Long-Term Randomized Placebo-Controlled Double-Blind Therapeutic Comparison of Glipizide and Glyburide

Glycemic control and insulin secretion during 15 months

KÅRE I. BIRKELAND, MD
KRISTIAN FURUSETH, MD
ARNE MELANDER, MD
PETTER MOWINCKEL, MSC
STEIN VAALER, MD

OBJECTIVE — To examine the long-term (15 months) effects on glycemic control and insulin secretion of glipizide and glyburide treatment in patients with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS — Prospective, randomized, double-blind, placebo-controlled study on 46 NIDDM patients comparing fasting levels and test-meal responses of glucose and insulin during 15 months of follow-up.

RESULTS — A comparable reduction in HbA_{1c} levels by both agents versus placebo was observed throughout the study period, but after a marked initial reduction in both sulfonylurea groups, all three groups showed gradually increasing HbA_{1c} levels. However, both glipizide and glyburide achieved and maintained lowered postprandial glucose levels and increased fasting and postprandial insulin levels compared with placebo.

CONCLUSIONS — Both glipizide and glyburide may achieve and maintain glycemic reduction and stimulation of insulin secretion during long-term treatment. However, these agents do not prevent the gradual increase in overall glycemia that develops over time in NIDDM patients.

From the Hormone Laboratory and the Department of Medicine, Aker Diabetes Research Center, Aker Hospital, Oslo, Norway; Ullensaker Medical Center, Jessheim, Norway; Departments of Clinical Pharmacology and Community Health Sciences, University of Lund, Malmö, Sweden; and Medstat Research, Lillestrom, Norway.

Address correspondence and reprint requests to Kåre I. Birkeland, MD, Hormone Laboratory, Aker Hospital, 0514 Oslo, Norway.

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NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; ANOVA, analysis of variance; AUC, area under the curve.

Sulfonylurea (SU) therapy reduces blood glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM). The primary mechanism is stimulation of insulin secretion (1–5), but insulin sensitivity may also be enhanced (6–13). The clinical efficacy of the two second generation SUs glipizide and glyburide has been compared in several studies (8,14–22). However, few studies have been double-blind and placebo-controlled, and many have used doses higher than recommended, at least in Europe. This is important because high SU dosage may be not only ineffective but even counterproductive, as it may downregulate β-cell sensitivity to these drugs (23–25).

The aim of this study was to assess and compare the long-term (15 months) effects of moderate doses of glipizide and glyburide on glycemic control and insulin secretion in a randomized placebo-controlled double-blind fashion.

RESEARCH DESIGN AND METHODS

— Forty-six patients with NIDDM (24 women and 22 men, mean age ± SD of 59 ± 7 years, known duration of diabetes 3.5 ± 3.1 years, body mass index (BMI) 26.4 ± 3.9 kg/m^2) who were nonpharmacologically treated were included. All had prestudy levels of HbA_{1c} between 7 and 11% and had considerable residual β-cell function; the C-peptide concentration 6 min after intravenous injection of 1 mg glucagon was >0.7 nM (1.67 ± 0.7 nM). None of the patients had severe intercurrent illness or signs of chronic cardiac, hepatic, pulmonary, or renal disease during the study period. All gave informed consent, and the protocol was approved by the regional ethics committee.

During a 3- to 6-month run-in period, the subjects were given (renewed) dietary advice according to the American Diabetes Association's Nutritional Recommendations and Principles for Individuals with Diabetes Mellitus, and they were

taught self-monitoring of blood glucose with a reflectance meter. They were then subjected to a stratified randomization procedure (26), taking into account their prestudy HbA_{1c}, duration of diabetes, age, and BMI, and allocated to treatment with glipizide (Mindiab, Famitalia Carlo Erba, Milan, Italy) (n = 15), glyburide (Daonil, Hoechst AG, Frankfurt, Germany) (n = 15), or placebo (n = 16). All tablets looked identical and contained either 1.75 mg glyburide, 2.5 mg glipizide, or placebo. The 1.75-mg glyburide tablet is a micronized formulation, yielding approximately the same bioavailability as 2.5 mg of the nonmicronized formulation marketed in the U.S. (27).

Treatment always started with one tablet in the morning, and the dose was adjusted weekly by adding one tablet at the time, to achieve fasting blood glucose <8.0 mM and HbA_{1c} <7.5% without hypoglycemia. The maximum dose was six tablets per day, given as four tablets before breakfast and two before dinner. After the initial dose adjustment, patients were seen in the outpatient clinic at 3-month intervals. At each visit, body weight was recorded and blood was drawn for measurements of fasting plasma glucose and HbA_{1c}. If HbA_{1c} was >11%, the patients were withdrawn from the study and treated with either SUs or insulin. Only patients that completed the study were included in the main data analysis, but the effect on HbA_{1c} was also evaluated for the whole group.

