

Importance of Early Insulin Secretion

Comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes

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OBJECTIVE — This study compared the effects of nateglinide, glyburide, and placebo on postmeal glucose excursions and insulin secretion in previously diet-treated patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This randomized, double-blind, placebo-controlled multicenter study was conducted in 152 patients who received either nateglinide (120 mg before three meals daily, $n = 51$), glyburide (5 mg q.d. titrated to 10 mg q.d. after 2 weeks, $n = 50$), or placebo ($n = 51$) for 8 weeks. Glucose, insulin, and C-peptide profiles during liquid meal challenges were measured at weeks 0 and 8. At weeks -1 and 7 , 19-point daytime glucose and insulin profiles, comprising three solid meals, were measured.

RESULTS — During the liquid-meal challenge, nateglinide reduced the incremental glucose area under the curve (AUC) more effectively than glyburide ($\Delta = -4.94$ vs. -2.71 mmol \cdot h/l, $P < 0.05$), whereas glyburide reduced fasting plasma glucose more effectively than nateglinide ($\Delta = -2.9$ vs. -1.0 mmol/l, respectively, $P < 0.001$). In contrast, C-peptide induced by glyburide was greater than that induced by nateglinide ($\Delta = +1.83$ vs. $+0.95$ nmol \cdot h/l, $P < 0.01$), and only glyburide increased fasting insulin levels. During the solid meal challenges, nateglinide and glyburide elicited similar overall glucose control (Δ 12-h incremental AUC = -13.2 vs. -15.3 mmol \cdot h/l), but the insulin AUC induced by nateglinide was significantly less than that induced by glyburide (Δ 12-h AUC = $+866$ vs. $+1,702$ pmol \cdot h/l, $P = 0.01$).

CONCLUSIONS — This study demonstrated that nateglinide selectively enhanced early insulin release and provided better mealtime glucose control with less total insulin exposure than glyburide.

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Insulin secretagogues, as exemplified by the sulfonylureas, continue to play an important role in the treatment of type 2 diabetes. The major effect of the sulfonylureas has been to lower basal glucose as characterized by the fasting plasma glucose level (1–4). The results of the Diabetes Control and Complications

Trial (5) and the U.K. Prospective Diabetes Study (6,7) have led to a more aggressive approach to glucose lowering in patients with type 2 diabetes. Optimal treatment would lead to normalization of blood glucose exposure balanced against the risk of hypoglycemia. Normalization of HbA_{1c} will require control not only of

fasting plasma glucose but also of excessive mealtime glucose excursions (8).

Excessive mealtime glucose excursions that occur in type 2 diabetes are one of the earliest manifestations of disease and are often believed to reflect insulin resistance (2,9). However, disruption of the normal kinetics of insulin secretion in the form of impaired early insulin release is seen just as early in the progression of disease (9,10) and may play at least as important a role in allowing excessive mealtime glucose excursions as does the insulin-resistant state (11). Therefore, an insulin secretagogue, which selectively enhances early meal-induced insulin secretion, and thus improves mealtime glucose excursions while decreasing overall insulin exposure, could be a valuable addition to the current options for the treatment of type 2 diabetes.

The D-phenylalanine derivative, nateglinide, is a rapid-onset/short-duration insulinotropic agent that has been shown to selectively increase early insulin release in a glucose-sensitive manner. These unique properties have been demonstrated in vitro (12) and in vivo in animals (13) and in patients with type 2 diabetes (14) and suggest that nateglinide may offer a new mechanism by which to treat excessive mealtime glucose excursions. The present study assesses this possibility by comparing and contrasting the effects of nateglinide with those of the sulfonylurea and glyburide on mealtime glucose excursions and insulin secretion in previously diet-treated patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This study included 152 patients, 32–75 years of age, who were diagnosed with type 2 diabetes at least 3 months before entry into the study. Patients were required to have been treated by diet modification alone for at least 4 weeks before the initial visit and to have a mean (weeks -4 and -2) HbA_{1c} between 6.8 and 11% and a BMI between 20 and 35 kg/m². Patients were excluded if they had a history

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Abbreviations: AUC, area under the curve; FPG, fasting plasma glucose.

