Mealtime Glucose Regulation With Nateglinide in Healthy Volunteers

Comparison with repaglinide and placebo

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OBJECTIVE — This study was designed to compare the pharmacodynamic effects of single doses of nateglinide (A-4166), repaglinide, and placebo on mealtime insulin secretion and glycemic control in healthy subjects.

RESEARCH DESIGN AND METHODS — Fifteen healthy volunteers participated in this open-label five-period crossover study. They received single 10-min preprandial doses of 120 mg nateglinide, 0.5 or 2 mg repaglinide, or placebo or 1 min preprandially of 2 mg repaglinide. Subjects received each dose only once, 48 h apart. Pharmacodynamic and pharmacokinetic assessments were performed from 0 to 12 h postdose.

RESULTS — Nateglinide induced insulin secretion more rapidly than 2 and 0.5 mg repaglinide and placebo (10 min preprandial), with mean rates of insulin rise of 2.3, 1.3, 1.15, and 0.8 $\mu U \cdot ml^{-1} \cdot min^{-1}$, respectively, over the 0- to 30-min postmeal interval. After peaking, insulin concentrations decreased rapidly in the nateglinide-treated group and were similar to placebo within 2 h postdose. After 2 mg repaglinide, peak insulin concentrations were delayed and returned to baseline more slowly than with nateglinide treatment. Nateglinide treatment produced lower average plasma glucose concentrations in the 0- to 2-h postdose interval than either dose of repaglinide and placebo ($P < 0.05$ vs. 0.5 mg repaglinide and placebo). Plasma glucose concentrations returned more rapidly to predose levels with nateglinide treatment than with either dose of repaglinide. Treatment with repaglinide produced a sustained hypoglycemic effect up to 6 h postdose.

CONCLUSIONS — In this single-dose study in nondiabetic volunteers, nateglinide provided a more rapid and shorter-lived stimulation of insulin secretion than repaglinide, resulting in lower meal-related glucose excursions. If similar results are observed in diabetes, nateglinide may produce a more physiological insulin secretory response with the potential for a reduced risk of postabsorptive hypoglycemia.

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Nateglinide (A-4166) is a novel oral agent for the treatment of type 2 diabetes awaiting marketing approval in North America and Europe and already on the market in Japan. A phenylalanine derivative, nateglinide is chemically and pharmacologically distinct from currently available oral antidiabetic agents (1,2). Animal and human studies have shown that nateglinide taken before meals stimulates the rapid and transient secretion of insulin and reduces or eliminates mealtime glucose excursions with minimal hyperinsulinemia or risk of hypoglycemia (2–9).

Repaglinide is an insulin secretagogue of the meglitinide class with a faster onset and shorter duration of action than sulfonylureas (10). In clinical trials in patients with type 2 diabetes, repaglinide provided a similar degree of overall glycemic control to that obtained with glibenclamide but more effectively controlled meal-related glucose excursions (10). Repaglinide is generally well tolerated; however, as with sulfonylureas, hypoglycemia is a potentially dose-limiting side effect (10).

Despite sharing a similar mechanism of action by inhibiting ATP-sensitive potassium channels in pancreatic β-cells (6), the molecular kinetics of nateglinide and repaglinide action differ considerably. Nateglinide imparts a three times more rapid and five times less persistent inhibition of β-cell K^+_{ATP} channels than repaglinide (11). Results from studies in a Cynomolgus monkey model of early type 2 diabetes indicate that the kinetic differences between these agents' actions may translate into a more effective control of mealtime glucose excursions with an equivalent or lower degree of insulin exposure (12).

To assess whether the effects of these two mealtime glucose regulators can be similarly distinguished in humans, the present study compared the effects of nateglinide, repaglinide, and placebo on mealtime insulin secretion and glucose excursions in healthy subjects without evidence of diabetes. The effect of the timing of a meal on the pharmacokinetics and pharmacodynamics of repaglinide was also evaluated for comparison with a similar study of nateglinide (13).

