Hypoglycemic Potential of Nateglinide Versus Glyburide in Patients With Type 2 Diabetes Mellitus

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Antidiabetic agents that augment insulin secretion can cause hypoglycemia. With the current trend toward early and aggressive treatment of patients with type 2 diabetes, the hypoglycemic potential of insulinotropic agents is of concern. This study aimed to compare the propensity of the "glinide," nateglinide, and the sulfonylurea (SU), glyburide, to elicit hypoglycemia in type 2 diabetic patients with moderately elevated fasting plasma glucose (FPG). Hyperglycemic clamps (target plasma glucose = 11.1 mmol/L) were initiated, and 30 minutes later patients received a single oral dose of nateglinide (120 mg, n = 15) or glyburide (10 mg, n = 12) in a double-blind fashion. At the end of the 2-hour clamp when the glucose infusion was terminated, plasma glucose and insulin levels were measured for 4 additional hours. The minimum plasma glucose level achieved after terminating the glucose infusion (glucose nadir) was used as an index of hypoglycemic potential. The mean (±SEM) glucose nadir was significantly lower in patients given glyburide (3.3 ± 0.2 mmol/L) versus nateglinide (4.4 ± 0.3 mmol/L, *P* = .025). Confirmed hypoglycemia (plasma glucose ≤ 2.8 mmol/L) occurred in 2 of 12 patients given glyburide and in none of those given nateglinide. Plasma insulin levels were significantly higher from 100 to 240 minutes after clamp termination in patients given glyburide versus nateglinide. Nateglinide has less hypoglycemic potential than glyburide, suggesting that nateglinide may be a more appropriate insulinotropic agent for patients with moderate fasting hyperglycemia, such as elderly patients and those with comorbid cardiac ischemia.

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HYPOGLYCEMIA is the limiting factor in achieving good glycemic control in patients with type 2 diabetes treated with insulin or insulin secretagogues.[1] In newly diagnosed patients with modestly elevated fasting plasma glucose (FPG) levels—a rapidly growing population due to increased screening—sulfonylurea (SU)-induced hypoglycemia may limit the ability to lower glucose to increasingly aggressive targets such as those recommended by the American Association of Clinical Endocrinologists (FPG ≤ 6.1 mmol/L, hemoglobin A_{1c} [HbA_{1c}] ≤ 6.5%).[2] However, the introduction of a new class of insulinotropic agents–the glinides–whose actions are rapid in onset and rapidly reversed,[3] raises the possibility that moderate hyperglycemia can be normalized with such agents with minimal risk of hypoglycemia.

The D-phenylalanine derivative, nateglinide, is one such rapid acting insulinotropic agent taken before meals to augment early insulin release and thereby reduce prandial glucose excursions. Because its effects are glucose-dependent[4] and rapidly reversed,[5] nateglinide can control postprandial hyperglycemia with minimal post-meal hyperinsulinemia[6] and a low incidence of hypoglycemia.[7,8]

The aim of the present study was to compare the hypoglycemic potential of nateglinide with that of the SU, glyburide, in patients with moderate fasting hyperglycemia. This study population was selected because it comprises patients who would most benefit from control of postprandial hyperglycemia yet are at the greatest risk of hypoglycemia when treated with an SU. The most commonly used and comparably insulinotropic doses[6] of nateglinide (120 mg) and glyburide (10 mg) were employed in this study. They were given in a single oral dose 30 minutes after initiation of a 2-hour hyperglycemic clamp (target plasma glucose, 11.1 mmol/L). Plasma glucose and insulin levels were monitored for 4 hours after termination of the glucose clamp, and the post-clamp glucose nadir was considered an index of the hypoglycemic potential of the agents.

MATERIALS AND METHODS

Subjects and Study Design

This was a multicenter, double-blind, active-controlled study to compare the hypoglycemic potential of nateglinide and glyburide in diet-treated patients with type 2 diabetes mellitus. Written informed consent was obtained from all participants; the study was performed in compliance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board/Independent Ethics Committee at each institution.

