Improved Control of Mealtime Glucose Excursions With Coadministration of Nateglinide and Metformin

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OBJECTIVE — Nateglinide, a new short-acting d-phenylalanine derivative for treating type 2 diabetes, reduces mealtime blood glucose excursions by physiologic regulation of insulin secretion. This study evaluated the pharmacokinetic and pharmacodynamic interactions of nateglinide and metformin in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 12 type 2 diabetic subjects with the following baseline characteristics were enrolled: age, 56 ± 13 years; BMI, 28.7 ± 4.5 kg/m²; HbA1c, 8.4 ± 1.3%; and fasting plasma glucose 13 ± 2.8 mmol/l. All subjects had been previously treated with glyburide and were switched to metformin monotherapy for 3 weeks before study start. Subjects then randomly received, in combination with 500 mg metformin, either 120 mg nateglinide or placebo before meals for 1 day, followed by the alternate treatment 7 days later. After 1 week of washout from both drugs, subjects received 1 day of open-label nateglinide treatment. Plasma concentrations of glucose, insulin, nateglinide, and metformin were assessed frequently during inpatient periods.

RESULTS — Postmeal plasma glucose levels were significantly lower in subjects treated with nateglinide plus metformin than in those treated with either drug alone (P < 0.001), especially after lunch and dinner. Coadministration of nateglinide and metformin did not affect the pharmacokinetics of either drug. All treatments were safe and well tolerated.

CONCLUSIONS — Combination therapy with nateglinide and metformin was more effective than either treatment alone and did not result in any pharmacokinetic interactions. Coadministration of nateglinide and metformin appears to be an excellent option for treating patients with type 2 diabetes not controlled with monotherapy.

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Nateglinide (A-4166), a d-phenylalanine derivative, is a new agent being investigated for the treatment of type 2 diabetes. It is chemically and pharmacologically distinct from sulfonylureas, repaglinide, and biguanides. Preclinical (1–6) and clinical (6–8) studies show that nateglinide, N-[(trans-4-isopropylcyclohexyl)-carbonyl]-d-phenylalanine, rapidly produces a short-lived insulin release by pancreatic ß-cells that is dependent on the concentration of glucose. Nateglinide raises insulin levels by inhibiting pancreatic ß-cell K⁺-ATP channels, which results in calcium influx and subsequent insulin release (1,2). As plasma glucose levels rise, ß-cell sensitivity to nateglinide increases, and the insulin release amplifies (1,2,4). Nateglinide effectively releases insulin when taken just before meals, as demonstrated in studies in animals (5,9) and humans (10). This nutrient-sensitive insulin release results in a reduction of mealtime blood glucose excursions. Short-term clinical studies demonstrated that nateglinide, given with or before meals, increased insulin levels and controlled mealtime hyperglycemia without symptomatic hypoglycemia (8).

Type 2 diabetes is progressive, and many patients eventually need combination treatment with more than one antidiabetic agent to achieve glycemic control. Therefore, it is important to evaluate the potential effectiveness of nateglinide in combination with other agents. One candidate for combination with nateglinide is metformin, a biguanide that does not stimulate insulin secretion but enhances insulin sensitivity, complementing the action of insulin-releasing agents (11). Combination therapy with metformin is already being used with sulfonylureas (12) and repaglinide (13). Metformin delays gastrointestinal absorption of glucose (14) and suppresses hepatic glucose output via inhibition of gluconeogenesis (15).

The present study assessed the safety and tolerability of 120 mg nateglinide and 500 mg metformin coadministered 10 min before three daily meals and evaluated their pharmacodynamic and pharmacokinetic interactions in type 2 diabetic subjects.
counter drugs; treatment with certain cardiovascular medications or medications that affect liver metabolism; history of impaired immunity, drug or alcohol abuse, pulmonary disease, autonomic dysfunction, or psychiatric disorder; or known contraindications to biguanides. Subjects with minor deviations from the entry criteria could be enrolled if their suitability or safety in the study was not affected.