RESEARCH DESIGN AND METHODS

Study participants
Fifteen healthy men and women, 18–45 years of age, entered the study. Participants were required to be nonsmokers and have body weights within ±15% of their normal

Figure 1—*Mean plasma insulin concentrations (± SEM) after treatments with 120 mg nateglinide (NAT), 0.5 and 2 mg repaglinide (REP), and placebo administered 10 min preprandial. P < 0.05 for the following treatment comparisons: *120 mg NAT vs. placebo; **2 mg REP vs. placebo; †120 mg NAT vs. 0.5 mg REP; and ‡120 mg NAT vs. 2 mg REP (comparisons between 0.05 mg repaglinide and placebo not shown).*

range and normal vital signs. Individuals with a history of liver or bronchospastic disease, with any conditions that might affect drug absorption and metabolism, or with clinically abnormal laboratory or electrocardiogram (ECG) results were excluded. Subjects were excluded if they had a recent significant illness or blood loss, a history of drug or alcohol abuse, or used prescription medications within the past 30 days.

All individuals provided written informed consent to participate, and the study protocol received Institutional Review Board (Southern IRB, Miami, FL) approval.

Study design
This open-label randomized crossover study consisted of five treatment periods separated by 48-h interdose intervals. Subjects received, in a fully randomized order, single oral doses of 120 mg nateglinide, 0.5 or 2 mg repaglinide, or placebo 10 min before or 2 mg repaglinide 1 min before a standardized 800-kcal breakfast (55% carbohydrate, 25% fat, and 20% protein).

Subjects remained at the clinical research center (Clinical Pharmacology Associates, Miami, FL) throughout the entire study. They fasted overnight before each treatment period. To explore the pharmacological effects, subjects resumed fasting and

were permitted only water and minimal physical activity for 8 h after breakfast.

Study evaluations
Pharmacokinetics and pharmacodynamics. Plasma concentrations of nateglinide and repaglinide were assessed predose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after drug administration. Plasma glucose and insulin concentrations were measured at multiple time-points from predose to 8 h postdose.
Safety assessments. During screening (days −28 to −2), baseline (day −1), and end-of-study evaluations (day 10), subjects received a complete physical examination, fasting routine laboratory tests, vital signs measurements, and an ECG. Vital signs were also measured during treatment periods, with fasting safety laboratory tests being performed predose during treatments (days 1, 3, 5, 7, and 9). Adverse events were monitored throughout the study.

Sample analysis
Nateglinide and repaglinide plasma concentrations were determined using validated reversed-phase high-performance liquid chromatography methods (4,14). Insulin concentrations were determined by a radioimmunoassay method (Pharma-

cia, Peapack, NJ). Glucose concentrations were measured using a hexokinase-based assay (Beckman, Fullerton, CA).

Statistical analysis
Pharmacokinetic parameters for area under the concentration-time curve (AUC) from 0 to 12 h, maximum plasma concentration (C_{max}), and time to reach C_{max} (t_{max}) were analyzed by standard noncompartmental methods using WinNonlin Professional pharmacokinetic software (version 1.5; Pharsight, Mountain View, CA). Plasma repaglinide concentrations above the limit of quantitation were available only in 3 subjects given 0.5 mg 10 min preprandially, 9 subjects given 2 mg 1 min preprandially, and 11 subjects given 2 mg 10 min preprandially.

Summary statistics, including mean and SEM, of glucose and insulin concentrations were computed by time point for each treatment. Treatments were compared at each time point using paired Student's t tests. Individual rise rates of insulin concentrations over the first 30 min after the meal were computed as (insulin at 30 min − insulin at 0 min)/30. Average insulin and glucose responses over 0–8 h postdose and various intervals therein were computed as the AUC using the trapezoidal rule divided by the length of the time interval. Treatments were compared with respect to these average responses using paired Student's t tests. No adjustments for multiplicity were made, so indications of significance are best interpreted in terms of general patterns.

All statistical tests were two-sided, and a significance level of $\alpha = 0.05$ was used. For comparisons among nateglinide, placebo, and repaglinide, the 10-min preprandial administrations of the latter were considered. The 1- and 10-min preprandial administrations of repaglinide were compared to assess the differences in pharmacodynamic responses associated with these different relative times of drug administration.