Patients were between 30 and 70 years of age with a documented history of type 2 diabetes mellitus for ≥ 3 months. They had FPG levels between 7.0 and 8.9 mmol/L (inclusive), body mass index (BMI) between 22 and 36 kg/m^2 (inclusive), and C-peptide levels greater than 0.6 μg/L (>0.2 nmol/L). Patients were SU-naive, diet-treated, and off oral antidiabetic drugs for at least 4 weeks before the screening period (week −2). Females were either nonfertile or using a medically approved contraceptive method.

Patients were excluded if they had a history of type 1 diabetes or secondary forms of diabetes, a history of chronic insulin treatment, or significant diabetic complications. Patients were also excluded if they had a history of seizure disorder; an electrocardiogram (ECG) consistent with a prior myocardial infarction; liver disease with ALT, AST, or alkaline phosphatase 2 times the upper limits of normal (ULN); direct bilirubin 1.3-fold greater than the ULN; fasting triglycerides greater than 7.0 mmol/L; or serum creatinine greater than 220 mmol/L. Sixty

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patients were screened and 32 patients patients failed to meet all eligibility requirements.

During visit 1, informed consent and a medical history were obtained. Patients underwent a physical examination, and the following tests were performed to verify eligibility: ECG, chemistry screen, lipid profile, hematology, urinalysis, thyrotropin, pregnancy test, FPG, C-peptide, and HbA_{1c}. The hyperglycemic clamp was performed on visit 2, which was scheduled within 17 days of visit 1, after laboratory results confirmed eligibility.

Hyperglycemic Clamp

Patients fasted for at least 10 hours before initiation of the clamp procedure. An intravenous (IV) catheter was inserted in 1 hand that was placed in a hand-heater box at 55°C for sampling of arterialized blood. A second IV catheter was placed in the opposite arm for infusion of glucose (20%) and potassium chloride (KCl; 80 mmol/L to avoid hypokalemia). The clamp was initiated (at time 0) by infusion of glucose to reach the target plateau level of 11.1 mmol/L, and KCl was infused at a constant rate of 50 mL/h. After 30 minutes, a single oral dose of nateglinide (120 mg) or glyburide (10 mg) was administered in a blinded fashion according to the randomization schedule. Steady-state hyperglycemia was maintained by adjusting the glucose infusion rate based on plasma glucose measurements obtained at 5-minute intervals at the study site. The glucose infusion was terminated 2 hours after its initiation, and samples for on-site glucose measurements were obtained at 10-minute intervals thereafter. Samples for central laboratory determination of plasma levels of glucose and immunoreactive insulin (IRI) were obtained at times −10, 0, 100, and 120 minutes and thereafter at 20-minute intervals for 4 hours post-clamp or until hypoglycemia was confirmed by symptoms accompanied by an on-site plasma glucose level ≤ 2.8 mmol/L. Vital signs and plasma potassium levels were monitored regularly before, during, and after the clamp.

Efficacy and Safety Assessments

The plasma glucose levels measured at the study sites used the hexokinase method and Beckman (Fullerton, OH) or YSI (Yellow Springs, OH) glucose analyzers. All other analyses were performed at a central laboratory (Clinical Reference Laboratory, Lenexa, KS) using standard methods. Insulin and C-peptide levels were measured by a chemiluminescent assay (Diagnostic Products Corp, Los Angeles, CA), and HbA_{1c} was measured by high-performance liquid chromatography using the ion-exchange method on a Bio-Rad Diamat or Variant analyzer (Bio-Rad, Hercules, CA). The HbA_{1c} results were standardized to the Diabetes Control and Complications Trial normal range. The normal range of FPG from this laboratory was 4.2 to 6.1 mmol/L.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination or laboratory test, was collected and recorded. This information included the duration, severity, relationship to study drug, and action taken. Confirmed hypoglycemia was defined as symptoms consistent with hypoglycemia accompanied by a plasma glucose level ≤ 2.8 mmol/L.