Study design
During the 3-week run-in phase of the study, all subjects discontinued their prior antidiabetic regimen and received 500 mg metformin three times a day 10 min before meals. The run-in was followed by a double-blind randomized two-way crossover, during which subjects continued to take metformin and were randomly assigned to receive 120 mg nateglinide (two 60-mg tablets) or placebo three times 10 min before meals during two sequential 24-h inpatient treatment periods (periods I and II). These periods were separated by a 6-day outpatient washout phase, during which metformin treatment was continued. In period III, after a 7-day washout with no hypoglycemic study medications, subjects received only open-label nateglinide three times 10 min before meals during a single 24-h inpatient period. Meals were served at approximately 0800, 1200, and 1700. Subjects were admitted to the study facility 24 h before dosing in each period and remained 24 h after each dosing period. They were provided with nutritional counseling and received a standard diabetic diet.

The study was conducted in accordance with the U.S. Code of Federal Regulations and the Declaration of Helsinki.

Study measurements
Evaluations at screening, at baseline, during study conduct, and at completion or discontinuation included a physical examination, vital signs, ECG, and pregnancy and standard laboratory tests. Standard 12-lead ECGs were performed within 30 min before and 5 and 24 h after each morning dose of nateglinide or placebo. Adverse events were recorded and followed until resolved. Venous blood samples for plasma glucose, nateglinide, and metformin determinations were collected over 15 h and at 24 h after the morning dose in each period. Samples for insulin concentrations were collected from 9 to 13 h and at 24 h postdose.

Laboratory determinations
Plasma glucose concentrations were determined by Medical Research Laboratories (Highland Heights, KY) using a coupled hexose kinase/glucose-6-phosphate dehydrogenase method. Plasma insulin concentrations were measured at the same laboratory by a radioimmunoassay-based Coat-A-Count insulin procedure with [125I]-labeled insulin (crossreactivity with proinsulin 40%; concentrations not corrected). Plasma concentrations of nateglinide were determined by validated high-performance liquid chromatography (HPLC) methods (10). Metformin plasma concentrations were determined by liquid-liquid extraction, followed by HPLC with ultraviolet detection, using phenformin as the internal standard (unpublished method).

Pharmacodynamic analyses
Pharmacodynamic analyses were performed on data from all subjects. Descriptive and inferential statistics were calculated for glucose and insulin concentrations at each time point, using unpaired t tests for comparisons within the crossover and paired t tests for the comparison with nateglinide-only treatment. In addition, the integrated plasma glucose or insulin response area under the curve (AUC), or the integrated response relative to baseline (AUC-R), was derived over the time intervals from 0 to 4, 0 to 15, and 9 to 13 h after the morning dose for plasma glucose and 9 to 13 h for plasma insulin. The average mean change from baseline was calculated from the AUC-R by dividing by the time interval (e.g., AUC-R[0–t]/4 h). The derived variables were compared between the combination (nateglinide and metformin) and single-treatment groups using analysis of variance (ANOVA) based on a crossover design (combination vs. metformin) or a randomized block design (combination vs. nateglinide). Significance was declared if P < 0.05.

Pharmacokinetic analyses
The one subject who discontinued prematurely was not included in the pharmacokinetic analysis. Maximal plasma concentration (Cmax), time to Cmax (tmax), and areas under the plasma drug concentration–time curve (AUC0–t) were calculated for each subject for the morning and evening dose, where t = 4, 6, or 15 h. The t1/2 was calculated after the evening dose only. ANOVA was used to analyze the pharmacokinetic parameters for the effect of metformin on nateglinide in each treatment group. Nonparametric Wilcoxon signed-rank tests for paired differences of tmax between treatments were performed and a probability level set at P < 0.05.

RESULTS
Subject characteristics
A total of 10 men and 2 women volunteers (10 Caucasian, 2 Hispanic) with a mean (±SD) duration of type 2 diabetes of 6.0 ± 7.2 years and mean HbA1c of 8.4 ± 1.2% were enrolled. All subjects had been previously treated with glyburide for at least 5 years, and three had added metformin to their sulfonylurea therapy within the past year. Mean (±SD) age, body weight, and BMI were 56 ± 13 years, 88 ± 17 kg, and 29 ± 4 kg/m2, respectively. None of the subjects had any clinically significant laboratory abnormalities other than those associated with type 2 diabetes.

Safety
Two subjects experienced adverse events during the study. One subject was withdrawn with an inferior-wall myocardial infarction while receiving placebo in period II. Subsequent cardiac catheterization revealed multivessel coronary artery disease. The other adverse event was a headache.