Before and after 3 and 15 months of treatment, a test meal was performed to assess the plasma glucose and serum insulin responses. Subjects arrived at 0800 and had a Teflon catheter placed in an antecubital vein for blood sampling. Blood was drawn every 30 min for 270 min. Plasma glucose was measured on site, whereas serum was frozen for later analysis of insulin. The meal was served at 35 min and consisted of bread and butter with jam, one glass of orange juice, and one glass of low-fat milk. This yielded 1,500 kJ, and 11% of the energy was protein, 75% carbohydrate (of which 25% was sugar), and 14% fat. The fiber content was 3.2 g. When the test meal was repeated after 3 and 15 months of treatment, two tablets (SU or placebo) were ingested 30 min before the meal.

Laboratory methods

Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer, Fullerton, CA). HbA_{1c} was determined by liquid chromatography (DIAMAT HbA_{1c} analyzer, Bio-Rad, Munich, Germany), the normal range is 4.3–6.1%. The serum levels of insulin were measured by an in-house radioimmunoassay (inter- and intra-assay coefficient of variation <8%, cross-reactivity with proinsulin 100%).

Statistical analysis

Data are given as means ± SD. Skewed data were log-transformed before calculating the mean. For comparison between groups, a standard one-way analysis of variance (ANOVA) was used (28), and to assess reponses to the test meal, we calculated the individual area under the curve (AUC) using a standard trapezoid rule. If a statistically significant difference was found, Duncan's multiple range test was used for pair-wise comparisons of group means (26). For the comparison between the groups at 0, 3, and 15 months, we used repeated measures ANOVA. A dummy variable regression analysis was conducted to test for differences between regression lines describing the relationship between glucose and insulin levels. Log insulin was the dependent and glucose the independent variable. The three times were entered into the model as a dummy variable with interaction to compare the three lines. Paired and unpaired Student's t tests were used to assess simple differences within and between groups. A two-sided significance level of 5% was used.

RESULTS

Glycemic control

Both glipizide and glyburide improved glycemic control to a similar degree, as indicated by reduced levels of HbA_{1c} (Fig. 1). The HbA_{1c} levels also were significantly lower on SU treatment than on placebo from 3 months and throughout. However, from 3 to 15 months, HbA_{1c} levels in all three groups increased continuously and significantly ($P < 0.01$).

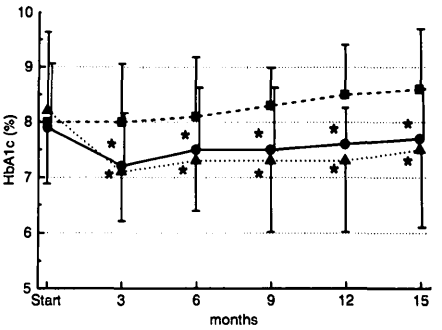

Figure 1—*HbA_{1c} levels during 15 months of treatment with glipizide (———), glyburide (·····), and placebo (– – – –). *P < 0.05 vs. placebo.*

The mean doses of glipizide were 5.0 and 9.4 mg/day, and the mean doses of glyburide were 2.6 and 5.5 mg/day at 3 and 15 months, respectively. No serious hypoglycemic episodes were observed, and only a few patients reported mild hypoglycemic symptoms in the initial phase. However, 2 patients on glyburide chose to withdraw from the trial because of discomfort related to hypoglycemia during the first week. In the placebo group, 4 subjects had to be withdrawn from the study after 2, 3, 3, and 12 months because of symptomatic hyperglycemia and/or HbA_{1c} >11%.

Fasting levels of glucose and insulin and responses to test meal

Fasting plasma glucose was lower after 3 and 15 months of glipizide treatment compared with the starting level, but only significantly so after 3 months of glyburide treatment (Table 1). Fasting serum insulin was significantly higher after 15 months of glipizide and glyburide treatment compared with pretreatment values.

After 3 months of treatment, sig-

Table 1—*Fasting levels of plasma glucose and serum insulin and responses to test meal for glucose and insulin.*

	Start	3 months	15 months
Fasting plasma glucose (mM)			
Glipizide	10.1 ± 2.7	9.1 + 2.1*	9.3 ± 2.4*
Glyburide	9.5 ± 2.4	7.7 + 1.7*	8.4 ± 3.1
Placebo	9.0 ± 2.0	9.8 + 3.1	10.1 ± 3.0
$Glucose_{AUC}$			
Glipizide	2773 ± 673	2345 ± 657†	2611 ± 786
Glyburide	2688 ± 811	2115 ± 623‡	2386 ± 1036
Placebo	2527 ± 601	2947 ± 852	3182 ± 768
Fasting serum insulin (pM)			
Glipizide	124 ± 55	139 ± 74	173 ± 70*
Glyburide	103 ± 53	114 ± 72	127 ± 60*
Placebo	101 ± 42	121 ± 56	133 ± 60
$Log\ insulin_{AUC}$			
Glipizide	813 ± 103	1041 ± 155*	1041 ± 137*†
Glyburide	765 ± 128	971 ± 190*	979 ± 141*‡
Placebo	765 ± 104	886 ± 154	895 ± 117

Data are means ± SD.
*$P < 0.05$ vs. start.
†$P < 0.05$ vs. placebo.
‡$P < 0.05$ vs. placebo and glipizide.

