Randomized Dose Ranging Study of the Reduction of Fasting and Postprandial Glucose in Type 2 Diabetes by Nateglinide (A-4166)

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OBJECTIVE — This randomized crossover double-blind placebo-controlled study aimed to assess the efficacy of nateglinide (A-4166), a novel phenylalanine-derived insulin secretagogue, in type 2 diabetic subjects while fasting and 5 min before a standard meal.

RESEARCH DESIGN AND METHODS — A single dose of nateglinide (60, 120, or 180 mg) or placebo was given to eight diet-treated overnight-fasted type 2 diabetic patients and to seven patients 5 min before a standard breakfast. Plasma glucose, radioimmunoassay insulin, and nateglinide were measured at baseline and for a further 180 min.

RESULTS — The time-averaged 180-min postdose mean decrease in fasting plasma glucose concentration was greater after nateglinide (1.8 mmol/l; 95% CI 1.5–2.0) than after placebo (0.7 mmol/l; 95% CI 0.3–1.2) ($P < 0.001$). Hypoglycemia did not develop in any of the subjects. Insulin concentrations increased 1.5-, 1.8-, and 1.9-fold with the 60-, 120-, and 180-mg doses, respectively ($P < 0.001$), peaking ~30 min after the dose. Nateglinide concentrations peaked after ~30 min, decreasing to 21% of peak by 180 min. In the meal test, the mean increase (2.9 mmol/l, 2.3–3.6) in plasma glucose over 180 min after placebo was reduced by 1.8 mmol/l ($P < 0.001$) with the two higher doses of nateglinide.

CONCLUSIONS — A single dose of nateglinide administered to diet-treated type 2 diabetic patients with fasting hyperglycemia increased insulin secretion and reduced fasting glucose without hypoglycemia. Administered 5 min before a meal, nateglinide reduced the postprandial glucose excursion by 64%. With its rapid onset and short duration of action, nateglinide is a promising oral prandial therapy in type 2 diabetes.

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The hyperglycemia of type 2 diabetes is associated with a relative impairment of insulin secretion and responds, in many cases, to the therapeutic use of oral insulin secretagogues such as sulfonylureas. These drugs, however, are commonly associated with hypoglycemic side effects due to the prolonged pharmacological action of many of the sulfonylureas in current use (1). In developing novel therapies without this drawback, one strategy has been to produce rapid-acting compounds with a short biological half-life.

Nateglinide (A-4166) is a novel rapid-acting nonsulfonylurea insulin secretagogue (2). Like the sulfonylureas, it stimulates insulin secretion by blocking ATP-sensitive K^+ (K_{ATP}) channels in the plasma membrane of the pancreatic β-cell (3–5). Closure of K_{ATP} channels enables β-cells to depolarize, thereby triggering the opening of voltage-gated calcium channels, calcium influx, and insulin release (6–8). Although not containing a sulfonylurea group, nateglinide binds to the same site in the β-cell as glibenclamide and has been shown to displace [^{3}H]glibenclamide binding from insulinoma cell membranes (4,9,10). Its action in vitro and in animal studies is, however, more rapidly reversible than that of glibenclamide (4,10,11).

K_{ATP} channels are also found in a variety of extrapancreatic tissues, including cardiac, skeletal, and smooth muscle and some neurons. The roles of these channels are incompletely understood, but their opening in cardiac muscle during hypoxia may provide some protection against ischemia. These K_{ATP} channels exhibit different sensitivities to sulfonylureas due to the presence of alternative types of sulfonylurea receptor subunit (12). Therefore, some sulfonylureas (e.g., glibenclamide) are effective blockers of K_{ATP} channels from a range of tissues, whereas others (e.g., gliclazide and tolbutamide) are more β-cell–specific (12). Nateglinide is also relatively specific for the pancreas, inhibiting β-cell K_{ATP} channels with ~50 times greater potency than smooth muscle K_{ATP} channels (13); however, it remains controversial whether blocking K_{ATP} channels in cardiac and smooth muscle produce clinically significant side effects.

Recent studies in type 2 diabetic subjects have shown that nateglinide enhances insulin release in response to an intravenous glucose tolerance test (14) and that it is well tolerated during 7 days of continuous therapy (15). We present here a dose-response study of the effects of nateglinide on plasma glucose and insulin when given to diet-treated type 2 diabetic subjects in both the fasting and

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Abbreviations: K_{ATP}, ATP-sensitive K^+ channel; UKPDS, U.K. Prospective Diabetes Study.

