Addition of Nateglinide to Rosiglitazone Monotherapy Suppresses Mealtime Hyperglycemia and Improves Overall Glycemic Control

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OBJECTIVE — To determine the effects of nateglinide added to rosiglitazone monotherapy on glycemic control and on postprandial glucose and insulin levels in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This 24-week, multicenter, double-blind, randomized study compared the efficacy of nateglinide (120 mg a.c.) and placebo added to rosiglitazone monotherapy (8 mg q.d.) in 402 patients with type 2 diabetes with HbA1c between 7 and 11% (inclusive). Efficacy parameters tested included HbA1c, and plasma glucose and insulin levels in the fasting state and after a standardized meal challenge. Safety data were also collected.

RESULTS — In placebo-treated patients, HbA1c did not change (Δ = 0.0 ± 0.1%). In patients randomized to nateglinide, HbA1c decreased from 8.3 to 7.5% (Δ = −0.8 ± 0.1%, P < 0.0001 vs. placebo). Target HbA1c (<7.0%) was achieved by 38% of patients treated with combination therapy and by 9% of patients remaining on rosiglitazone monotherapy. In nateglinide-treated patients, fasting plasma glucose levels decreased by 0.7 mmol/l, 2-h postprandial glucose levels decreased by 2.7 mmol/l, and 30-min insulin levels increased by 165 pmol/l compared with no changes from baseline of these parameters with placebo added to rosiglitazone (P < 0.001).

CONCLUSIONS — By selectively augmenting early insulin release and decreasing prandial glucose excursions, nateglinide produced a clinically meaningful improvement in overall glycemic exposure in patients with type 2 diabetes inadequately controlled with rosiglitazone. Therefore, nateglinide substantially improves the likelihood of achieving a therapeutic target of HbA1c <7.0%.

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Whereas the U.K. Prospective Diabetes Study established that improving glycemic control in patients with type 2 diabetes reduces the risk of chronic complications (1), it also determined that over time there is a progressive requirement for multiple therapies to maintain a target HbA1c level of <7.0% (2). The introduction of new therapeutic agents that address the different defects underlying type 2 diabetes offers hope that good glycemic control may be achievable through combination therapy.

Nateglinide is an insulinotropic agent that differs from sulfonylureas and repaglinide in that its effects are more rapidly manifest, more rapidly reversed (3,4), and more glucose dependent (5,6). Accordingly, when taken before meals, nateglinide selectively augments early insulin release and suppresses postprandial hyperglycemia with minimal postmeal hyperinsulinemia or hypoglycemia (7). When used as monotherapy in patients with type 2 diabetes, nateglinide (120 mg a.c.) is reported to reduce HbA1c levels by 0.5–1.1% relative to baseline (8–10).

The thiazolidinedione (TZD) rosiglitazone is an insulin-sensitizing agent that improves glycemic control primarily by reducing fasting plasma glucose (FPG) levels (11,12). When used as monotherapy in patients with type 2 diabetes, rosiglitazone (8 mg total daily dose) is reported to decrease HbA1c levels by 0.3–0.7% relative to baseline (11,12). A higher dose does not provide additional benefit (13); therefore, patients failing to achieve glycemic targets with 8 mg of rosiglitazone require addition of another agent.

The purpose of the present study was to determine whether addition of nateglinide would provide therapeutic benefit by improving glycemic control in patients with type 2 diabetes inadequately controlled with rosiglitazone monotherapy. Safety and tolerability were also assessed, as were insulin and glucose profiles during standardized meal challenges.

RESEARCH DESIGN AND METHODS

Patients
The study randomized 402 patients with type 2 diabetes diagnosed at least 6 months previously and treated with rosiglitazone monotherapy (8 mg), diet, and...
Nateglinide and rosiglitazone combination

exercise for at least 3 months before the 4-week run-in period. Patients were aged ≥21 years and had BMI between 22 and 40 kg/m² (inclusive). FPG between 6.1 and 13.3 mmol/l and HbA1c between 7 and 11% (inclusive) while receiving rosiglitazone monotherapy. Patients treated with any oral agent other than nateglinide or insulin within 3 or 6 months of the run-in period were excluded, as were patients with significant cardiac medical history, edema, congestive heart failure (CHF) of New York Heart Association Stage III or IV, decompensated CHF, or persistent elevations of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase >2 times the upper limit of normal or direct bilirubin >1.3 times the upper limit of normal.