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

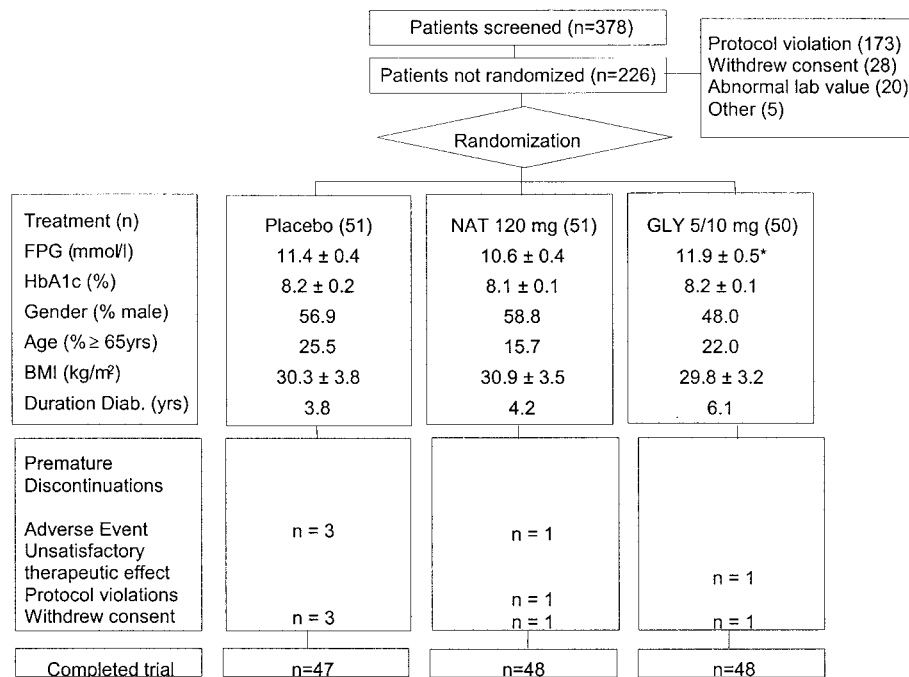


Figure 1—Disposition of patients screened and baseline characteristics of patients in the intent-to-treat population. *P < 0.001 relative to either nateglinide or placebo.

of acute metabolic or other significant diabetic complications, chronic insulin treatment, known sensitivity to nateglinide or glyburide, or a history of active substance abuse. Patients were also excluded if they had a history of significant cardiovascular or liver disease, elevated fasting triglyceride levels, or other clinically significant laboratory abnormalities. Oral corticosteroids, dicoumarin derivatives, and antidiabetic agents other than those used in the study were not permitted. Patient characteristics for each treatment group are reported in Fig. 1.

All patients gave written informed consent to participate in the study, and a complete physical examination, electrocardiography, and laboratory evaluation was performed on each patient during screening and at the completion of the study. The study protocol received Institutional Review Board approval at each participating site and was conducted in accordance with the U.S. Code of Federal Regulations, the rules governing medical procedures in the European Community, and the Declaration of Helsinki.

During a 4-week, single-blind, placebo run-in period, all patients received a nateglinide-matched placebo tablet before each meal and a glyburide-matched placebo capsule with or immediately after

breakfast. For the 8 weeks of double-blind treatment, patients were randomized to one of three treatment groups: nateglinide 120 mg before each of three main meals; glyburide, 5 mg (weeks 0–2) titrated to 10 mg q.d. (weeks 3–8); or placebo. Placebo tablets and nateglinide and glyburide capsules were used to maintain the double-blind and double-dummy designs, respectively. Liquid-meal challenges (240 ml of Sustacal consumed in lieu of normal breakfast) were performed immediately before (week 0) and after 8 weeks of treatment. Solid-meal challenges were performed before (week –1) and after 7 weeks of treatment. During the solid-meal challenge, patients were required to consume each meal within 15 min.