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

Table 1—*Patient characteristics*

	Fasting study	Meal study
n	8	7
Sex (M/F)	4/4	6/1
Age (years)	55 ± 8	55 ± 8
BMI (kg/m^2)	32.8 ± 10.2	31.0 ± 4.5
Duration of diabetes (years)	1.3 (5–15)	7 (0.4–10)
Fasting plasma glucose (mmol/l)	9.8 ± 1.6	9.7 ± 1.6
HbA_{1c} (%)	7.4 ± 1.2	7.1 ± 1.2

Data are *n*, means ± SD, or median (range).

prandial states. We used a double-blind randomized crossover placebo-controlled design to examine the effects of a single dose of 60, 120, or 180 mg of nateglinide.

RESEARCH DESIGN AND METHODS

— The patients recruited were between the ages of 35 and 70 years and had type 2 diabetes treated with diet alone. Patients were excluded if they suffered from active cardiovascular disease or were women of child-bearing potential. Eight subjects participated in the fasting study, and seven subjects participated in the meal study. The patient characteristics are presented in Table 1. The protocol was approved by the Central Oxfordshire Research Ethics Committee. All subjects gave written informed consent.

Protocol

Both studies used a double-blind randomized crossover placebo-controlled design. Drug and placebo tablets, supplied by the manufacturer before the initiation of the study, were indistinguishable and individually randomized.

In the fasting study, subjects attended after an overnight fast on four occasions. Each subject took a single dose of either placebo or 60, 120, or 180 mg of nateglinide orally in randomized order at time 0 min. Treatment was blinded to both patient and investigators. Blood samples were collected at −10, −5, 0, 10, 20, 30, 45, 60, 90, 120, 150, and 180 min from ingestion of the tablets from a cannula in a distal vein that was arterialized by heating with an electric blanket.

In the meal study, subjects attended after an overnight fast and were given a standard breakfast consisting of 56.6 g carbohydrate, 19.5 g protein, 11.5 fat, and 395 kcal at time 0 min, having taken a single dose of nateglinide 3–5 min prior to this. Doses and sample times were the same as in the fasting study.

Biochemistry

Plasma glucose was determined by a hexokinase method on a Cobas MIRA discrete analyzer (Roche Diagnostica, Herts, U.K.). Plasma radioimmunoassay insulin was measured in heparinized plasma by double antibody radioimmunoassay, with Sepharose attached to the second antibody for separation by decanting (Pharmacia, Milton Keynes, Bucks, U.K.). The insulin assay crossreacts 100% with intact proinsulins and ~90% with split