The study protocol was approved by the institutional review board/independent ethics committee at each participating center. Written informed consent was obtained from all participants; they also agreed to maintain their previous diet and exercise habits. The study was conducted in accordance with the Declaration of Helsinki and Title 21 of the Code of Federal Regulations dealing with clinical studies.

Study design
A 4-week, single-blind, run-in period preceded randomization, during which patients received nateglinide placebo before each meal and rosiglitazone 8 mg administered with breakfast. Visits occurred at weeks −4, −2, and 0, and baseline assessments (physical examination, electrocardiogram, HbA1c, FPG, lipid profile, and standard biochemistry and hematology) were performed. At week 0, the patients underwent a 4-h standardized meal challenge. A 24-week, double-blind, active treatment period followed randomization to placebo or nateglinide (120 mg), and visits occurred at weeks 4, 8, 16, and 24. Patients were instructed to take the blinded medication before each meal and to take one rosiglitazone tablet with breakfast. Assessments of FPG, HbA1c, lipid profile, hematology, and biochemistry were performed at various intervals, and the standardized meal challenge was repeated after the final dose of blinded medication at week 24 or at an early termination visit.

Each adverse event (AE) was recorded and judged for severity and possible relationship to study medication. Patients were given with home blood glucose monitoring devices and instructed regarding their use. Hypoglycemia was defined as signs or symptoms consistent with hypoglycemia that reversed with carbohydrate administration and was confirmed by a blood glucose level <2.8 mmol/l (3.1 mmol/l plasma glucose equivalents) recorded at the time of the event.

For the meal challenges, patients who had fasted overnight received a standardized breakfast (~55% carbohydrate, 15% protein, 30% fat with total caloric content [414–788 kcal] adjusted for height and sex) that was consumed within 15 min. Samples for glucose and insulin determination were obtained 5 min before the start of the meal (time 0) and at 15, 30, 60, 90, 120, 180, and 240 min thereafter.

Sample analysis
Plasma glucose and insulin levels during the meal challenges and HbA1c levels were measured at the Diabetes Diagnostic Laboratory (Columbia, MO), as described previously (14). All other analyses were processed through a central laboratory (Clinical Reference Laboratory, Lenexa, KS) using Good Laboratory Practices according to their standard operating procedures.

Statistics
The primary efficacy evaluation was based on the change in HbA1c from baseline. Secondary efficacy variables included FPG, 2-h postprandial glucose (PPG), 30-min postprandial insulin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, body weight, and 4-h area under the curve (AUC) for glucose and insulin during meal challenges.

Total and incremental AUCs were calculated with the trapezoidal method. Homeostasis model assessment (HOMA) of β-cell function and insulin resistance were calculated according to the following formulae: HOMA-B = [20 × fasting IRI (μU/ml)/(FPG − 3.5)] and HOMA-R = fasting IRI (μU/ml)/FPG/22.5. The insulinogenic index was calculated as Δ IRI (pmol/l)/Δ glucose (mmol/l) at 30 min postmeal.

Changes from baseline (mean of weeks −2 and 0 for HbA1c and FPG; week 0 for other variables) at the study end point for all primary and secondary efficacy variables were analyzed using an ANCOVA model with treatment, center, baseline measure, and treatment-by-baseline interaction as factors for the intent-to-treat (ITT) population, with the last observation carried forward. The tests were conducted at the two-sided significance level of 0.05. Comparability of background and demographic characteristics between treatment groups or between patients achieving or failing to achieve target HbA1c <7.0% was assessed with a Cochran-Mantel-Haenszel χ² test for categorical variables and a two-sided Student's t test for continuous variables.

RESULTS

Patients
A total of 634 patients were screened; 402 patients met eligibility requirements and were randomized to receive nateglinide (120 mg a.c., n = 200) or placebo (n = 202) added to ongoing treatment with rosiglitazone (8 mg q.d.). A total of 85% of the ITT population in the combination arm (n = 198) completed the study: 8 patients discontinued because of AEs, 5 patients discontinued due to treatment failure, 3 patients was discontinued because of protocol violation, 10 patients withdrew consent, 2 patients were lost to follow-up, and 1 patient was discontinued due to administrative errors. A total of 80% of the ITT population in the rosiglitazone monotherapy arm (n = 197) completed the 24-week study: 6 patients discontinued because of AEs, 19 patients discontinued due to treatment failure, 7 patients withdrew consent, and 7 patients were lost to follow-up.

In general, the two groups were similar: mean age ~57 years, HbA1c ~8.4%, FPG ~10 mmol/l, an average duration of diabetes ~6 years. However, baseline BMI in patients randomized to nateglinide was higher (31.6 kg/m²) than in patients maintaining rosiglitazone monotherapy (30.5 kg/m², P < 0.05) (Table 1).