Study measurements

The Diabetes Diagnostic Laboratory at the University of Missouri performed plasma glucose (Roche Cobas Analyzer; Roche, Montclair, NJ), serum insulin (Pharmacia RIA; Pharmacia, Piscataway, NJ), C-peptide (Diagnostic Product Corporation RIA; Diagnostic Product Corporation), and proinsulin (Linco RIA; Linco) analyses. Standard laboratory values obtained for screening purposes were performed at Clinical Research Laboratories (Lenexa,

KY). The overall percent coefficient of variation for the assays in this study were <2% for HbA_{1c}, <2% for glucose, and <5% for insulin.

Statistical analysis and data presentation

Demographic and background data were summarized by treatment group with contingency tables for qualitative variables. Baseline comparability between the three treatment groups was examined by the Cochran-Mantel-Haenszel test for qualitative variables and an F test from a one-way analysis of variance for quantitative variables. Efficacy data from the intent-to-treat population, using last observation carried forward, were analyzed by analysis of covariance with treatment center and baseline values as factors. Pairwise comparisons using the analysis of covariance model were performed at the two-sided significance level of 0.05. Absolute and incremental areas under the curve (AUCs) for glucose and insulin were calculated by the trapezoidal method.

RESULTS

Liquid-meal challenge

To directly compare the mealtime glucose control produced by the amino acid derivative, nateglinide, and the sulfonylurea (glyburide), a liquid-meal (Sustacal; Mead Johnson Nutritionals, Evansville, IN) challenge was performed at week 0 (immediately before initiation of treatment) and after 8 weeks of treatment. Nateglinide was more effective than glyburide to reduce mealtime glucose excursions, whereas glyburide had a larger effect to reduce fasting plasma glucose. Nateglinide reduced the glucose spike (fasting to peak glucose levels) from 4.45 to 3.71 mmol/l ($\Delta = -0.80 \pm 0.21, P < 0.001$ vs. placebo), whereas the reduction induced by glyburide (from 5.15 to 4.63 mmol/l, $\Delta = -0.19 \pm 0.20$) failed to achieve statistical significance. Accordingly, ~30% of patients treated with nateglinide achieved good glucose control (2-h postprandial glucose <7.8 mmol/l), whereas only 13% of glyburide-treated patients achieved this level of control ($P < 0.05$ vs. nateglinide). Approximately 60% of patients treated with glyburide or nateglinide achieved 2-h postprandial glucose levels <11.1 mmol/l. Fasting plasma glucose (FPG) levels in patients randomized to

Table 1—Fasting glucose and insulin values

	Placebo			Nateglinide			Glyburide		
	Before Rx	After Rx	LMS PWC*	Before Rx	After Rx	LMS PWC*	Before Rx	After Rx	LMS PWC*
FPG (mmol/l)	11.4 ± 0.4	11.6 ± 0.4	0.5 ± 0.0†	10.6 ± 0.4	9.8 ± 0.4	-1.0 ± 0.3‡	11.9 ± 0.5	8.4 ± 0.3	-2.9 ± 0.3§
Fasting insulin (pmol/l)	111 ± 9	110 ± 9	-2 ± 8†	121 ± 9	136 ± 12	9 ± 8†	107 ± 7	138 ± 11	33 ± 8§
Fasting C-peptide (nmol/l)	1.0 ± 0.1	0.9 ± 0.1	0.05 ± 0.05†	1.2 ± 0.1	1.2 ± 0.1	0.00 ± 0.05†	1.0 ± 0.0	1.2 ± 0.1	0.21 ± 0.05§
Fasting proinsulin (pmol/l)	37.7 ± 3.3	40.5 ± 4.1	1.69 ± 2.9†	40.4 ± 3.3	39.8 ± 3.9	2.83 ± 3.07†	34.5 ± 2.5	44.6 ± 4.5	12.8 ± 3.1§

Data are means ± SEM. LMS, least means square; PWC, pairwise statistical comparison; Rx, treatment. * Δ , from baseline; † $P = NS$; ‡ $P < 0.03$; § $P < 0.001$.

glyburide were 1.3 mmol/l ($P < 0.001$) higher at baseline than in patients randomized to nateglinide (Table 1). At 8 weeks of treatment, FPG was reduced by 1.9 mmol/l ($P < 0.001$) more with glyburide than with nateglinide treatment. FPG tended to increase over 8 weeks in the placebo-treated group.