RESULTS

Demographics and safety
A total of 12 healthy men and 3 healthy women participated in the study. Three of the participants were white, six were black, and six were Hispanic. The mean (± SD) age, body weight, and BMI were 33 ± 8 years, 73 ± 14 kg, and 24 ± 2.8 kg/m², respectively. Fourteen participants completed the study; one discontinued because
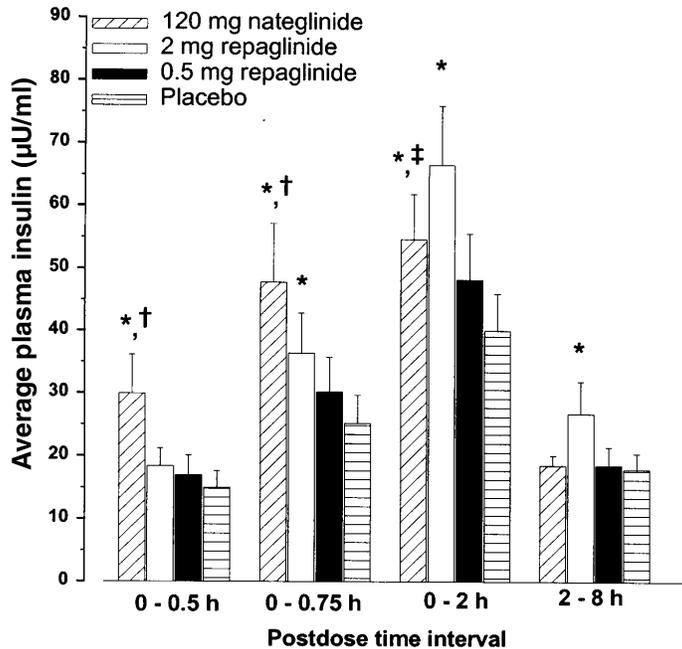
Figure 2—*Average plasma insulin concentrations (± SEM) over specified time intervals after treatment with 120 mg nateglinide (NAT), 2 and 0.5 mg repaglinide (REP), and placebo administered 10 min preprandially. P < 0.05 for the following comparisons: *vs. placebo; †vs. 0.5 mg REP; and ‡vs. 2 mg REP.*

of elevated transaminases after three repaglinide treatment periods.

No clinically meaningful changes in ECGs or vital signs were reported during the study or at the end-of-study evaluations. Six subjects reported a total of nine mild adverse events. These were mostly central nervous system–related (i.e., dizziness, headache, and somnolence) and were comparable across treatments. The one event of moderately elevated transaminases (3–5 × normal) was resolved within 20 days of the last dose.

Pharmacodynamics

All active drug treatments increased plasma insulin levels in response to breakfast relative to placebo. During the initial 30-min post-meal interval (10–40 min postdose), 120 mg nateglinide produced a more rapid induction of insulin secretion than 2 and 0.5 mg repaglinide and placebo (Fig. 1), with mean rates of rise in insulin secretion of 2.3, 1.3, 1.15, and 0.8 $\mu U \cdot ml^{-1} \cdot min^{-1}$, respectively. Plasma insulin concentrations at 10 and 15 min postdose were significantly higher with nateglinide ($P < 0.05$) than with either dose of repaglinide. Mean plasma insulin concentrations peaked at 45 min postdose with nateglinide (94.1 ± 17.1 µU/ml), compared with 1 h for both 2 mg (105.4 ± 19.6 µU/ml) and 0.5 mg (78.7 ± 17.1 µU/ml) repaglinide. After reaching

peak concentrations, mean plasma insulin decreased rapidly in the nateglinide-treated group and was similar to placebo by 2 h postdose. After 1 h postdose, mean plasma

insulin concentrations induced by 2 mg repaglinide were significantly greater than those with nateglinide treatment at every time point ($P < 0.05$), and they remained significantly elevated for at least another 2 h.

The rapid effects of nateglinide resulted in higher average plasma insulin over the early 0- to 0.5-h and 0- to 0.75-h postdose intervals, compared with repaglinide 0.5 mg ($P < 0.05$) and 2 mg ($P < 0.06$ and $P < 0.08$, respectively) (Fig. 2). Late average plasma insulin (2–8 h postdose) after nateglinide was similar to levels observed with placebo, whereas 2 mg repaglinide treatment continued to stimulate insulin secretion from 2 h postdose onwards, resulting in significantly higher insulin exposure than placebo ($P < 0.05$) during the later postdose hours. The average insulin response over the entire 0- to 8-h postdose interval was 25% lower with nateglinide (28 ± 3 µU/ml) than with 2 mg repaglinide (37 ± 6 µU/ml) ($P < 0.05$).

