Control of Postprandial Hyperglycemia

Optimal use of short-acting insulin secretagogues

MARY F. CARROLL, MD
Ahmad Izard, BS
KATRINA RIBONI, BS

MARK R. BURGE, MD
DAVID S. SCHADE, MD

OBJECTIVE — This study was designed to compare the efficacy of acute premeal administration of glipizide versus nateglinide in controlling postprandial hyperglycemia in subjects with non–insulin-requiring type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 20 subjects (10 female, 10 male) with non–insulin-requiring type 2 diabetes were admitted overnight to the General Clinical Research Center on four occasions. In random order, 10 mg glipizide (30 min premeal), 120 mg nateglinide (15 min premeal), 10 mg glipizide plus nateglinide (30 and 15 min premeal, respectively), or placebo pills (30 and 15 min premeal) were administered in a double-blind fashion before a standardized breakfast. Blood was drawn for analysis of glucose, insulin, and C-peptide at −0.05, 0, 0.5, 1, 2, 3, and 4 h relative to the meal.

RESULTS — The subjects were aged 56 ± 2 years and were moderately obese (BMI 31 ± 1 kg/m²), with a mean HbA₁c of 7.4 ± 0.4%. The peak postprandial glucose excursion above baseline was higher with placebo (6.1 ± 0.5 mmol/l) than glipizide (4.3 ± 0.6 mmol/l, P = 0.002), nateglinide (4.2 ± 0.4 mmol/l, P = 0.001), or glipizide plus nateglinide (4.1 ± 0.5 mmol/l, P = 0.001). The area under the curve for the glucose excursion above baseline was also higher with placebo (14.1 ± 1.8 mmol·h/l) compared with glipizide (6.9 ± 2.4 mmol·h/l, P = 0.002), nateglinide (9.7 ± 2.0 mmol·h/l, P = 0.004), or glipizide plus nateglinide (5.6 ± 2.2 mmol·h/l, P < 0.001). Peak and integrated glucose excursions did not differ significantly between glipizide and nateglinide. However, by 4 h postmeal, plasma glucose levels were significantly higher with nateglinide (9 ± 0.9 mmol/l) compared with the premeal baseline (7.8 ± 0.6 mmol/l, P = 0.04) and compared with the 4-h postprandial glucose level after administration of glipizide (7.6 ± 0.6 mmol/l, P = 0.02). Integrated postprandial insulin levels were higher with glipizide (1,556 ± 349 pmol/h·l) than nateglinide (1,364 ± 231 pmol/h·l, P = 0.03). Early insulin secretion, as measured by insulin levels at 30 min postmeal, did not differ between glipizide and nateglinide.

CONCLUSIONS — Acute premeal administration of nateglinide or glipizide has equal efficacy in controlling postbreakfast hyperglycemia in type 2 diabetes when each drug is administered at the optimum time before the meal. Glipizide causes a more pronounced and sustained postmeal insulin secretory response compared with nateglinide. Glipizide facilitates the return to near-fasting glucose levels at 4 h postmeal, but with the possible risk of increased frequency of postmeal hypoglycemia in drug-naive patients. The clinical decision to use glipizide versus nateglinide should be based on factors other than the control of postprandial hyperglycemia in type 2 diabetes.

From the New Mexico Health Sciences Center, Department of Internal Medicine, Albuquerque, New Mexico. Address correspondence and reprint requests to Mary F. Carroll, University of New Mexico Health Sciences Center, Department of Internal Medicine, 5-ACC, 2211 Lomas Blvd. NE, Albuquerque, NM 87131. E-mail: mcarroll@salud.unm.edu.

Received for publication 30 April 2002 and accepted in revised form 5 September 2002.

Abbreviations: AUC, area under the curve.

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

The U.K. Prospective Diabetes Study confirmed that intensive control of blood glucose and reduction of HbA₁c levels in type 2 diabetes substantially reduces the risk of complications over a 10-year period (1). HbA₁c represents an integration of fasting and postmeal blood glucose levels. Postprandial hyperglycemia is a prominent and early defect in subjects with type 2 diabetes. The exaggerated mealtime blood glucose excursion characteristic of type 2 diabetes is due to inadequate suppression of endogenous glucose production caused by loss of early-phase insulin response (2–4). Recent studies have shown that mealtime hyperglycemia may be a more accurate predictor of HbA₁c levels (5) and of cardiovascular mortality (6,7) than fasting hyperglycemia. This information has focused attention on postmeal glycemic control. The ideal oral agent to target postprandial hyperglycemia should restore early phase insulin release without late hyperinsulinemia or an increased risk of hypoglycemia (8,9).