Treatment with nateglinide did not affect fasting levels of C-peptide, insulin, or proinsulin (Table 1). In contrast, glyburide treatment increased fasting C-peptide versus placebo or nateglinide ($P < 0.001$), insulin versus placebo ($P < 0.001$) and nateglinide ($P < 0.05$), and proinsulin versus placebo ($P < 0.001$) and nateglinide ($P < 0.025$). To adjust for the baseline imbalance in FPG between treatment groups, we determined the change from baseline (pretreatment) in the 4-h incremental glucose AUC during the Sustacal challenges. The reduction of mealtime glucose excursions induced by nateglinide was approximately twice that induced by glyburide (-4.94 ± 0.74 vs. -2.71 ± 0.71 mmol · h/l, $P < 0.03$), whereas insulin secretion as reflected by the C-peptide AUCs was approximately twice that in glyburide-treated patients than in nateglinide-treated patients (1.83 ± 0.24 vs. 0.95 ± 0.23 nmol · h/l, $P < 0.001$). Nateglinide and glyburide also increased the insulin AUCs ($\Delta = +266 \pm 50$ and $+401 \pm 52$ pmol · h/l, respectively) but the ~50% greater stimulation by glyburide did not achieve statistical significance ($P = 0.063$ vs. nateglinide).

Solid-meal challenge

Solid-meal challenges were performed at weeks -1 and 7 of treatment, and a 12-h (19-point) profile was obtained to allow comparison throughout the day, encompassing three standard meals. As illustrated in Fig. 2, nateglinide and glyburide both augmented the insulin response to solid meals, but with markedly differing

kinetics. Nateglinide primarily increased early insulin release, and levels returned to placebo-treated control or baseline levels between meals (Fig. 2A). The insulin response to meals in glyburide-treated patients was delayed and prolonged relative to nateglinide (Fig. 2B). This was particularly apparent after the morning meal, when the maximum insulin levels were not seen until 2 h postmeal and insulin levels did not return to placebo-treated control or baseline levels between meals.

Figure 2C depicts the change of 12-h insulin profiles from week -1 to week 7 of treatment with nateglinide, glyburide, or placebo (illustrating the treatment-mediated effects). In placebo-treated patients, the profiles on weeks -1 and 7 were nearly superimposable (data not shown), resulting in a nearly flat line for the incremental profile. In nateglinide-treated patients, marked increases of insulin were observed at the first postmeal time point (30 min), maximal augmentation occurred at 60 min after each meal, and insulin levels normalized within 3 h of breakfast and lunch. In glyburide-treated patients, maximum insulin levels occurred at 2 h after breakfast; 2 h after dinner, there was minimal augmentation of insulin levels after lunch, and insulin levels failed to return to baseline at any time during the 12-h sampling period. Using the data depicted in Fig. 3, the treatment-induced changes of 12-h insulin AUCs were calculated. Glyburide treatment increased overall daytime insulin exposure nearly twofold relative to nateglinide ($\Delta = +1,702 \pm 228$ vs. $+866 \pm 217$ pmol · h/l, respectively, $P = 0.01$).

As depicted in Fig. 3, nateglinide was also more effective than glyburide in reducing glucose excursions after a solid meal, particularly after an overnight fast. The peak incremental postbreakfast glucose was significantly reduced by nateglinide ($\Delta = -1.7 \pm 0.4$ mmol/l, $P < 0.001$; Fig. 3A), whereas the modest re-

duction that occurred in glyburide-treated patients ($\Delta = -0.6 \pm 0.4$ mmol/l; Fig. 3B) failed to achieve statistical significance compared with placebo ($P < 0.005$ vs. nateglinide).