No clinically meaningful changes from baseline in vital signs, physical examination, or laboratory tests were noted for any subject. In four of the seven subjects with ECG abnormalities during the study, the abnormality was minor and already present at screening or prerandomization. In addition, the subject with the myocardial infarction, one subject had occasional mild sinus bradycardia (53–61 beats per min) during the study, which was present at screening and was not associated with a particular treatment, and another had minor nonspecific ST-T wave changes after randomization. These ECG changes were not considered clinically significant.

Pharmacodynamic analyses
Predose fasting plasma glucose concentrations were comparable during the two-period crossover (metformin plus nateglinide: 13.5 ± 3.2 mmol/l; metformin plus placebo: 12.9 ± 3.5 mmol/l) and slightly higher after the 7-day washout at 14.8 ± 3.9 mmol/l before the nateglinide-only period.

After breakfast, mealtime plasma glucose levels in all three groups increased rapidly, peaking within 1.5 h (Fig. 1).
Plasma glucose decreased over time, and levels were lower in the combination group than in the single-treatment groups. Mean plasma glucose concentrations in the combination group continued to decline after lunch, reaching a nadir of 4.8 mmol/l below baseline, whereas mean concentrations in the single-treatment groups rose slightly after lunch. The additional plasma glucose-lowering effects of the combination treatment were most notable 2–5 h after lunch and persisted 6 h after the evening dose. Between 1 and 15 h after the morning dose, combination treatment resulted in significantly lower mean glucose levels than did metformin plus placebo (\( P < 0.05 \)).

Mean plasma insulin concentrations increased in all three groups after the evening meal. Mean (± SEM) plasma insulin AUCs from hours 9 to 13 were 163 ± 24 (combination) and 175 ± 30 µU · h · ml\(^{-1} \) (metformin), compared with 129 ± 20 µU · h · ml\(^{-1} \) after metformin plus placebo. As expected, the amount of insulin secreted after both nateglinide treatments, alone and plus metformin, was larger than after metformin plus placebo, and reflects both a larger postmeal insulin peak and significantly higher plasma insulin AUC over the 4-h postmeal period (\( P < 0.05 \)).

**Pharmacokinetics**

Of the measured nateglinide pharmacokinetic parameters, only \( t_{\text{max}} \) after the evening meal was increased significantly (\( P = 0.03 \)) by metformin coadministration (Table 1). The lack of an obvious nateglinide absorption phase in one subject may have contributed to this result, inasmuch as the difference in \( t_{\text{max}} \) became nonsignificant when this subject was removed from the analysis. Nateglinide was absorbed rapidly, with or without coadministered metformin, with a \( t_{\text{max}} \) of \(< 1 \) h after the morning dose. Once \( t_{\text{max}} \) was achieved, plasma concentrations of nateglinide rapidly diminished, with a \( t_{1/2} \) of 1.84 h.

AUC (0–4 h) values for metformin concentrations after the morning dose tended to be higher in the combination group (2.7 ± 0.8 µg · h · ml\(^{-1} \)) than in the metformin group (2.4 ± 0.6 µg · h · ml\(^{-1} \); \( P = 0.01 \)).
Nateglinide and metformin coadministration

Table 1—Pharmacokinetic parameters of nateglinide and metformin administered alone or in combination

<table>
<thead>
<tr>
<th>Dose</th>
<th>Parameter</th>
<th>Nateglinide (n =11)</th>
<th>Metformin (n =12)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nateglinide + metformin</td>
<td>Nateglinide</td>
</tr>
<tr>
<td>Morning</td>
<td>AUC (0-4 h) (µg · h · ml⁻¹)</td>
<td>10.6 ± 3.4</td>
<td>10.3 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>Cₘₚ (µg/ml)</td>
<td>6.7 ± 2.9</td>
<td>6.1 ± 1.9</td>
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<tr>
<td></td>
<td>tₘₚ (h)</td>
<td>0.91 ± 0.30</td>
<td>0.96 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>AUC (0-6 h) (µg · h · ml⁻¹)</td>
<td>11.6 ± 3.7</td>
<td>11.8 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>Cₘₚ (µg/ml)</td>
<td>13.8 ± 4.2</td>
<td>13.4 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>tₘₚ (h)</td>
<td>5.8 ± 3.3</td>
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</tr>
<tr>
<td></td>
<td>t₁/₂ (h)</td>
<td>1.7 ± 1.01</td>
<td>0.82 ± 0.46*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8 ± 0.47†</td>
<td>1.8 ± 0.60†</td>
</tr>
</tbody>
</table>

Data are means ± SD. *P < 0.05 vs. nateglinide + metformin; † all other means are not significantly different. ‡ n = 11.