Data Analysis

The primary efficacy variable was the plasma glucose nadir reached after discontinuation of the hyperglycemic clamp. Treatment difference was tested by analysis of variance (ANOVA) with center and treatment as factors in the model. Secondary efficacy variables were the 4-hour glucose and insulin areas under the curve (AUCs) after termination of glucose infusion. These AUCs were calculated by the trapezoidal method. When samples were missing (eg, due to hypoglycemia or problems with the IV catheters), the last measured value was carried forward for the remainder of the 4-hour period. Two patients receiving nateglinide and 1 patient receiving glyburide had catheter problems requiring glucose values to be carried forward. Summary statistics of the time course of plasma IRI and the on-site–determined plasma glucose levels were calculated and comparisons of the slopes of the post-clamp decline in glucose and insulin levels were made with, 2-sample *t* tests.

Table 1. Characteristics of the Patients Studied (mean ± SEM)

	Nateglinide	Glyburide
Patients (n)	15	12
Age (yr)	49.8 ± 2.2	57.9 ± 1.8*
Range	(34-62)	(49-67)
Gender (%)		
Male	5 (33.3%)	6 (50.0%)
Female	10 (66.7%)	6 (50.0%)
BMI (kg/m^2)	30.8 ± 1.0	31.2 ± 1.0
Duration of type 2 diabetes (mo)	28.3 ± 14.2	23.9 ± 5.4
C-peptide (nmol/L)	1.41 ± 0.11	1.15 ± 0.08
HbA_{1c} (%)	6.95 ± 0.3	6.73 ± 0.1
FPG (mmol/L)	7.7 ± 0.2	8.0 ± 0.2
Insulin (pmol/L)	66 ± 7.1	59 ± 9.0

*$P < .05$.

RESULTS

Study Participants

Table 1 gives the baseline characteristics of the 15 patients who received nateglinide and the 12 patients who received glyburide. The BMI and duration of known diabetes were similar between groups, as were the baseline levels of plasma C-peptide, insulin, HbA_{1c}, and FPG. The mean age of the patients who received glyburide was modestly but statistically significantly higher than that of the patients who received nateglinide. Three of the 15 nateglinide-treated patients and 2 of the 12 glyburide-treated patients had received metformin treatment in the past (but were treated with diet alone for at least 4 weeks before the screening period) and the remaining patients were oral therapy-naïve. Twelve of 15 patients receiving nateglinide and 9 of 12 patients receiving glyburide were Caucasian.

Clamp Results

Figure 1 depicts the on-site–determined plasma glucose levels before, during, and after the 2-hour hyperglycemic clamp (target plasma glucose, 11.1 mmol/L). The baseline (pre-clamp and pre-drug) FPG levels measured at the study sites averaged 7.6 ± 0.2 and 7.4 ± 0.2 mmol/L in the patients randomized to nateglinide and glyburide, respectively (P = not significant [NS]). Similar steady-state hyperglycemia was achieved in both groups during the second hour of the clamp. The mean (±SEM) values from 60 to 120 minutes of the clamp were 11.6 ± 0.2 and 11.3 ± 0.1 mmol/L in patients given nateglinide and glyburide, respectively (P = NS). Following discontinuation of the glucose infusion, plasma glucose levels fell rapidly in both groups. However, the rate of decline in plasma glucose (slope of glucose *v* time) was significantly greater in patients given glyburide (−0.053 ± 0.002 mmol/L/min) than in those given nateglinide (−0.042 ± 0.002 mmol/L/min, $P < .001$).

Plasma glucose and IRI were measured at the central labo-

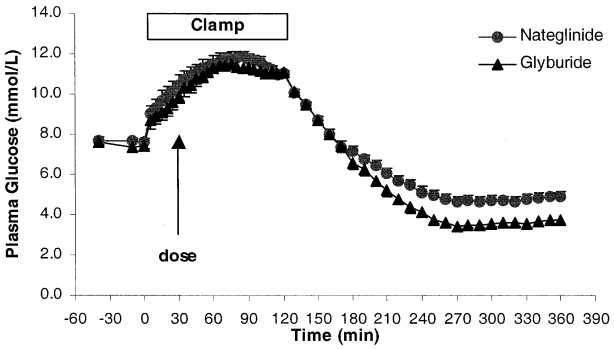

Fig 1. Plasma levels of site-determined glucose before, during, and after hyperglycemic clamps in patients given nateglinide (120 mg, n = 15) or glyburide (10 mg, n = 12) at 30 minutes. Mean ± SEM. Time 0 = clamp initiation.