The n-phenylalanine derivative nateglinide is a rapidly acting short-duration insulinotropic agent that stimulates insulin release in a glucose-dependent manner (10). Clinical studies suggest that nateglinide partially restores early insulin release in type 2 diabetes (11,12). Nateglinide acts at the same pancreatic β-cell K⁺ATP channel that mediates the insulinotropic effects of the sulfonylureas. Nateglinide, however, dissociates from the receptor within seconds, compared with the prolonged occupation by sulfonylureas and repaglinide (13). The rapid and short-lived action of nateglinide restores early postprandial insulin secretion without late hyperinsulinemia. Clinical trials have demonstrated that nateglinide can reduce postprandial and mean hyperglycemia (14–16).

Members of the sulfonylurea class of drugs have also been shown to reduce prandial glucose excursions. In contrast to nateglinide, most sulfonylureas enhance late insulin secretion, causing delayed hyperinsulinemia and an increased risk of prolonged hypoglycemia. Although all sulfonylureas act at the same receptor in the pancreas, they vary in potency and pharmacokinetics, resulting in important clinical differences. Neither glazide nor glyburide were shown to restore early-phase insulin response in type 2 diabetic patients tested using a 1-h hyperglycemic clamp (12,17). However,
studies have shown that glipizide can normalize early insulin release and reduce postprandial hyperglycemia (18,19). Glipizide is a potent, generic, second-generation sulfonylurea with the most rapid onset of action and the shortest effect duration when compared with other first- and second-generation sulfonylureas (20,21). Glipizide may also enhance the availability of peripheral insulin through nonpancreatic effects (22), an effect not demonstrable with nateglinide.

There is a clear need to achieve good control of postprandial hyperglycemia if overall glycemic control and complications are to be reduced in type 2 diabetes. No studies to date have compared the prandial glucose-lowering efficacy of a short-acting sulfonylurea to nateglinide when both drugs were administered at the recommended time premeal. The aim of this study was to compare the efficacy of acute premeal administration of glipizide versus nateglinide in controlling postprandial hyperglycemia in subjects with non-insulin-requiring type 2 diabetes.

RESEARCH DESIGN AND METHODS — The study enrolled 20 subjects (10 men and 10 women) with non-insulin-requiring type 2 diabetes of at least 6-months duration. Volunteers attended a screening visit at which a history was obtained and physical, electrocardiogram, and screening laboratory tests were performed. Eligible patients were managed with diet and exercise or oral hypoglycemic agents and had reasonable glycemic control and a BMI <40 kg/m². Subjects were excluded if they had significantly abnormal vital signs, electrocardiogram tracings, or hematological, electrolyte, or liver laboratory results at screening. Other important exclusion criteria were pregnancy, chronic insulin treatment, medications that affect liver metabolism, active substance abuse, use of oral corticosteroids, known sensitivity to nateglinide or glipizide, or a history of gastroparesis. All patients gave written informed consent before participating in the study. The study protocol received approval from the University of New Mexico institutional review board.

Study protocol
This study had a randomized, placebo-controlled, crossover design. Participants were admitted overnight to the General Clinical Research Center for stabilization on four separate occasions. Subjects were fed a standardized snack at 10:00 p.m. and then fasted until morning. Participants’ usual diabetes medications were withheld on the morning of the study. In random order, 120 mg nateglinide (15 min premeal), 10 mg glipizide (30 min premeal), 10 mg glipizide plus 120 mg nateglinide (15 and 30 min premeal, respectively), or placebo pills (15 and 30 min premeal) were administered in a double-blind fashion.