Mean plasma glucose concentrations rose rapidly after breakfast and reached peak levels 45 min postdose after all treatments (Fig. 3). The peak of the mean glucose concentration (i.e., the glucose spike) was lower with nateglinide than with either repaglinide dose or placebo ($P < 0.01$ vs. 0.5 mg repaglinide and placebo; $P < 0.07$ vs. 2 mg repaglinide). For all active drug
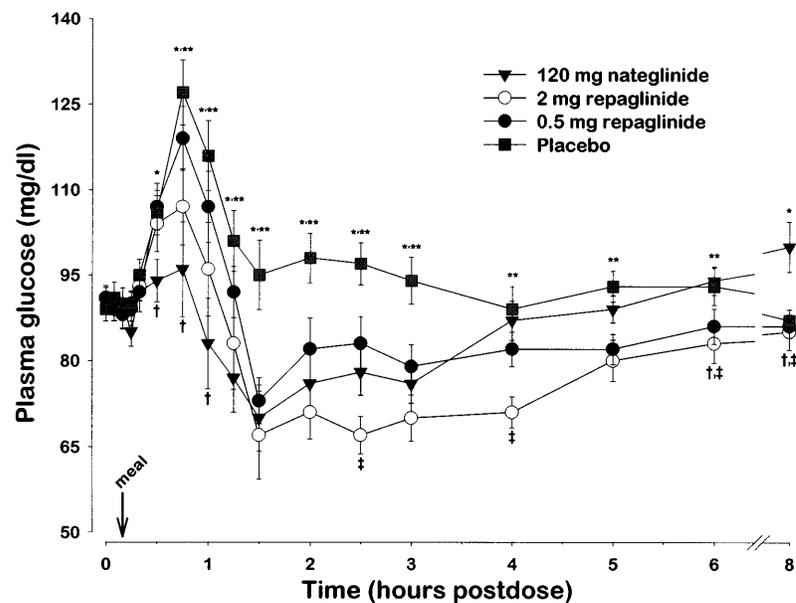
Figure 3—*Mean plasma glucose concentrations (± SEM) after treatments with 120 mg nateglinide (NAT), 2 and 0.5 mg repaglinide (REP), and placebo administered 10 min preprandially. P < 0.05 for the following treatment comparisons: *120 mg NAT vs. placebo; **2 mg REP vs. placebo; †120 mg NAT vs. 0.5 mg REP; and ‡120 mg NAT vs. 2 mg REP (comparisons between 0.05 mg repaglinide and placebo not shown).*
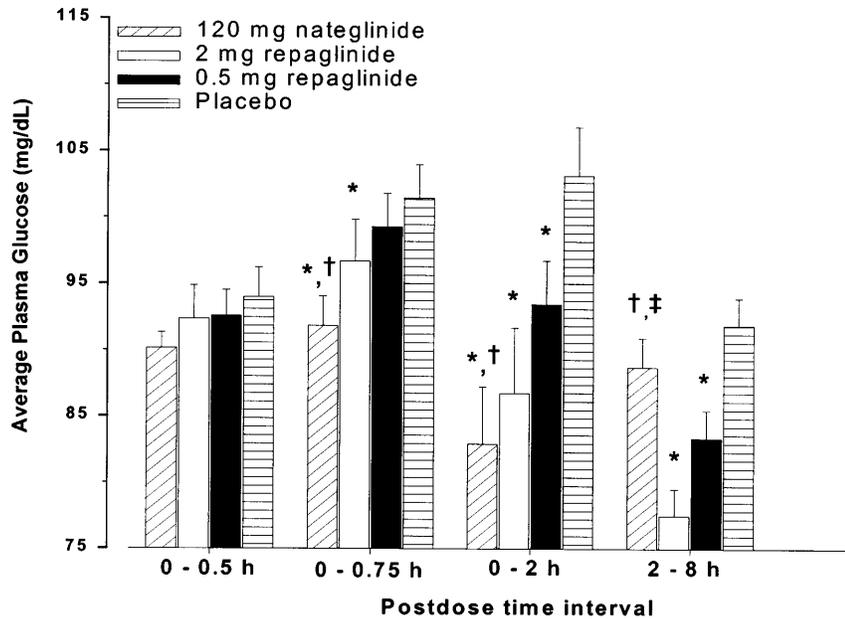
Figure 4—*Average plasma glucose concentrations (± SEM) over specified time intervals after treatments with 120 mg nateglinide (NAT), 2 and 0.5 mg repaglinide (REP), and placebo administered 10 min preprandially.* P < 0.05 *for the following comparisons:* *vs. placebo; †vs. 0.5 mg REP; and ‡vs. 2 mg REP.*