Efficacy
In patients receiving rosiglitazone monotherapy, HbA1c did not change significantly from the baseline of ~8.4% (Δ = 0.0 ± 0.1%); however, in patients in whom nateglinide was added, HbA1c decreased considerably from the baseline of ~8.4% within 8 weeks and reached a plateau from week 16 to 24 (Fig. 1). The change from baseline to end point in nateglinide-treated patients was −0.8 ± 0.1% (P < 0.0001 vs. baseline or rosigli-
tazone monotherapy). Of the 194 patients treated with combination therapy for whom baseline and end-point values were available, 63.4% had an absolute reduction in HbA1c from baseline of ≥0.5%; 37.6% achieved the target end point of <7.0%, and 16.5% achieved an end point of <6.5%. The corresponding percentages for patients who continued rosiglitazone monotherapy (n = 191) were 29.8, 8.9, and 4.2%, respectively. In patients randomized to combination therapy, FPG decreased from 9.8 to 9.0 mmol/l (Δ = −0.7 ± 0.1 mmol/l, P < 0.001). This reduction was apparent within 4 weeks and was maintained throughout the study. In patients maintaining rosiglitazone monotherapy, FPG did not change significantly from the baseline of 10.0 mmol/l (Δ = 0.0 ± 0.2 mmol/l). There were no statistically significant changes in total cholesterol, LDL cholesterol, or triglycerides in either group. A small but significant increase from baseline in HDL cholesterol was seen both in patients receiving combination therapy (Δ = +0.03 mmol/l, P < 0.025) and in those remaining on rosiglitazone monotherapy (Δ = +0.04 mmol/l, P < 0.005). Body weight also increased significantly in both groups. The mean change from baseline in patients randomized to combination therapy (+3.1 ± 0.3 kg) was significantly greater than in patients maintaining rosiglitazone monotherapy (+1.1 ± 0.3 kg, P < 0.0001).

### Standardized meal challenges

Meal challenges were performed at week 0 and at the end point (week 24 or last observation carried forward). The glucose and insulin profiles (Fig. 2A and B, respectively) were essentially identical in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients who maintained rosiglitazone monotherapy. However, addition of nateglinide greatly reduced postprandial hyperglycemia and increased insulin levels, primarily at the early postmeal time points. The 2-h PPG in patients receiving nateglinide plus rosiglitazone decreased from 14.0 to 11.4 mmol/l (Δ = −2.6 ± 0.3 mmol/l, P < 0.0001). In contrast, 2-h PPG in patients maintaining rosiglitazone monotherapy increased slightly from 14.4 to 14.8 mmol/l (Δ = +0.4 ± 0.3 mmol/l, P < 0.0001 vs. combination). The maximum augmentation of insulin levels induced by addition of nateglinide occurred at 30 min postmeal. The change from baseline to end point in the 30-min plasma insulin was +165 ± 16 pmol/l (P < 0.0001 vs. baseline or rosiglitazone). The magnitude of the difference between baseline and end point in the postmeal insulin concentrations in patients receiving combination therapy decreased thereafter, and the insulin levels were similar pre- and posttreatment by 180 min after the meal.

As is apparent from the prandial glucose profiles, both the total and incremental glucose AUCs(0→12 h) were significantly reduced in nateglinide-treated patients (Δ = −8.6 ± 0.8 and −6.2 ± 0.5 h · mmol/l, respectively, P < 0.0001 vs. baseline or rosiglitazone for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC. As is apparent from the prandial insulin profiles, both the total and incremental insulin AUCs(0→12 h) were increased in nateglinide-treated patients (Δ = +425 ± 37 and +395 ± 33 h · pmol/l, respectively, P < 0.0001 vs. baseline or rosiglitazone for both total and incremental AUCs). This represents a 46% increase in the total and a 69% increase in the incremental insulin AUC.

The 30-min insulinogenic index and HOMA-β were calculated as indexes of β-cell function, as in the ADOPRT study (15). These parameters were unchanged from baseline to end point in patients continuing rosiglitazone monotherapy. In contrast, in patients in whom nateglinide was added, the insulinogenic index increased from 39 to 130 (Δ = 91 ± 11, P < 0.0001) and the HOMA-β increased from 45 to 57 (Δ = +12 ± 3, P < 0.001).