ratory in samples obtained prior to initiation of the clamp (Table 1), during the final 20 minutes of the clamp, and at 20-minute intervals for 4 hours after termination of the clamp. Mean plasma IRI levels in the final minutes of the clamp were modestly but not significantly higher in the glyburide-treated patients (257 ± 36 pmol/L) than in the nateglinide-treated patients (190 ± 23 pmol/L, $P = .193$).

Figure 2 illustrates the differential time courses of the glucose and IRI profiles in nateglinide- (Fig 2A) and glyburide-treated (Fig 2B) patients after clamp discontinuation. Also shown are the normal range for FPG at the central laboratory and the mean baseline (pre-clamp) insulin levels. In patients given nateglinide, the mean plasma glucose levels fell rapidly after termination of the clamp (time 0) but remained within the euglycemic range from 100 minutes post-clamp onward. Plasma IRI levels fell steadily from 40 minutes to 240 minutes post-clamp, and were below the baseline values during the final hour of sampling. In patients given glyburide, plasma glucose levels also decreased rapidly after termination of the clamp, but fell below the normal range for the final 2 hours of sampling. In glyburide-treated patients, plasma IRI levels decreased gradually from 40 to 220 minutes post-clamp; however, they remained approximately 2-fold higher than baseline for the final hour of sampling, despite plasma glucose levels below the normal range. Although plasma IRI levels were significantly higher in patients given glyburide versus nateglinide at each time-point from 100 to 240 minutes post-clamp ($P < .05$ or better), the rate of decline of insulin did not differ significantly between groups.

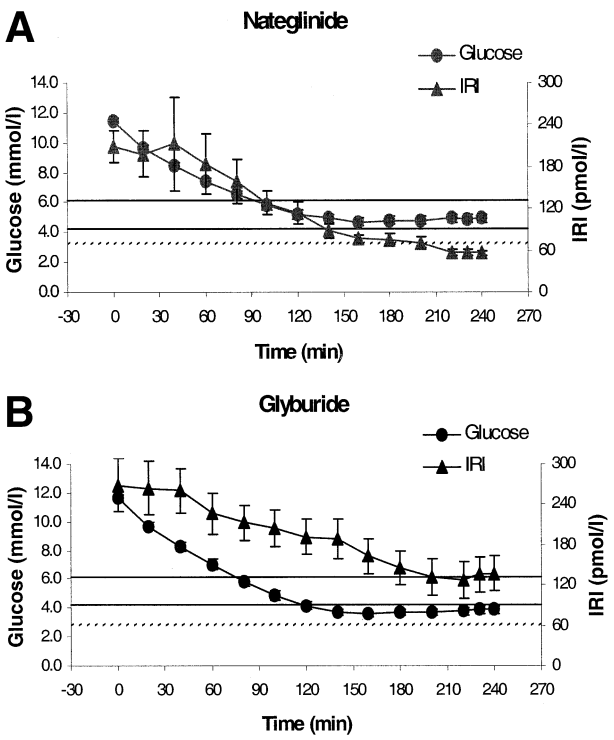

Fig 2. Central laboratory-determined levels of glucose and IRI after terminating glucose infusions in patients treated 90 minutes previously with (A) nateglinide (120 mg, n = 15) or (B) glyburide (10 mg, n = 12). The upper and lower limits of normal are shown with solid lines and the baseline (pre-clamp) mean insulin level is shown with a dashed line. Mean ± SEM. Time 0 = clamp discontinuation.

Table 2. Mean (± SEM) Post-Clamp Glucose Nadirs and Mean Time at Which They Occurred

	Nateglinide	Glyburide
Glucose nadir (mmol/L)	4.4 ± 0.3	3.3 ± 0.2*
Time to glucose nadir (minutes post-clamp)	175 ± 11	150 ± 6

*$P < .025$ *v* nateglinide by ANOVA.

