dose of trial medication. Where observations were missing, the last observation for that patient was used for analysis (last observation carried forward). Differences at a 95% CI ($P \leq 0.05$) were considered statistically significant.

RESULTS — Of the 408 patients randomized, 394 received at least one dose of study medication and attended at least one clinic visit. The study was completed by 316 patients: 219 in the repaglinide group and 97 in the placebo group. Withdrawal was significantly more frequent in the placebo group than in the repaglinide group ($P = 0.013$), the principal reason being ineffective therapy. At 4 weeks, 32% of patients in the repaglinide group and 54% in the placebo group had their doses increased.

Patient groups were well matched at baseline, with no significant differences in characteristics (Table 1). No differences were detected in the baseline demographic characteristics or level of glycemic control between completers and noncompleters in either the treatment or placebo groups.

Glycemic control

Glycemic control improved significantly in patients treated with repaglinide during the 16 weeks of the study compared with baseline and with the placebo group. In the repaglinide group, HbA_{1c} levels decreased from baseline by a mean 1.14% ($P < 0.001$); in the placebo group, a nonsignificant decline of 0.15% was recorded ($P = 0.16$; Fig. 1). At the end of the study, mean HbA_{1c} levels were 0.99% lower in the repaglinide group than in the placebo group ($P < 0.001$). Few patients were withdrawn because of a decline in HbA_{1c} ≥1%: four recipients of repaglinide and five of placebo.

Data from individual countries confirmed the overall efficacy result: mean HbA_{1c} levels for repaglinide-treated patients declined in every country, and the difference in HbA_{1c} change between study groups was in favor of repaglinide in 12 of the 13 countries. In the remaining country (Croatia), data were available for just eight patients, of whom only two were assigned to placebo.

FPG levels also decreased significantly in the repaglinide group during the study, with a mean reduction of 1.80 mmol/l ($P <$ 0.001 from baseline; Fig. 1). A mean 1.44

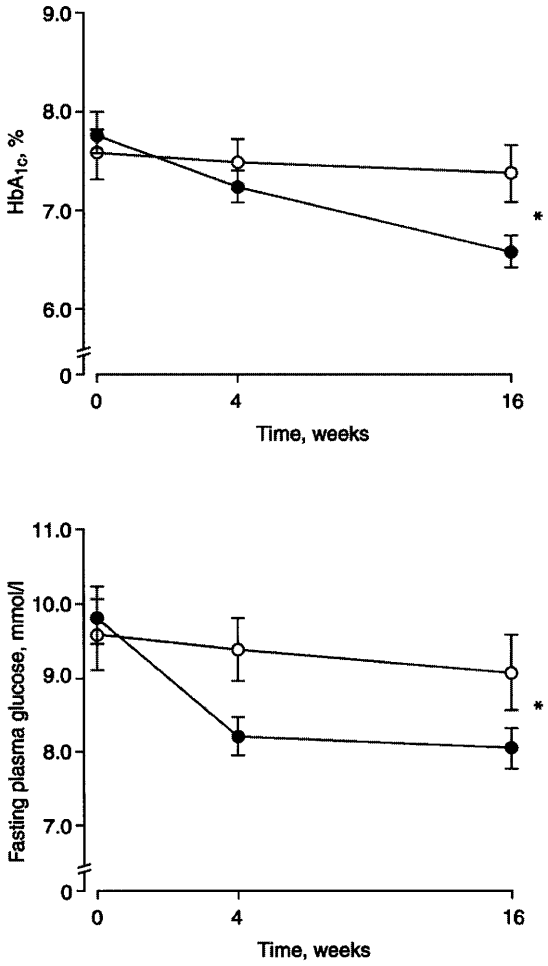

Figure 1—*Changes in HbA_{1c} and FPG in type 2 diabetic patients uncontrolled by diet and treated with repaglinide (●) or placebo (○). Data are means ± 2 SEM. *P < 0.001.*

mmol/l greater reduction in the repaglinide group compared with the placebo group was statistically significant ($P < 0.001$). The improvement in FPG was near maximal at 4 weeks, with HbA_{1c} predictably decreasing further over the remaining 12 weeks.

The improvement in glycemic control with repaglinide was reflected by changes in the classification of patients by European guidelines (15). At baseline, 50% of repaglinide-treated patients were classified as being in poor control (HbA_{1c} >7.5%), but at end point, 25% of these patients had achieved good control ($HbA_{1c} \leq 6.5\%$), and a further 45% achieved borderline control (HbA_{1c} >6.5 and ≤ 7.5%). Overall, 50% of repaglinide-treated patients ended the study in good glycemic control compared with 24% at baseline. Baseline levels of control in the placebo group were similar to those in the repaglinide group and changed little during the study.

Improvement in HbA_{1c} in the repaglinide group was independent of the recorded meal pattern. Thus, patients whose most frequent number of daily meals was two or fewer (67 patients), those having three meals a day (177 patients), and those reporting four or more meals (15 patients) all achieved significant improvements in HbA_{1c} ($P \leq 0.05$) compared with baseline and with the corresponding placebo groups. There was a trend toward a greater improvement in HbA_{1c} in repaglinide-treated patients who recorded four or more meals compared with those recording fewer meals (Table 2). However, meal frequency was not a significant predictor of HbA_{1c} improvement, confirming that response to repaglinide treatment is independent of meal pattern.