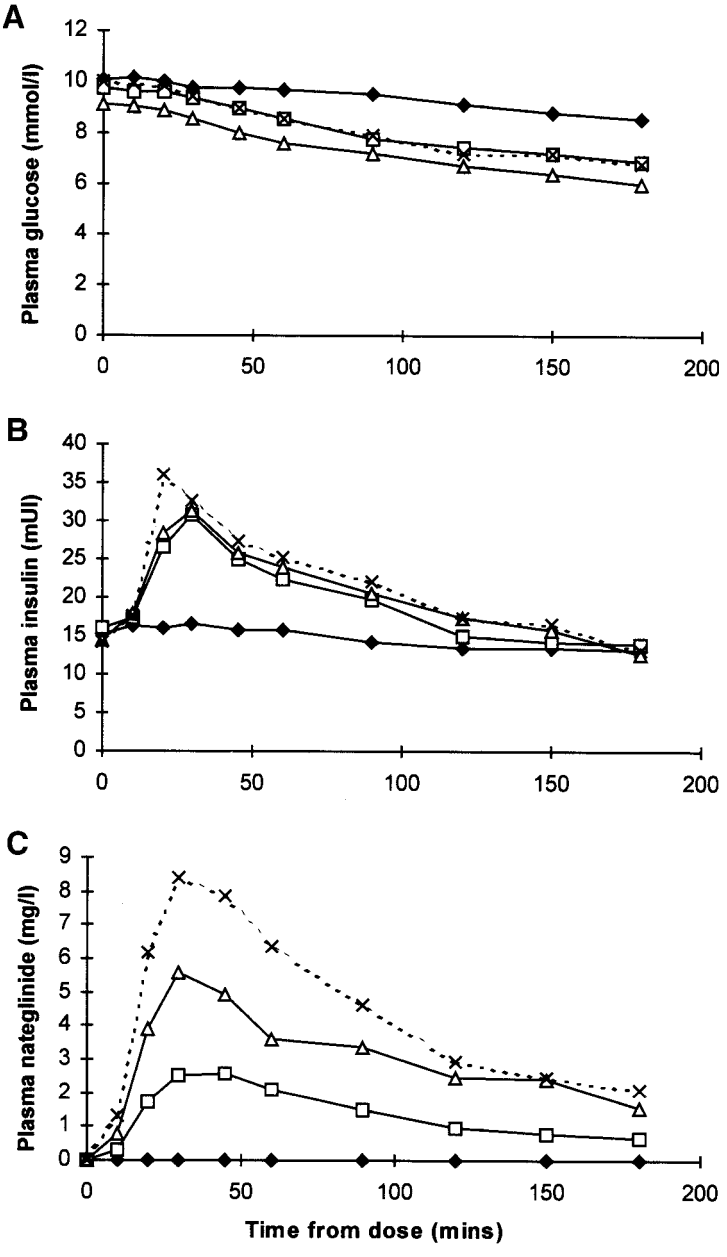

Figure 1—*Fasting plasma glucose (A), insulin (B), and nateglinide (C) profiles after oral administration of placebo (▲) or 60 mg (□), 120 mg (△), or 180 mg (×) nateglinide to type 2 diabetic subjects.*

proinsulins. Plasma nateglinide concentrations were measured by Inveresk Research International (Edinburgh, U.K.). HBA_{1c} was measured using the Bio-Rad Variant HPLC Haemoglobin Testing System (Bio-Rad, Richmond, CA), certified by the National Glycohemoglobin Standardization Program as comparable to the Diabetes Control and Complications Trial (normal range 4.7–6.4%).

Statistics

For each study, the primary outcome measures were the plasma concentrations of glucose, insulin, and nateglinide after dosing. The glucose and nateglinide responses were calculated as the incremental or decremental time-averaged mean concentrations (trapezoidal area under the curve divided by the total time interval) during the 180-min sampling period. Insulin responses were calculated as proportional changes from baseline to take into account differences in insulin sensitivity between subjects. The overall insulin response is reported as the time-averaged mean of the proportional increase from 0 to 90 min in order to avoid the confounding effect of altered glucose concentrations in the second half of the study. Results are expressed as arithmetic means for glucose and nateglinide concentrations and as geometric means for insulin responses; 95% CIs are shown in parentheses. Secondary outcome measures were the mean times to reach peak concentrations for insulin and nateglinide, calculated using the combined data for the three drug doses, and are presented as the geometric mean (95% CI). Analysis was performed using analysis of variance, with subject and period as fixed variables and with trend tests across different doses. Residual plots showed no marked deviation from normality, so untransformed values were used. The analysis after logarithmic transformation yielded no significant differences. Paired *t* tests between individual doses were performed when significant differences were detected by analysis of variance. Analysis was performed using SPSS release 6.1.4 for VAX/VMS (SPSS, Chicago, IL).

RESULTS

Fasting test

Plasma glucose concentrations on placebo decreased by a time-averaged mean of 0.7 mmol/l (95% CI 0.3–1.2) over the 3 h of continued fast, but a greater reduction was achieved after administration of nateglinide, with no significant difference between the three doses (Fig. 1*A*). The mean decrease in plasma glucose for the combined doses of nateglinide was 1.8 mmol/l (1.5–2.0) ($P < 0.001$ vs. placebo). No biochemical or symptomatic hypoglycemia was experienced. The insulin profiles are shown in Fig. 1*B*. Insulin concentrations did not change significantly after administration of placebo but rose after administration of all doses of nateglinide, with proportional increases of 1.48-fold (1.35–1.61), 1.76-fold (1.43–2.09), and 1.89-fold (1.52–2.26) at 60, 120, and 180 mg, respectively ($P < 0.001$ for trend across doses). Insulin concentrations increased within 10 min after administration of the 120- and 180-mg doses, reaching a peak at 29 min (25–34). Nateglinide concentrations increased within 10 min, with a time to peak of 42 min (33–53). At 3 h, the nateglinide concentration decreased to 21–22% of the peak values at each dose (Fig. 1*C*). The 180-min time-averaged mean nateglinide