The AUCs of glucose and insulin for the 4 hours following termination of the clamps were calculated to assess the overall degree of glucose lowering and insulin stimulation induced by nateglinide and glyburide. The glucose AUC in patients given glyburide (24.4 ± 1.4 mmol · h/L) was modestly lower, but not significantly different from that in patients given nateglinide (26.7 ± 1.1 mmol · h/L, $P = .08$). The IRI AUC in patients receiving glyburide (694 ± 134 pmol · h/L) was modestly higher, but not significantly different from that in patients receiving nateglinide (447 ± 104 pmol · h/L, $P = .066$).

As reported in Table 2, the mean glucose nadir in patients given glyburide (3.3 ± 0.2 mmol/L) was significantly lower ($P < .025$) than that in patients given nateglinide (4.4 ± 0.2 mmol/L) and tended to occur at an earlier time (150 ± 6 minutes *v* 175 ± 11 minutes post-clamp, P = NS). Confirmed hypoglycemia was defined a priori as hypoglycemic symptoms accompanied by a plasma glucose measurement ≤ 2.8 mmol/L. None of the nateglinide-treated patients had confirmed hypoglycemia, compared with 2 of 12 (16.7%) glyburide-treated patients. When a higher cutoff of plasma glucose (≤3.3 mmol/L) was used to define hypoglycemia, 2 of 15 (13.3%) nateglinide-treated patients had a hypoglycemic event; 1 was classified as mild and 1 as moderate. In contrast, 4 of 12 (33.3%) glyburide-treated patients had an event with glucose ≤ 3.3 mmol/L, all of which were classified as moderate.

DISCUSSION

The purpose of the present study was to compare the hypoglycemic potential of nateglinide and glyburide in patients with mild-to-moderate fasting hyperglycemia. This issue is of particular importance because there is a trend toward earlier and more aggressive treatment of diabetes, screening for "prediabetes" has been recommended,[9] and pharmacologic intervention will be needed for patients who cannot maintain lifestyle modification. The patients were enrolled primarily based on having only modestly elevated FPG (≤8.9 mmol/L). This cutoff was selected because such patients are likely to derive the greatest benefit from control of postprandial hyperglycemia, but are also at the most risk of hypoglycemia with SUs.

To assess the hypoglycemic potential, a single oral dose of nateglinide (120 mg) or glyburide (10 mg) was administered 30 minutes after beginning a hyperglycemic clamp. When steady-state hyperglycemia and hyperinsulinemia were achieved (120 minutes after starting the glucose infusion), the clamp was abruptly discontinued and glucose levels were allowed to fall. The post-clamp glucose nadir was considered an index of the propensity of the agents to elicit hypoglycemia.

It was found that the post-clamp glucose nadir in patients receiving glyburide (3.3 mmol/L) was significantly lower than that in the nateglinide-treated patients (4.4 mmol/L), and that confirmed hypoglycemia (≤2.8 mmol/L) occurred in 2 of 12 glyburide-treated patients and in none of the patients who received nateglinide. These results demonstrate that nateglinide is less prone to elicit hypoglycemia than is glyburide, and are consistent with earlier reports that nateglinide treatment was associated with less hypoglycemia than glyburide when a meal was skipped.[10] Further, in a placebo-controlled, hyperglycemic clamp study similar to the present work, nateglinide was found to have less hypoglycemic potential than repaglinide,[11] an insulinotropic agent with a similarly short half-life of approximately 1 hour.[12] Thus, the plasma half-life per se does not appear to determine the hypoglycemic potential of an insulinotropic agent.