Improvement in glycemic control was similar in patients aged >65 and ≤65 years (Table 2). Glycemic control was also independent of degree of obesity, with equivalent efficacy in patients with high BMI (>30 kg/m^2) compared with leaner patients. Indeed, there was a suggestion that more obese patients benefited more from the active treatment (Table 2).

Body weight

Repaglinide therapy had no significant effect on body weight, with respect to placebo. In both treatment groups, a slight increase occurred during the study (on a case, observed basis), but there was no significant difference between groups in body weight change during the 12-week maintenance period (P = 0.49, NS; Fig. 2) despite the superiority of repaglinide in improving glycemic control. Analysis using the last-observation-carried-forward method confirmed the weight-neutral effect

Table 2—*Changes in HbA_{1c} with repaglinide and placebo according to meal pattern, age, and BMI and weight change according to meal pattern*

	Most frequent number of meals			Age (years)		BMI (kg/m^2)		
	≤2	3	≥4	≤65	>65	≤25	26–30	>30
Repaglinide								
Change in HbA_{1c} (%)	−0.89 ± 0.17	−1.15 ± 0.14	−1.98 ± 0.52	−1.14 ± 0.10	−1.16 ± 0.17	−1.01 ± 0.19	−1.08 ± 0.14	−1.24 ± 0.13
Change in weight (kg)	−0.1 ± 3.3	0.7 ± 3.2	1.3 ± 3.3	—	—	—	—	—
Placebo								
Change in HbA_{1c} (%)	−0.29 ± 0.22	−0.03 ± 0.17	0.15 ± 0.57	−0.18 ± 0.10	−0.06 ± 0.12	0.02 ± 0.24	−0.26 ± 0.13	−0.11 ± 0.12
Change in weight (kg)	−0.1 ± 2.4	−1.3 ± 3.4	0.3 ± 2.4	—	—	—	—	—

Data for HbA_{1c} are means ± SEM; data for weight are means ± SD. Data are calculated on an intention-to-treat basis.

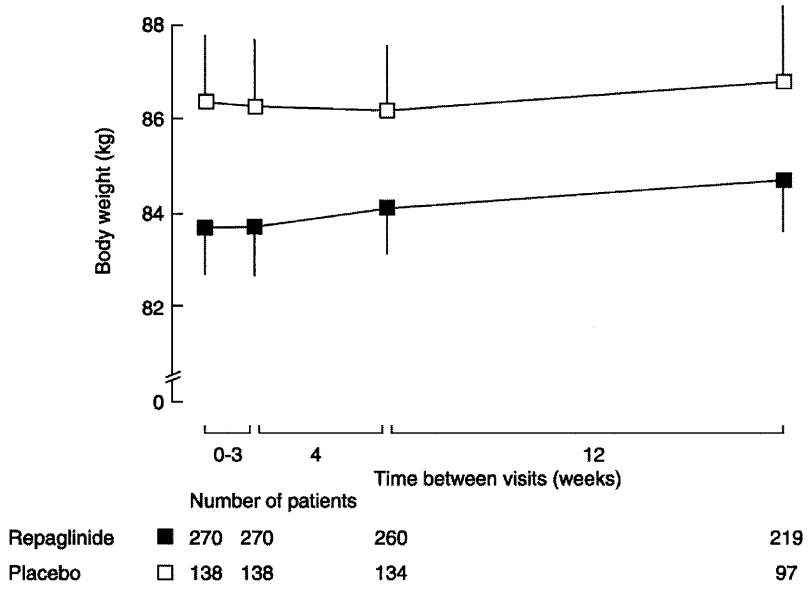

Figure 2—*Changes in body weight during the study. Data are means ± SEM of observed cases.*

of repaglinide, with a nonsignificant 0.35 kg weight increase in this group. An analysis of weight change by preferred daily meal frequency revealed no clear trends because the magnitude of mean weight change between baseline and end point was small, but with wide standard deviations in all patient categories (Table 2).

Safety and adverse events

As expected, the most frequent adverse event during the study was hypoglycemia. Some 17% of patients in the repaglinide group (18% during treatment with 0.5 mg/meal, 11% during treatment with 1.0 mg/meal) and 3% in the placebo group reported minor episodes during the study. Three repaglinide-treated patients (1%) reported a total of four major hypoglycemic events. The baseline HbA_{1c} values for these patients were 7.2, 7.8, and 8.5%. One major event occurred in a patient receiving 0.5 mg/meal repaglinide (16-week patient incidence 0.5%), and the remainder occurred in patients receiving 1 mg/meal (16-week patient incidence 2.4%); no hypoglycemic events required hospitalization or intravenous glucose or glucagon.