Figure 3C depicts the change from week -1 to week 7 in the 12-h incremental glucose profiles in the three groups of patients. The antihyperglycemic effect of nateglinide seemed to be most pronounced after the morning meal, with more moderate effects at lunch and dinner, whereas the most pronounced antihyperglycemic effect of glyburide occurred after lunch, with only modest effects at breakfast and dinner. Accordingly, the change in the 12-h incremental AUC of glucose was reduced by nateglinide and glyburide with a similar efficacy ($\Delta = -13.2 \pm 3.4$ vs. -15.3 ± 3.9 mmol · h/l, respectively; $P < 0.001$ for either treatment versus placebo, $P = 0.684$ for nateglinide versus glyburide). However, nateglinide had a more clearly meal-related effect, which resulted in a reduction in the glucose fluctuations throughout the day. This is highlighted by the finding that nateglinide significantly reduced the standard deviation of the plasma glucose levels obtained during the 19-point profile ($\Delta = -0.17 \pm 0.08$, $P < 0.05$), whereas glyburide increased the standard deviation ($\Delta = +0.24 \pm 0.08$, $P < 0.002$).

To assess potential effects on β -cell function, the effects of nateglinide and glyburide on the insulinogenic index was calculated for time 15 min after ingestion of the standard breakfast. This index represents the ratio of the change of insulin to the change of glucose and assesses the effectiveness of the glucose contained in the meal to stimulate insulin release. Whereas glyburide did not influence the insulinogenic index at 15 min postbreakfast ($\Delta = +18 \pm 71$ pmol/mmol), nateglinide markedly increased the insulinogenic index