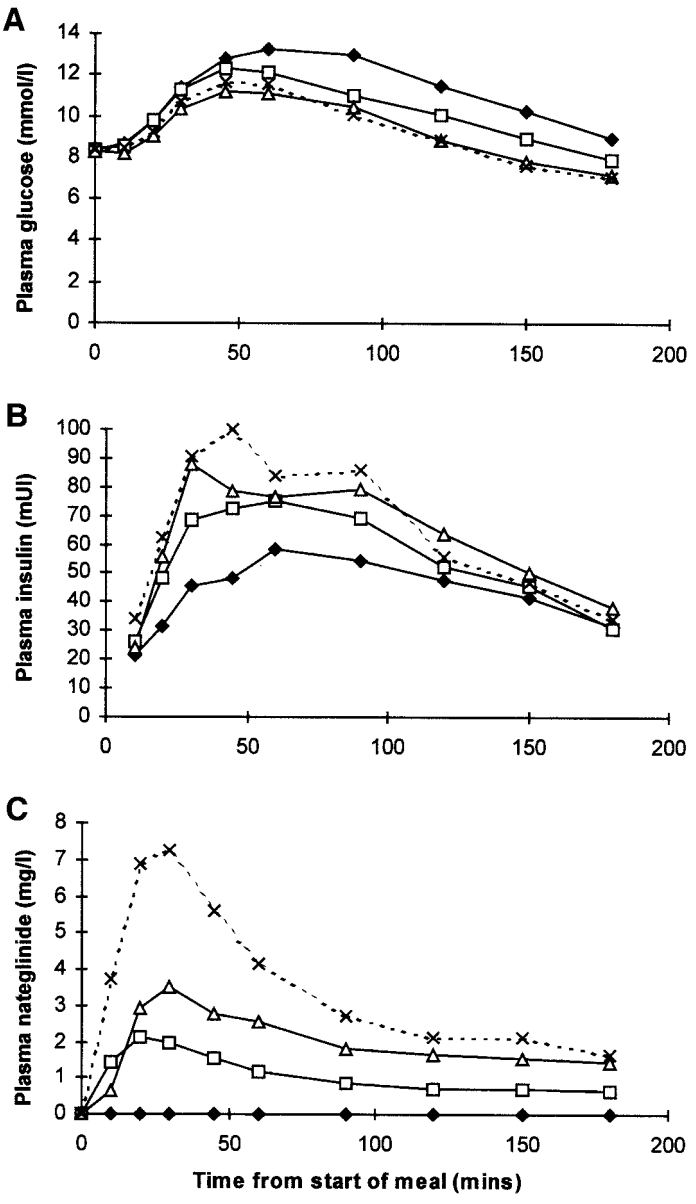

Figure 2—*Postprandial plasma glucose* (A)*, insulin* (B)*, and nateglinide* (C)*profiles of type 2 diabetic subjects. The meal was started at time 0; 3–5 min earlier, the patients were given either placebo* (▲) *or 60 mg* (□)*, 120 mg* (△)*, or 180 mg* (×) *nateglinide.*

nide concentrations were proportional to the ingested dose ($r = 0.93$, $P < 0.0001$).

Meal test

The mean increase in the plasma glucose concentration during the 180-min period after the meal was 2.9 mmol/l (2.3–3.6) on placebo, and this was reduced to 1.8 (1.1–2.6), 1.1 (0.5–1.7), and 1.0 mmol/l (0.2–1.9) after administration of the 60-, 120-, and 180-mg doses of nateglinide, respectively ($P < 0.001$ for trend across doses, with no significant difference between the two higher doses) (Fig. 2*A*). The mean postprandial glucose during the 3-h period for the two combined higher doses was reduced by 1.8 mmol/l, i.e., by 64% compared with the postprandial increase on placebo. Plasma insulin concentrations also increased after the meal and were further enhanced by nateglinide (Fig. 2*B*). The mean proportional increase in plasma insulin above the fasting level during the first 90 min after the meal increased 3.3-fold (3.0–3.5) on placebo, compared with 5.3-fold (4.1–6.6), 5.1-fold (4.2–6.0), and 6.2-fold (4.7–7.7) on 60, 120, and 180 mg of nateglinide, respectively ($P = 0.001$ for trend). At 3 h, the insulin concentrations after nateglinide had decreased to concentrations similar to those seen on placebo, although in the context of lower plasma glucose concentrations at this time point. Nateglinide concentrations (Fig. 2*C*) increased within 10 min and reached a peak at median 30 min (range 20–180). The 180-min time-averaged mean nateglinide concentrations over the first 90 min were proportional to the ingested dose ($r = 0.74$, $P < 0.0001$).