There are several possible explanations for the lesser hypoglycemic potential of nateglinide versus glyburide, the most likely of which is that the insulinotropic effect of nateglinide is more glucose-dependent than is that of glyburide. This was suggested by preclinical studies using isolated rat islets.[4] At a concentration that exerted half-maximal stimulation of insulin release at an ambient glucose level of 8.0 mmol/L, nateglinide did not stimulate insulin release at an ambient glucose level of 3.0 mmol/L. In contrast, a concentration of glyburide that elicited half-maximal insulin stimulation at 8.0 mmol/L glucose elicited more than half-maximal stimulation of insulin release in the presence of 3.0 mmol/L glucose. Evidence of the stronger glucose-dependence of the insulinotropic effect of nateglinide, relative to glyburide, can also be found in the present study. Thus, in patients receiving glyburide, the post-clamp insulin levels remained nearly 2-fold above baseline throughout the 4-hour post-clamp observation period, long after glucose levels reached a nadir. In patients receiving nateglinide, insulin levels fell below the pre-clamp baseline coincident with the glucose nadir.

Differential pharmacokinetics could also contribute to the differential hypoglycemic potentials of glyburide and nateglinide. Although drug levels were not measured in the present study, it is known that the plasma half-life of glyburide in humans (~10 hours)[13] is much longer than that of nateglinide (~1.5 hours),[14] leading to glyburide's longer duration of action and more pronounced effect on FPG. However, it is unlikely that waning drug concentrations could represent the sole explanation for the rapid decline of insulin levels following termination of the glucose infusion seen in patients receiving nateglinide for 2 reasons. First, the time to peak drug levels for both glyburide and nateglinide is approximately 2 hours.[14,15] Since both agents were administered 30 minutes after the start of the 2-hour glucose clamp, drug levels would have been just reaching their peak at the time insulin levels were falling. Second, based on earlier pharmacokinetic and pharmacodynamic studies with nateglinide, 4 hours after administration of 120 mg, plasma levels would be expected to remain well above those required to initiate insulin secretion in the context of hyperglycemia.[14,16] In the present study, 4 hours after nateglinide administration (150 minutes post-clamp) plasma insulin had returned to baseline and corresponded to glucose levels in the normal range. Accordingly, it is suggested that the pharmacokinetic contribution to the low hypoglycemic potential of nateglinide is less important than is that of glucose-dependence.

This is consistent with a study by Kahn et al that compared the actions of nateglinide (120 mg) and glyburide (10 mg) given in the fasted state and prior to an IV glucose tolerance test.[17] It was found that in the fasted state, nateglinide elicited a rapid burst of insulin secretion but plasma insulin levels returned to baseline very rapidly when glucose levels fell. In contrast, when nateglinide was given prior to a glucose load, the potentiation of insulin release was greatly prolonged, suggesting that hyperglycemia extends the duration of action of nateglinide. The present findings, as well as those of Kahn et al, are also in accordance with a study showing a prolonged (>4 hours) square-wave response to nateglinide during hyperglycemic (7.8 mmol/L) clamp but only a transient effect during hypoglycemic (3.7 mmol/L) clamp (J.F. McLeod, unpublished observations).

Although the glucose dependence and short duration of action of nateglinide in the presence of low glucose levels would predict that nateglinide would have a lower hypoglycemic potential than glyburide, it has not been verified in human studies until now. Head-to-head comparison of the frequency of hypoglycemia in large clinical trials in patients with modestly elevated FPG would be the best way to directly address the question; however, these have not been performed due to safety considerations. Therefore, the present small mechanistic study was designed specifically to assess the hypoglycemic potential of the 2 agents in a controlled clinical setting. While glyburide may have the potential to lower glucose to a greater extent than nateglinide, such a perceived "advantage" may actually be detrimental if the rate of hypoglycemia is higher, particularly in elderly patients, those with comorbid cardiac ischemia, and those who are in the early stages of the disease.

In summary, as suggested by preclinical studies, the present work confirmed that nateglinide has a significantly lower hypoglycemic potential than does glyburide in patients with type 2 diabetes and moderate fasting hypergly-

cemia. The insulinotropic effects of glyburide were not suppressed, even as glucose levels fell into the hypoglycemic range, whereas those of nateglinide were rapidly reversed when glucose levels fell into this range. It may be concluded that nateglinide may be a more appropriate insulinotropic agent for patients with moderate fasting hyperglycemia, particularly elderly patients and those with comorbid cardiac ischemia.

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