After baseline blood draws, subjects ate a standardized 8-kcal/kg breakfast between 8:00 and 8:15 A.M. The breakfast was prepared in the metabolic kitchen and consisted of an English muffin, bacon, scrambled eggs, and a noncaloric decaffeinated beverage. A test meal for a prandial glucose excursion was also higher compared to glipizide (4.2 ± 0.4 mmol/l, P = 0.001), or glipizide plus nateglinide (4.1 ± 0.5 mmol/l, P = 0.001). The AUC for the glucose excursion was also higher with placebo (14.1 ± 1.8 mmol/l·h) compared with glipizide (6.9 ± 2.4 mmol/l·h, P = 0.004), nateglinide (9.7 ± 2 mmol/l·h, P = 0.02), or glipizide plus nateglinide (5.6 ± 2.2 mmol/l·h, P = 0.002). At 4 h postmeal, plasma glucose levels were not significantly different between the nateglinide (9 ± 0.9 mmol/l) and placebo (9.6 ± 1 mmol/l) groups, and 4-h glucose levels for both of these groups remained significantly higher than the fasting baseline glucose level (7.8 ± 0.6 mmol/l, P = 0.04). For glipizide (7.6 ± 0.9 mmol/l) or glipizide plus
nateglinide (7.4 ± 0.8 mmol/l), the 4-h postmeal plasma glucose was significantly lower than either placebo (P = 0.003 vs. glipizide, P = 0.006 vs. glipizide plus nateglinide) or nateglinide (P = 0.02 vs. glipizide, P = 0.009 vs. glipizide plus nateglinide) and had returned to premeal glucose levels (7.4 mmol/l for glipizide, 7.1 mmol/l for glipizide plus nateglinide). Using ANOVA, we found no study arm sequence effect on the glucose response.

Insulin and C-peptide levels
Peak and integrated insulin excursions were higher with glipizide (peak 566 ± 130 pmol/l, AUC 1,556 ± 349 pmol/h·l) than placebo (peak 401 ± 71 pmol/l, P = 0.01; AUC 1,097 ± 211 pmol/h·l, P = 0.009) or nateglinide (peak 493 ± 125 pmol/l, P = 0.02; AUC 1,364 ± 231 pmol/h·l, P = 0.04). The combination of glipizide plus nateglinide produced similar integrated insulin levels compared with glipizide or nateglinide alone. Absolute or baseline corrected peak or integrated plasma insulin excursion levels did not differ between nateglinide and placebo. However, nateglinide (682 ± 22 pmol/h·l) did result in significantly higher insulin levels in the first 2 h postmeal [AUC insulin (0–2 h)] compared with placebo (481 ± 25 pmol/h·l, P = 0.02). Compared with placebo, early insulin secretion as measured by the insulin levels at 30 min postmeal was significantly higher when either of the two oral hypoglycemic agents was given (overall P = 0.001). This difference persisted for glipizide or glipizide plus nateglinide when the insulin levels were corrected for the ambient plasma glucose levels. Using ANOVA, we found no differences in the insulin data when subjects were treated with sulfonylurea compared with nonsulfonylurea therapy between study days. C-peptide changes postmeal mirrored the changes in insulin levels (Fig. 1C). The highest C-peptide excursion levels were measured after the administration of glipizide, and the lowest levels were measured after placebo.

Adverse events
Six episodes of postprandial hypoglycemia (plasma glucose <3.3 mmol/l) occurred. The same three participants experienced hypoglycemia during the glipizide-only and glipizide-plus-nateglinide studies. For two of these subjects, diabetes management consisted of diet and exercise only. Two of the three hypoglycemic episodes in the glipizide-only studies were symptomatic and required treatment with oral glucose. The hypoglycemic values were recorded at 2–3 h postmeal. There were no episodes of severe hypoglycemia (plasma glucose <2.2 mmol/l).

CONCLUSIONS — This study demonstrates that the acute premeal administration of 10 mg glipizide has equal efficacy compared with 120 mg nateglinide in controlling postbreakfast hyperglycemia in type 2 diabetes. These results are in contrast to a previous study by Hollander et al. (16), who found that the long-acting sulfonylurea glyburide was less effective than nateglinide in stimulating early insulin release and in limiting mealtime glycemic excursions. However, in Hollander et al.‘s study, nateglinide was administered at the optimal time premeal, whereas glyburide (which has a delayed onset), was also administered 10 min before the test meals. Previous studies suggest that glyburide, like glipizide, may be more effective when given before rather than with breakfast (23). In the current protocol, glipizide was administered 30 min before the test meals as recommended in the package insert (24,25). In this setting, glipizide alone or glipizide plus nateglinide blunted the postprandial glucose rise and facilitated the return of glucose to the premeal baseline level by 4 h after a standardized mixed-composition meal. In doing so, glipizide resulted in a lower postprandial glucose nadir, causing hypoglycemia in 3 of 20 (15%) of the study subjects. Two of these three hypoglycemic episodes occurred in drug-naive patients, whereas only one hypoglycemic episode was recorded in a subject previously treated with oral hypoglycemic agents. More prolonged postprandial sampling may have demonstrated a further fall in glucose levels to below fasting levels in more of the subjects when treated with glipizide.