CONCLUSIONS — This study investigated the effects of nateglinide at three different doses in diet-treated type 2 diabetic subjects with inadequate glycemic control. A double-blind randomized crossover placebo-controlled design was used to examine the effects of the drug in the fasting and prandial states.

The fasting study was aimed at determining the pharmacodynamics and safety of the drug when administered after an overnight fast. This allowed the assessment of direct effects of the drug on insulin secretion. Nateglinide was absorbed rapidly and was 80% eliminated within 3 h. This may be compared with the short-acting sulfonylureas tolbutamide and glipizide, the concentrations of which, in a comparison study by Sartor et al. (16), reached peak values by 2–2.5 hours, were still present at concentrations >80% of peak at 3 h, and did not reach 20% of peak concentrations until ~24 and 8 h, respectively. The insulin response after administration of nateglinide was prompt, producing a significant reduction in plasma glucose, but in accordance with the short plasma half-life of the drug, the insulin response was not prolonged and, in these patients with fasting hyperglycemia, did not provoke hypoglycemia. Hypoglycemia is a recognized side effect of standard sulfonylurea therapy. In the U.K. Prospective Diabetes Study (UKPDS), 11% of patients taking chlorpropamide and 17% of patients taking glibenclamide experienced at least one episode of symptomatic hypoglycemia per year in the first 10 years after diagnosis, and major hypoglycemia was recorded in 0.4% of the chlorpropamide-treated group and 0.5% of the glibenclamide-treated group during this period. The rate of hypoglycemia was greatest in the earlier years of follow-up (1). Although chlorpropamide is rarely used because of its very long elimination time, glibenclamide is still the most widely prescribed oral therapy for type 2 diabetes.

The importance of achieving tight glucose control at the earliest stages of type 2 diabetes emphasizes the need for drugs that more effectively mimic the physiological insulin response to meals. The pharmacokinetics of nateglinide would allow repeated preprandial dosage with less danger of either drug accumulation or the development of hypoglycemia before the next meal. This study would not exclude the possibility that a hypoglycemic effect may occur in subjects treated more vigorously, to normal fasting plasma glucose concentrations (for instance, in combination with metformin or a thiazolidinedione). However, the patients studied with a mean HBA_{1c} of just above 7% (close to the UKPDS-recommended glycemic target) would be at significant risk for developing hypoglycemia if treated with a longer-acting sulfonylurea.

The daily postprandial glucose excursion contributes significantly to the total glycemic exposure in type 2 diabetes, and although therapy with chronic long-acting sulfonylurea reduces fasting plasma glucose, it has relatively little impact on meal-related increases (17). There is currently great interest in developing therapies that specifically target the postprandial increase in glucose. Acarbose slows intestinal absorption of glucose but is associated with dose-related side effects that limit its acceptability to patients (18). Repaglinide is a recently licensed short-acting insulin secretagogue that also produces significant reductions in fasting glycemia (19,20). Our results suggest that nateglinide has a similar rapid action and elimination. At doses that do not produce hypoglycemia in the fasting state, nateglinide improved the postprandial glucose excursion by a clinically significant amount at all doses, reaching a 64% decrease at the two higher doses. This represents an 18% reduction in the total glucose exposure during the 3 hours after the meal.

In conclusion, nateglinide displays characteristics that are of potential use for the treatment of early type 2 diabetes. The present study demonstrates that the drug stimulates a prompt insulin response in type 2 diabetic subjects and results in a clinically significant reduction of both fasting hyperglycemia and postprandial glucose excursion. With these characteristics, the drug would be particularly suited to a preprandial dose regimen, allowing increased safety and more flexibility in meal timing.

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