treatments, mean plasma glucose levels declined to a similar nadir of ~70 mg/dl by 1.5 h postdose, yet they returned to predose glycemia at considerably different rates. Plasma glucose concentrations returned to predose levels by 4 h with nateglinide treatment, whereas the repaglinide-treated groups did not reach predose glycemic levels until after 6 h postdose.

Compared with repaglinide or placebo, nateglinide treatment produced lower average plasma glucose concentrations over the 0- to 0.75-h postdose interval (Fig. 4; $P < 0.01$ vs. 0.5 mg repaglinide and placebo; $P < 0.07$ vs. 2 mg repaglinide) as well as the 0- to 2-h interval ($P < 0.05$ vs. 0.5 mg repaglinide and placebo). From 2 to 8 h postdose, nateglinide did not suppress average glucose levels compared with placebo, whereas both repaglinide doses had a significantly prolonged hypoglycemic effect versus placebo ($P < 0.05$).

Effect of meal timing on repaglinide effects

In a previous study with nateglinide in patients with type 2 diabetes, reduction of the interval between drug administration and meal ingestion had little effect on glucose and insulin pharmacodynamics and resulted in a small improvement in the pharmacokinetic profile (13). To explore the meal-dose-time relationship of repaglinide, a 2-mg dose was administered 1 min prepran-

dially. The total amount of insulin secreted over the first 2 h postdose when 2 mg repaglinide was administered 1 min preprandially ($87.4 \pm 12.6 \, \mu U \cdot h \cdot ml^{-1}$) was significantly greater than that with the 10-min preprandial ($66.6 \pm 9.4 \, \mu U \cdot h \cdot ml^{-1}$) administration ($P < 0.05$). Significant differences were also observed between the two-dose regimens for the 0- to 0.5-h (17.2 ± 11.2 vs. $9.2 \pm 5.3 \, \mu U \cdot h \cdot ml^{-1}$, 1- and 10-min administrations, respectively) and 0- to 0.75-h (42.7 ± 25.1 vs. $27.3 \pm 18.0 \, \mu U \cdot h \cdot ml^{-1}$) postdose intervals. Despite the higher plasma insulin concentrations after the 1-min preprandial administration of 2 mg repaglinide, no greater reduction in peak mealtime glucose concentrations was observed. The postmeal glucose excursion after the 1-min preprandial dose was significantly larger than that after the 10-min preprandial dose, resulting in higher glucose concentrations during the 0- to 0.5-h (50.2 ± 4.5 vs. $46.2 \pm 4.7 \, mg \cdot h \cdot dl^{-1}$) and 0- to 0.75-h intervals (78.8 ± 8.4 vs. $72.5 \pm 8.8 \, mg \cdot h \cdot dl^{-1}$) ($P < 0.05$) as well as a significantly higher glucose peak (121 ± 4 vs. $106 \pm 6 \, mg/dl$). Otherwise, the glycemic profiles for the 1- and 10-min preprandial intervals were similar.

Pharmacokinetics

Nateglinide was rapidly absorbed, and peak plasma concentrations ($6.06 \pm 4.2 \, \mu g/ml$) were reached within 2 h postdose in 12 of 14 subjects (t_{max} 1.5 ± 1.1 h). The

nateglinide AUC over 12 h was $13.4 \pm 3.2 \, \mu g \cdot h \cdot ml^{-1}$.