### Characterizing patients responding well to nateglinide/rosiglitazone

To identify factors that may have contributed to therapeutic success in patients receiving combination therapy, baseline demographics and metabolic indexes were compared between patients achieving target HbA1c < 7.0% (“responders”) and those failing to achieve target HbA1c levels (“nonresponders”). Responders to combination therapy had significantly lower baseline HbA1c, FPG, 2-h-PKG, and total and incremental glucose AUCs and HOMA-R and had significantly higher incremental insulin AUC and HOMA-β than nonresponders (P < 0.05 or better for all parameters). In addition, the baseline ratio of HbA1c to FPG was significantly higher in responders versus nonresponders (0.92 ± 0.02 vs. 0.85 ± 0.01, P < 0.001). No other characteristic or metabolic parameter differed significantly between groups, although the re-

![Figure 1](https://example.com/figure1.png)
sponders tended to be older than the nonresponders (58.2 vs. 55.5 years).

**Safety and tolerability**
A total of 73.5% of patients randomized to combination therapy and 71.8% of patients randomized to rosiglitazone monotherapy experienced one or more AE. The most common AEs were fatigue, upper respiratory tract infection, viral infection, tremor, weight increase, headache, and dizziness; most were classified as mild or moderate. In the combination therapy group, 10 serious AEs (SAEs) were reported in six patients; none were suspected to be related to study medication, and one resulted in withdrawal of the patient from the study. In the rosiglitazone monotherapy group, 19 SAEs were reported in 12 patients. One incident of worsening CHF was suspected to be related to study medication; this and two other SAES led to withdrawal of three patients from the study.

Anemia, various forms of edema, and cardiac failure are AEs that have been associated with TZDs. These occurred in a small number of patients in both treatment groups, and their frequencies in the combination therapy group (0.0%–4.0%) were similar to those in the rosiglitazone monotherapy group (0.5%–5.0%). Hypoglycemia is an AE associated with insulinotropic agents; no confirmed hypoglycemia developed in patients continuing rosiglitazone therapy, and 14 incidents of confirmed hypoglycemia occurred in nine patients (4.5%) receiving nateglinide plus rosiglitazone. One of the incidents was accompanied by a plasma glucose level of 2.49 mmol/l, whereas the remainder were accompanied by a plasma glucose level between 2.5 and 3.1 mmol/l. None of the hypoglycemic events were severe enough to require the assistance of another person.

**CONCLUSIONS** — In this study, the addition of nateglinide (120 mg a.c.) to rosiglitazone (8 mg) was very effective in reducing overall glycemic exposure as reflected by a 0.8% reduction of HbA1c relative to baseline, whereas HbA1c was unchanged in patients continuing rosiglitazone monotherapy. Moreover, a clinically meaningful improvement ($\Delta$HbA1c = −0.5% or greater) occurred in 63% of patients, and a target HbA1c level of <7.0% was achieved in 38% of patients treated with combination therapy.

The efficacy of nateglinide added to rosiglitazone treatment seen in this study was similar to the added benefit provided by nateglinide combined with troglitazone in an earlier study (9). That study, however, compared effects of placebo, troglitazone, nateglinide, and the initial combination of both agents in patients with a baseline HbA1c level of ~8.3%. It was found that after 24 weeks of treatment, HbA1c increased by 0.3% in patients receiving placebo, decreased by 1.0% and 0.7% in patients receiving troglitazone and nateglinide monotherapy, respectively, and decreased by 1.8% in patients treated with initial nateglinide/troglitazone combination. Therefore, it seems that a nateglinide/TZD combination is a useful approach to treating type 2 diabetes, whether instituted in stages, as in the present study, or as initial combination therapy, as in the earlier study.

Although the efficacy of a nateglinide/pioglitazone combination has yet to be assessed, with respect to glycemic control, the therapeutic equivalence of TZDs can be inferred from findings that HbA1c did not change when patients who were previously stabilized with troglitazone were switched to pioglitazone or rosiglitazone (16). It is likely, therefore, that nateglinide combined with any of the TZDs will have similar efficacy, although side-effect profiles may vary due to differential effects of distinctive TZDs on lipid parameters and hepatic function. It is noteworthy that nateglinide has been shown to be similarly effective and safe when combined with metformin, which has an insulin-sensitizing effect in the liver and a mechanism of action different from the TZDs (8).