The other measured pharmacokinetic parameters of metformin (Cₘₚ, tₘₚ, t₁/₂, and AUC (0-15 h)) were not affected significantly by coadministered nateglinide. Metformin given with or without nateglinide was rapidly absorbed, with a tₘₚ of <2 h after either the morning or evening dose. The Wilcoxon's signed-rank test result for tₘₚ was not significant for either the morning or evening dose. Plasma concentrations declined rapidly after Cₘₚ was achieved, with a t₁/₂ of ~5 h.

CONCLUSIONS—Nateglinide is a new amino acid–derivative, nonsulfonylurea agent under investigation for the treatment of type 2 diabetes. Previously reported findings in animals (6) and humans (8) demonstrate that nateglinide effectively decreases mealtime plasma glucose excursions when taken just before meals.

Nateglinide inhibits K⁺-ATP channels, stimulating the influx of extracellular calcium into pancreatic β-cells. This insulin-secreting effect appears to be augmented at higher plasma glucose levels (1,2,4). This agent is rapidly absorbed and has a short duration of action, which makes it pharmacologically distinct from other oral antidiabetic agents (6,9,16). These characteristics render nateglinide useful as a mealtime glucose regulator that can increase insulin levels briefly in response to glucose excursions without the risk of prolonged hypoglycemia.

In this study, nateglinide and metformin acted together to produce greater reductions in mealtime glucose excursions than those produced by either drug alone. Greater glycemic control was achieved with combination treatment, particularly after the noon and evening meals, than with single-drug treatment, as assessed by mean plasma glucose concentrations and mean AUC-R, an integrated measure of glucose response. Subjects treated with both nateglinide and metformin had lower peak postmeal glucose concentrations, which persisted for 6 h after the evening meal, and significantly lower AUC-R values than did those treated with either metformin (P < 0.001) or nateglinide (P < 0.001) alone. Nateglinide alone was as effective as metformin plus placebo in lowering daytime plasma glucose, according to AUC-R (0-15 h) analysis.

Plasma insulin concentrations after the evening dose and meal were higher in the group that received metformin in combination with nateglinide than in the group that received metformin plus placebo. The lower glucose levels in the combination group indicate that the enhanced glucose-lowering effects are probably due to a combination of increased insulin levels caused by nateglinide and improved insulin sensitivity stimulated by metformin. Our findings are consistent with reported observations that nateglinide promotes the release of insulin (3,4,8) and metformin promotes insulin sensitization in the liver and peripheral tissues.

The results of this study support the use of nateglinide as an effective alternative to sulfonylureas or repaglinide for combination therapy with metformin. Combination therapy with metformin and sulfonylureas has been shown to reduce plasma glucose levels effectively in patients with type 2 diabetes. However, the insulin-stimulating effects of sulfonylureas continue once glucose has returned to fasting levels, making hypoglycemia a definite and serious risk (17). This risk may be reduced with a short-acting agent such as nateglinide that does not continue to stimulate insulin release once glucose levels have fallen (6).

A clinically relevant pharmacokinetic drug interaction between nateglinide, which undergoes hepatic metabolism (18), and metformin, which is predominantly excreted unchanged in the urine, was not observed in our study, as reported previously (19). The pharmacokinetic parameters observed for metformin given alone or with nateglinide concur with previous reports of metformin's pharmacokinetics (20). The low or absent plasma protein binding of metformin and the lack of hepatic metabolism are probably responsible for the lack of pharmacokinetic interaction with nateglinide.

A dose of 120 mg nateglinide taken alone before meals was safe and well tolerated by subjects with type 2 diabetes, as was combination therapy with 500 mg metformin three times a day. Hypoglycemia was not reported in any subject in this study, similar to what was observed in prior studies of healthy and type 2 diabetic subjects given nateglinide (6,8). No clinically relevant adverse events or changes in ECG, vital signs, or laboratory values were noted, with one exception. While receiving placebo, one subject with previously undetected multivessel coronary artery disease experienced a myocardial infarction and withdrew from the study.

The combination of 120 mg nateglinide and metformin in the present study more effectively reduced mealtime blood glucose excursions than with either drug alone. Coadministration of nateglinide and metformin appears to be an excellent option for treating patients with type 2 diabetes not controlled with monotherapy.

References