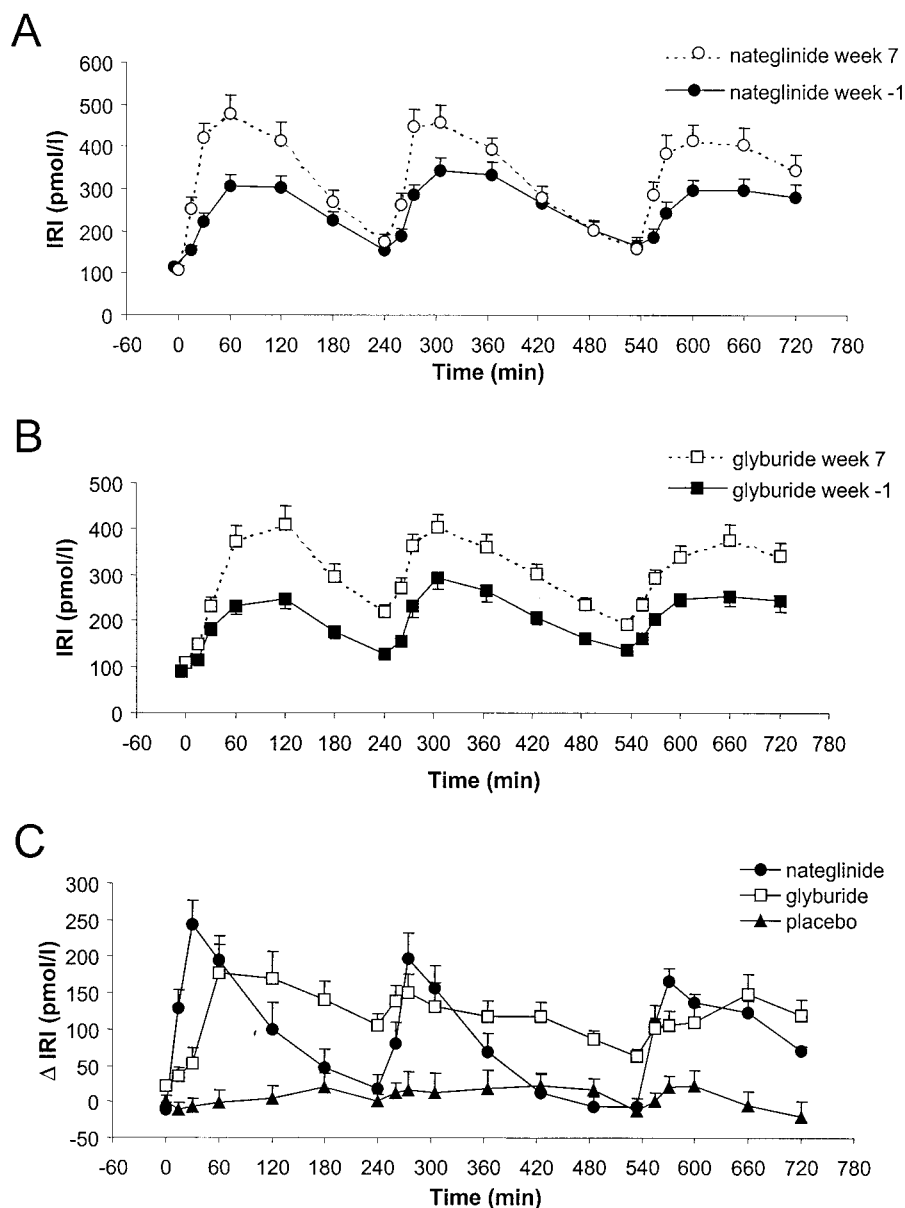


Figure 2—A: Plasma levels of immunoreactive insulin (IRI) during the 12-h 19-point profiles obtained during the solid-meal challenges performed before (week -1) and after (week 7) treatment with nateglinide (120 mg, before meals). B: Plasma levels of IRI during the 12-h 19-point profiles obtained during the solid-meal challenges performed before (week -1) and after (week 7) treatment with glyburide (10 mg, q.d.). C: Change from baseline (pretreatment) in the 12-h IRI profiles during the solid-meal challenges performed before and after 7 weeks of treatment with nateglinide (120 mg, before meals), glyburide (10 mg, q.d.), or placebo. All data are represented as the mean \pm SEM.

($\Delta = +244 \pm 72$ pmol/mmol, $P < 0.025$ vs. glyburide or placebo).

Safety and tolerability

The only treatment-emergent side effect reported by patients in this study was an increase in symptoms suggestive of hypoglycemia for both active treatment arms. Patients were instructed to obtain and re-

cord a blood glucose measurement when symptoms arose, and most reported events were accompanied by self-monitored blood glucose measurements. Nateglinide-treated patients had significantly fewer events suggestive of hypoglycemia than glyburide-treated patients but more events than placebo-treated patients (12 vs. 53 vs. 2, respectively). The compar-

ison was of the percentage of patients reporting at least one event of symptoms suggestive of hypoglycemia. This comparison was statistically significantly different ($P < 0.05$) in favor of nateglinide, based on Mantel-Haenszel statistics. The frequency of hypoglycemia confirmed by self-monitored blood glucose followed the same order (3 vs. 14 vs. 1 for nateglinide, glyburide, and placebo, respectively).

CONCLUSIONS— The purpose of this study was to compare the effects of nateglinide and glyburide on control of postmeal glucose excursions and insulin secretion patterns in patients with type 2 diabetes. It was found that nateglinide and glyburide produced similar degrees of overall mealtime glucose control, but nateglinide had a greater effect on mealtime glucose excursions and glyburide on reducing FPG. Nateglinide selectively increased early insulin release, whereas glyburide increased fasting insulin levels and increased insulin levels persistently throughout the day. Thus, overall insulin exposure was reduced by the rapid-onset/short-duration insulinotropic agent, nateglinide, relative to the sulfonylurea, glyburide, as was the incidence of events suggestive of hypoglycemia.

The mechanism by which the normal rapid burst of insulin that occurs at the onset of a meal minimizes prandial glucose excursions has been reviewed recently (15). In brief, rapid direct (16) and indirect (17) effects of insulin to suppress hepatic glucose production allow glucose flux from the gut to replace endogenous production of glucose to nearly exactly balance glucose use by the central nervous system, with only minimal extra glucose remaining to be taken up and stored by peripheral tissues. Nateglinide, by restoring or mimicking the normal early burst of insulin that is lost in type 2 diabetes, effectively reduces the generation of the glucose excursion and thereby reduces reactive hyperinsulinemia. Thus, in contrast to a slower, longer-acting agent (e.g., glyburide) premeal administration of nateglinide effectively controlled postmeal hyperglycemia with only half the total insulin exposure produced by even once-daily administration of glyburide.