Repaglinide, in doses of 2 and 0.5 mg, was also rapidly absorbed. Peak plasma concentrations were reached within 1 h postdose for all treatments. Peak plasma levels for the 2-mg dose given 10 or 1 min preprandial (30.8 ± 25.9 and 34.5 ± 21.0 ng/ml, respectively), as well as the AUC over 12 h (47.5 ± 34.3 and 43.7 ± 25.3 ng $\cdot$ h $\cdot$ ml^{-1}, respectively), were comparable.

CONCLUSIONS — In recent years, emerging data have allowed for a better understanding of the significance of mealtime glycemia on overall glycemic control and coronary artery disease mortality (15,16). The first phase of insulin secretion in response to a meal, which plays a critical role in the regulation of mealtime plasma glucose levels, is impaired in type 2 diabetes, and this deficiency results in excessive meal-related glucose excursions (17). Glyburide and tolbutamide have little effect on meal-related glucose excursions because of their relatively slow onset of action, and they carry the potential risk of inducing hypoglycemia because of their long-acting nature (18,19). In contrast, nateglinide restores the first phase of insulin in type 2 diabetic subjects without inducing the markedly low plasma glucose concentrations observed with glyburide (20).

This study compared the effects of nateglinide and repaglinide on the early and extended profiles of mealtime insulin secretion in healthy individuals, as well as the associated effects on the glycemic response to a meal. In these healthy subjects, nateglinide stimulated early insulin release in response to a meal more rapidly and to a greater extent than either dose of repaglinide. Consistent with the more physiological nature of nateglinide's insulin stimulatory effects, insulin concentrations returned to preprandial levels more promptly, resulting in lower overall insulin exposure relative to repaglinide.

The importance of early insulin secretion in the control of mealtime glucose excursions was evident in the early postdose glycemic profiles and the average overall glucose exposure resulting from each drug treatment. Despite stimulating less insulin release overall, nateglinide was more effective than repaglinide in reducing mealtime glycemic excursions within the first 2 h postdose, with a more rapid return to pretreatment plasma glucose levels. The

relatively slower onset of repaglinide action led to glucose excursions of greater magnitude, and the relatively longer duration of its stimulatory effect resulted in a more prolonged insulin exposure and the corresponding hypoglycemic effect.

Both nateglinide and repaglinide have similar initial pharmacokinetic profiles with comparable short terminal half-lives (1–1.5 h). Because repaglinide concentrations were low at the late time points, the sensitivity of the repaglinide assay used in the present study limited our ability to accurately estimate the elimination half-life. In contrast to the apparent short plasma residence time of repaglinide, the persistent insulin stimulation observed after its administration points to a much longer lived pharmacodynamic effect. This pharmacokinetic/pharmacodynamic disparity may be a result of an unobserved longer terminal drug elimination phase or a protracted receptor residence time, as suggested by in vivo findings of a fivefold longer residence time of repaglinide compared with nateglinide (11).

It is recommended that repaglinide be taken up to 30 min before a meal, and the recommendation for nateglinide will be similar. Because of concerns of potential hypoglycemia arising from a missed or delayed meal, patients will likely wish to reduce the interval between the administration of a mealtime glucose regulator and the ingestion of a meal, with just before the meal administration preferable in some situations. In a previous study in healthy Japanese subjects, pharmacodynamic effects of both repaglinide and nateglinide had the desirable property of being insensitive to the meal-dose interval (6).

In contrast, in the Western subjects participating in this study, repaglinide (2 mg) less effectively reduced mealtime plasma glucose when taken 1 min before a meal as compared with 10 min preprandially, despite the overall higher levels of insulin secretion induced by the 1-min preprandial administration. The difference between the two studies may be potentially related to meal composition, study design, or ethnic differences. Previous work with nateglinide in both Japanese and Western subjects has shown that 1-min preprandial administration of 90–120 mg provides comparable glycemic control in comparison with 10-min preprandial administration, allowing for potentially more flexibility in dosing (6,13).

In summary, nateglinide has a more rapid onset and shorter duration of action than repaglinide. If these findings translate into patients with type 2 diabetes, they will allow for the potential of improved regulation of meal-related glycemia with a lower chance of inducing postabsorptive hypoglycemia than repaglinide. These properties suggest that nateglinide may offer additional clinical benefits and be a safe and effective mealtime glucose regulator.

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