In contrast to glipizide, plasma glucose levels had not fallen to fasting levels by 4 h postmeal when nateglinide was administered before the test meal. It is possible that continued postprandial sampling may have allowed time for subjects to return to baseline fasting glucose levels in the nateglinide arm. However, this longer sampling time would not reflect the typical duration of the interprandial period between breakfast and lunch for most patients. The postprandial glucose nadir was higher with nateglinide than with glipizide. However, no subject experienced hypoglycemia after preprandial dosing of nateglinide.

Glipizide caused a more pronounced and sustained postmeal insulin secretory response than nateglinide. However, when comparing the insulin profiles of glipizide and nateglinide, there was no difference in insulin levels achieved during the first 30 min postmeal. Therefore, when glipizide is administered 30 min premeal, it is as effective as nateglinide in stimulating early insulin release in subjects with type 2 diabetes. However, the proportion of insulin secreted during the first 2 h postmeal was more pronounced with nateglinide than with glipizide. These differences in insulin secretion explain the higher incidence of postprandial hyperglycemia with glipizide and the waning effectiveness of nateglinide in the control of late postprandial hyperglycemia.

The coadministration of nateglinide and glipizide resulted in increased early insulin release compared with nateglinide alone but did not significantly change the postprandial glucose profile compared with the administration of either agent. Because sulfonylureas and nateglinide act at the same K⁺ATPase channels on the pancreatic ß-cell, it is possible that com-

Table 1—Prebreakfast (t = 0) glucose, insulin, and C-peptide levels according to study treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glipizide</th>
<th>Nateglinide</th>
<th>Glipizide + nateglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prebreakfast glucose (mmol/l)</td>
<td>7.7 ± 0.5 (4.8–11.3)</td>
<td>7.4 ± 0.6 (4.3–11.4)</td>
<td>7.8 ± 0.6 (4.9–11.9)</td>
<td>7.1 ± 0.5* (4.1–12.3)</td>
</tr>
<tr>
<td>Prebreakfast insulin (pmol/l)</td>
<td>85 ± 13 (29–268)</td>
<td>122 ± 25 (39–271)</td>
<td>128 ± 35 (28–720)</td>
<td>123 ± 23 (20–362)</td>
</tr>
<tr>
<td>Prebreakfast C-peptide (nmol/l)</td>
<td>1.1 ± 0.1 (0.5–2.1)</td>
<td>1.3 ± 0.1 (0.8–2.2)</td>
<td>1.2 ± 0.2 (0.6–3.0)</td>
<td>1.1 ± 0.1 (0.6–1.8)</td>
</tr>
</tbody>
</table>

Data are means ± SE (range). Glipizide and nateglinide were administered at −30 and −15 min prebreakfast, respectively. *P = 0.02 compared with placebo.
petitive antagonism occurred when the two agents were given together. The C-peptide profiles paralleled the postprandial insulin profiles, suggesting that all of the plasma insulin measured was released directly from the pancreas and that neither agent altered the peripheral availability or hepatic metabolism of insulin, as has been suggested in previous studies with glipizide (21).

In conclusion, we have demonstrated that glipizide taken 30 min premeal can ameliorate the defect in early phase insulin release, which plays a critical role in the control of postprandial hyperglycemia.
mia in type 2 diabetes. Moreover, glipizide has a glucose-lowering efficacy similar to nateglinide when administered acutely before a standardized solid meal. Postmeal hypoglycemia may be more frequent with glipizide compared with nateglinide, particularly in drug-naive diabetic subjects. However, the insulin secretagogue and glucose-lowering effects of nateglinide appear to be insufficient to provide sustained postprandial glycemic control lasting until the next scheduled mealtime dose. We hypothesize that the time of administration and pharmacokinetic properties of individual insulin secretagogues are major determinants of their effectiveness in the control of postmeal hyperglycemia. When administered 30 min premeal, the generic sulfonylurea glipizide has equal efficacy to nateglinide in the control of postmeal glucose excursions. Therefore, the clinical decision to use glipizide versus nateglinide should be based on factors other than the control of postprandial hyperglycemia in type 2 diabetes. These factors include the relative cost of the medications, the presence of sulfonylurea allergy, the hazards of delayed hyperinsulinemia (such as postmeal hypoglycemia and potential weight gain), and the relative inconvenience of taking a medication 30 versus 10 min before meals.

**Acknowledgments** — This research was supported by the University of New Mexico General Clinical Research Center (National Institutes of Health, National Center for Research Resources, General Clinical Research Center Grant 5 MO1-RR00097).

The authors acknowledge the expert assistance of Carolyn King in the preparation of this manuscript for publication.

**References**


Control of postprandial hyperglycemia