In the present study, nateglinide was found to reduce mealtime glucose excursions, particularly with the morning meal. This breakfast effect may be related to the greater ability of early insulin secretion to

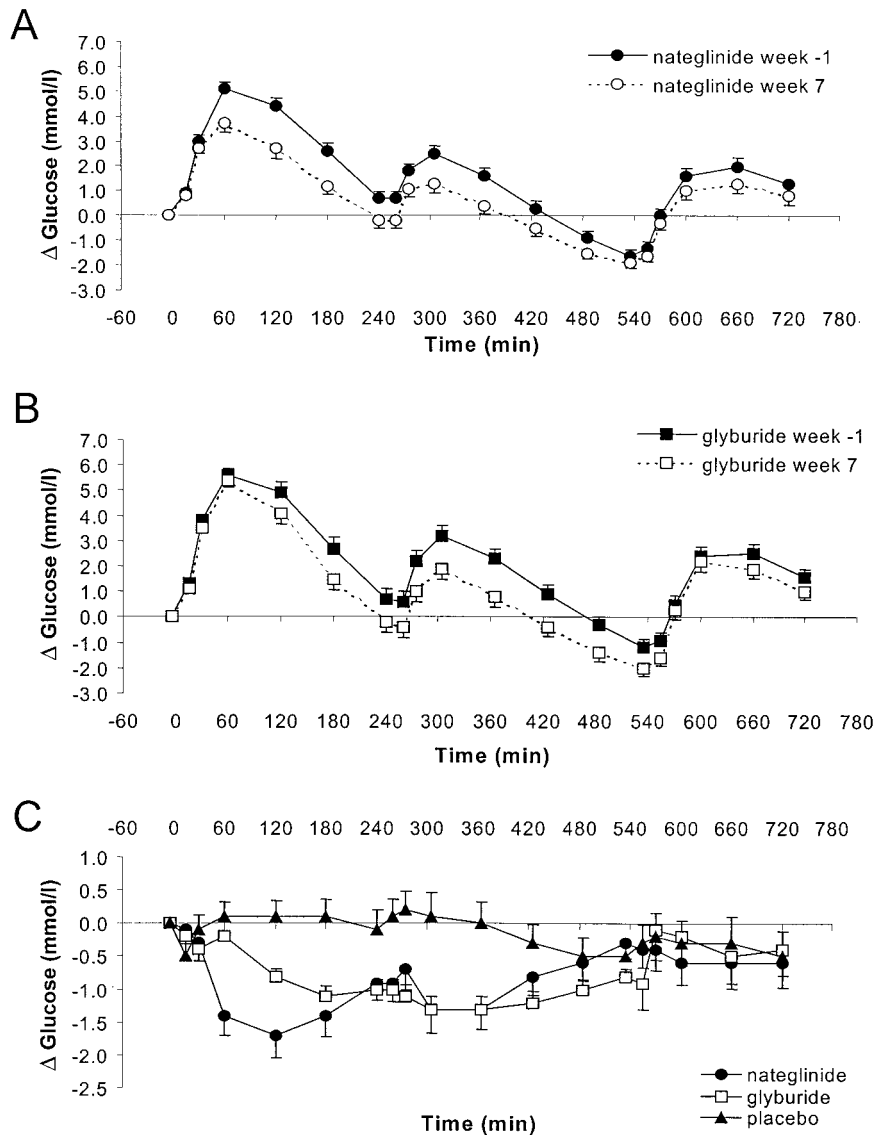


Figure 3—A: Incremental (FPG-adjusted) plasma glucose levels during the 12-h 19-point profiles obtained during the solid-meal challenges performed before (week -1) and after (week 7) treatment with nateglinide (120 mg, before meals). B: Incremental (FPG-adjusted) plasma glucose levels during the 12-h 19-point profiles obtained during the solid-meal challenges performed before (week -1) and after 7 weeks of treatment with glyburide (10 mg, q.d.). C: Change from baseline (pretreatment) in the FPG-adjusted 12-h glucose profiles during the solid-meal challenges performed before and after 7 weeks of treatment with nateglinide (120 mg, before meals), glyburide (10 mg, q.d.), or placebo. All data are represented as the mean \pm SEM.