The insulin-sensitizing effects of TZDs (17) and the insulinotropic effects of nateglinide (4,18) are well established, and it is therefore predictable that their use in combination would be highly effective in providing overall glycemic control, because such a combination addresses two fundamental abnormalities in the pathogenesis of type 2 diabetes—insulin resistance and loss of first-phase insulin secretion (19). The particular advantage of a nateglinide/TZD combination vis-à-vis TZD combined with other insulinotropic agents lies in the unique rapid onset and rapid reversibility of the effects of nateglinide to stimulate insulin release.

As confirmed in this study, the nateglinide-induced augmentation of meal-stimulated insulin levels is clearly apparent within 15 min of food consumption and subsides when glucose levels decrease. Through this selective stimulation of early insulin release, nateglinide greatly reduces prandial glucose excursions.
while minimizing overall insulin exposure. This study demonstrates that this specific action of nateglinide may be more important than any effect a TZD may have on postprandial peripheral glucose disposal; therefore, early insulin secretion is a prime determinant of PPG control.

The brevity of the effects of nateglinide to augment meal-stimulated insulin release may confer considerable advantage over other insulinotropic agents when used in combination with a TZD. There is less total insulin exposure and, importantly, because insulin levels in nateglinide-treated patients return toward baseline in parallel with glucose, nateglinide has less potential than other insulinotropic agents to elicit postmeal hypoglycemia (6). Furthermore, although FPG decreased to a greater extent in patients receiving combination therapy (perhaps related to decreasing glucose toxicity), fasting plasma insulin was not increased, thus decreasing the risk of fasting hypoglycemia. The incidence of confirmed hypoglycemia (plasma glucose level <3.1 mmol/l) was 4.5% in this study. In contrast, in a study of combination therapy with repaglinide and troglitazone, the incidence of confirmed hypoglycemia using a more stringent criterion (plasma glucose level <2.5 mmol/l) was reported to be 8%; if this definition of hypoglycemia was used in the present study, the incidence would be 0.5% for nateglinide/rosiglitazone combination therapy. It should be recognized, however, that definitive conclusions about safety and/or efficacy of different combination therapies will require head-to-head comparative studies.

When comparing the baseline demographic and metabolic characteristics of patients achieving target glycemic control (HbA1c <7.0%) and those failing to do so, it seemed that patients with more severe disease (e.g., high HbA1c, FPG, and HOMA-R or low HOMA-B) were less likely to achieve target levels. This, in itself, is unremarkable, although it may be of interest to note that the (known) duration of disease was no different between groups and that the responders tended to be older than nonresponders. The finding that responders had a significantly higher ratio of HbA1c to FPG at baseline than nonresponders (indicating more substantial postprandial versus fasting hyperglycemia) has been described previously (18). This is consistent with the predominant effect of nateglinide on PPG and may suggest a useful approach to making clinical judgments regarding choice of therapeutic regimen.

In this study, the overall safety, tolerability, and effects on lipid parameters were similar in the two treatment groups; however, confirmed hypoglycemia and weight gain were more prevalent in patients receiving combination treatment versus rosiglitazone monotherapy. These side effects are frequently associated with improved glycemic control and were less pronounced in this study (hypoglycemia in 4.5% of patients and mean weight gain of 3 kg) than what has been reported for a TZD combined with other insulinotropic agents or with insulin. For example, addition of rosiglitazone (8 mg) in patients stabilized on insulin therapy was associated with a rate of confirmed hypoglycemia (blood glucose level ≤2.8 mmol/l) of 14% and a mean weight gain of 5.3 kg (20). Similarly, in patients with type 2 diabetes inadequately controlled with maximum doses of glyburide, addition of troglitazone (600 mg) increased body weight by 5.9 kg, although the rate of confirmed hypoglycemia (blood glucose level <3.1 mmol/l) was low (3%) in patients with relatively advanced disease (typified by HbA1c level ~9.5%) while receiving maximum sulfonylurea therapy (21). Weight gain associated with repaglinide added to pioglitazone or to rosiglitazone was 5.5 and 4.5 kg, respectively (22).

In summary, in patients with type 2 diabetes inadequately controlled by rosiglitazone monotherapy (8 mg q.d.), addition of nateglinide (120 mg a.c.) selectively augmented meal-stimulated insulin release, suppressed prandial glucose excursions, and reduced HbA1c by 0.8%, with a favorable safety and tolerability profile. There was a low incidence of hypoglycemia and only modest weight gain in patients receiving nateglinide/rosiglitazone combination therapy. It may be concluded that the rapid-onset/rapidly reversible insulin secretagogue nateglinide is a useful agent to combine with an insulin-sensitizing TZD when attempting to achieve glycemic targets in patients with type 2 diabetes.

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