There was no indication that the risk of hypoglycemia in the repaglinide group was related to meal pattern: 15% of patients taking two or fewer meals daily had a hypoglycemic episode compared with 19% of patients taking three meals and 7% of patients taking four or more meals daily.

Other adverse events were infrequent and similar in frequency between treatment groups. The overall tolerability of repaglinide was similar to placebo: excluding hypoglycemia, 29% of patients in the repaglinide group and 30% in the placebo group reported an adverse event. The nature and distribution of these events was similar in the two study groups. Adverse events leading to withdrawal were mostly minor and included liver enzyme elevations (two placebo, one repaglinide patient); abdominal pain, dyspepsia, or constipation (four repaglinide patients); and facial edema (one repaglinide patient). A total of 12 serious adverse events were recorded, involving 2.6% of patients in the repaglinide group and 2.9% in the placebo group. Three repaglinide patients withdrew after serious adverse events (grand mal convulsions, paresthesia, and pancreatitis).

CONCLUSIONS — The aim of the present study was to assess, in a situation close to everyday clinical practice, the efficacy and safety of repaglinide used in a flexible prandial regimen. Earlier comparative studies have suggested that the levels of glycemic control achievable with fixed-dose fixed-mealtime schedules of repaglinide are at least equivalent to those of other antidiabetic agents, including sulfonylureas (8–11,16). One previous 20-day study randomized 25 patients to receive prandial repaglinide taken either with three regular daily meals or with varied alternating numbers of daily meals/doses (12). This study concluded that meal-associated repaglinide was well tolerated and reduced total plasma glucose exposure regardless of the meal/dose schedule. The present study builds on the validation of flexible prandial glucose regulation with repaglinide as a treatment strategy for type 2 diabetes by examining a larger cohort of patients over 16 weeks under placebo control.

Since baseline status influences the magnitude of improvement in glycemic control and rate of hypoglycemia that can be achieved, it is not appropriate to compare absolute results from previous studies with those of the present study. Rather, we sought to determine whether the clinical profile of repaglinide differed from placebo and varied across different meal schedules. The flexible prandial application of repaglinide markedly improved glycemic control in patients naive to oral antidiabetic agents, producing improvements in FPG and HbA_{1c} that were both statistically significant and clinically relevant. Importantly, the present study demonstrated that these improvements, together with the risk of hypoglycemia, were independent of the meal pattern chosen.

This finding is of clinical significance because a rapid onset and short duration of action with insulin secretagogue therapy does not guarantee meal flexibility. A recent placebo-controlled study involving the short-acting secretagogue nateglinide, for example, showed a modest change in fasting glucose to reach statistical significance with only one of four dose levels (17), while another study of this agent showed that 24-h glucose exposure was only reduced by four prandial doses per day (18). In the present study, however, fasting blood glucose and HbA_{1c} improved significantly in patients taking two, three, or four meals/doses per day. Although the numbers of patients in the four meals/day group was small, the trend in this group was to greater improvement in glycemic control and less frequent hypoglycemia than found in the other groups.

The doses of repaglinide used in the present study (0.5–1.0 mg) were relatively low compared with the recommended maximum of 4 mg/meal. In practice, therefore, further dose titration in individuals remaining poorly controlled could be expected to provide further improvement. However, our cohort comprised antidiabetic medication–naive patients who were not in outstandingly poor glycemic control, so further dose escalation was not consid-

ered appropriate. Indeed, our cohort may have been more representative of a clinical population in whom instigation of oral antidiabetic medication would first be considered than defined by HbA_{1c} criteria.

The lack of weight gain in the repaglinide group in this study is particularly encouraging, since improved glycemic control is often associated with significant increases in weight, particularly with therapies that increase total insulin exposure (19). Such treatment-induced weight gain is clinically undesirable in the obese patient with type 2 diabetes and could be disheartening for patients advised to lose weight. Overall weight changes in this study were slight and nonsignificant; body weight remained relatively stable over time, with the repaglinide group paralleling the placebo group (Fig. 2). These results are concordant with those of a recently completed open-label study involving a cohort of nearly 6,000 patients with type 2 diabetes that showed no weight gain associated with flexible prandial repaglinide in patients naive to antidiabetic drug therapy or switched from alternative antidiabetic agents (20). This study also showed that patients switched from sulfonylureas reduced their daily frequency of supplementary snacks. A treatment strategy that improves glycemic control by increasing prandial insulin secretion without incurring a penalty of significant weight gain would be clinically welcome.

In summary, this is the first randomized placebo-controlled study to examine the flexible prandial use of repaglinide in a clinical setting. There was no indication that deviations from a three meals per day pattern led to compromised glycemic control, weight gain, or an increased incidence of hypoglycemia. These data imply that patients can truly individualize the number and timing of their meals while treated with prandial repaglinide. The majority of patients chose to follow the traditional pattern of three daily meals, but it is nevertheless reassuring to establish that patients can choose alternative meal patterns even if only on an occasional ad hoc basis. We would anticipate that providing patients with type 2 diabetes with greater flexibility in their daily lives, while maintaining safety and glycemic control, is likely to markedly improve treatment acceptance and compliance.

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