reduce the size of the glucose excursion under conditions in which the meal is ingested at a time when the gluconeogenic rate and the levels of free fatty acids are higher and liver glycogen is lower than at any other time during the day. Glucose variability was also reduced, as was reactive (late) insulin secretion. Therefore, nateglinide provided postmeal glucose control similar to or better than that provided by glyburide, but with markedly re-

duced daytime glucose variability and with approximately one-half the total insulin. In summary, premeal administration of nateglinide selectively augmented the early insulin response to meals. Nateglinide clearly enhanced the insulinogenic index of the morning meal, indicating improved efficiency of glucose to stimulate insulin release. This effect leads to reduced mealtime glucose exposure and reduced overall glucose variability

while minimizing total insulin exposure (compared with commonly used insulinotropic agents).

The results of this study suggest that the mealtime insulin secretion profile with nateglinide may be an appropriate option for treatment of early-stage diabetes, especially when the persistent insulin secretion profile with a sulfonylurea such as glyburide is not an appropriate option. Moreover, the results also indicate that nateglinide would be an attractive partner for combination therapy with antidiabetic drugs, which target insulin action, especially when treating to near-normal targets. In fact, a recent report of a trial of metformin plus nateglinide showed significant improvement in glucose control when the combination was compared with either drug used as monotherapy (18).

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References

- Lebovitz HE: Insulin secretagogues: old and new. *Diabetes Rev* 7:139–153, 1999
- Kelly D: Approaches to preventing prandial hyperglycemia excursions. *Curr Opin Endocrinol Diabetes* 6:S7–S11, 1999
- Jeng C-Y, Hollenbeck CB, Wu MS, Chen YD, Reaven GM: How does glibenclamide lower plasma glucose concentrations in patients with type 2 diabetes? *Diabet Med* 6:303–308, 1989
- Rosenstock J, Samols E, Muchmore DB, Schneider J, and The Glimepiride Study Group: Glimepiride, a new once-daily

- sulfonylurea. *Diabetes Care* 19:1194–1199, 1996
5. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
 6. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352:837–853, 1998
 7. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet* 352:854–865, 1998
 8. Mahler RJ, Adler ML: Type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment. *J Clin Endocrinol Metab* 84:1165–1171, 1999
 9. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
 10. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensnick JW, Bierman EL, Porte D Jr: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 42:222–229, 1976
 11. Calles-Escandon J, Robbins DC: Loss of early phase of insulin release in humans impairs glucose tolerance and blunts thermic effect of glucose. *Diabetes* 36:1167–1172, 1987
 12. Leclercq-Meyer V, Ladriere L, Fuhlen-dorff J, Malaisse WJ: Stimulation of insulin and somatostatin release by two meglitinide analogs. *Endocr J* 7:311–317, 1997
 13. de Souza CJ, Russo P, Lozito R, Dunning BE: Differential effects of short and long duration insulinotropic agents on meal-related glucose excursions. *Diabetes Obes Metab* 3:73–83, 2001
 14. Hanefeld M, Dickinson S, Bouter KP, Guillard C: Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 23:202–207, 2000
 15. Dunning BE, Foley JE: New therapies to increase insulin secretion. In *Diabetes Mellitus, A Fundamental and Clinical Text*. LeRoith D, Taylor SI, Olefsky JM, Eds. Philadelphia, Lippincott Williams & Wilkins, 2000, p. 836–842
 16. Sindelar DK, Chu CA, Venson P, Donahue EP, Neal DW, Cherrington AD: Basal hepatic glucose production is regulated by the portal vein insulin concentration. *Diabetes* 47:523–529, 1998
 17. Bergman RN: New concepts in extracellular signaling for insulin action: the single gateway hypothesis. *Recent Prog Horm Res* 52:359–387, 1997
 18. Horton E, Clinkingbeard C, Gatlin M, Foley J: Nateglinide alone and in combination with Metformin improves glycaemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 23:1660–1665, 2000