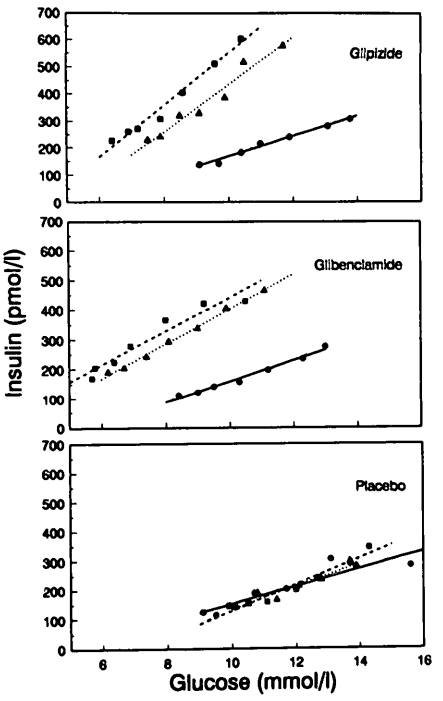

Figure 2—*Mean serum insulin concentrations versus corresponding plasma glucose concentrations at 60–240 min during the test meal before (●——●) and after 3 (■----■) and 15 (▲····▲) months of treatment. Error bars have been omitted for reasons of clarity. See METHODS for statistical comparisons.*

nificant differences were noted in the $glucose_{AUC}$ during a test meal between the groups, with glyburide at the lowest level, glipizide at the in-between level, and placebo at the highest level. A similar tendency occurred at 15 months that just failed to reach significance ($P = 0.07$).

The insulin response to the meal differed significantly between the groups after 15 months of treatment, with $insulin_{AUC}$ being highest in the glipizide group and lowest in the placebo group; the glyburide group fell in between. A similar nonsignificant trend occurred after 3 months of treatment ($P = 0.07$).

We observed a time trend in all three groups for $glucose_{AUC}$ ($P < 0.01$), and this trend was significantly different between the SU and placebo groups. The two SU groups had a decrease from the start to 3 months and then a slight increase, whereas the placebo group had an increase throughout the study period. The insulin responses increased in all three groups from start to 3 months ($P = 0.01$), and the increase was just greater in the treatment group compared with the placebo group ($P = 0.04$). From 3 to 15 months, insulin response did not differ within the three groups.

In the glipizide group, we observed a significant increase in the mean insulin level from −30 to 0 min at 3 months and a similar nonsignificant trend at 15 months ($P = 0.11$) as a result of an acute response to the administration of the drug. In contrast, no such acute responses were observed in the glyburide or placebo groups.

Figure 2 correlates the mean values of log-insulin at 60–240 min and the corresponding glucose values during test meals at the start and after 3 and 15 months. A highly significant linear correlation was found between the actual glucose and insulin concentrations. From the start to 3 months, the regression lines in the SU groups were shifted leftward and were steeper. The regression lines at 3 and 15 months were parallel and not significantly different. The regression lines in the placebo group did not change.

CONCLUSIONS— This study showed a significant, parallel, and sustained improvement in metabolic control by glipizide and glyburide during 15 months of treatment compared with placebo. No difference in HbA_{1c} level was observed between the two SU-treated groups, but this finding must be interpreted with caution because of the relatively small number of subjects studied. Because one-fourth of the placebo patients withdrew as a result of deteriorating glycemic control and hence were excluded from the data analysis, the observed differences between SU and placebo therapy underestimates the drug effects. The subjects studied had a relatively mild degree of hyperglycemia at inclusion into the study, and our results may not apply to diabetes of greater severity.

The exclusion from analysis of 4 subjects in the placebo group and 2 in the glyburide group is unfortunate in a randomized trial and calls for caution in interpreting the results. However, we also evaluated the effect by including all the randomized subjects and found that sustained (15 months) acceptable glycemic control as defined by the European NIDDM Policy Group (HbA_{1c} <7.9%) (29) was achieved in 11 of 15 randomized to glipizide, 8 of 15 to glyburide (2 dropouts because of hypoglycemia), and 3 of 16 to placebo. The slight but continuous increase in HbA_{1c}, occurring despite the successive increase in drug dose, was apparently a result of the natural course of the disease (2,30–32) rather than a genuine loss of drug effect, as the improvement in glycemic control relative to placebo essentially remained.

Particular care was taken to avoid hypoglycemic events, which partially explain the modest mean SU doses used. No controlled studies show that the efficacy of these drugs is increased at daily doses beyond 10–15 mg. Higher doses may actually reduce rather than improve glycemic control and insulin secretion (24,25), possibly related to downregulation of SU sensitivity at continuous exposure to high drug levels (23).

A significant acute (−30 to 0 min) increase in insulin levels was observed in the glipizide group at 3 months, and a similar tendency was noted at 15 months. This was not present in the glyburide group, and the difference is presumably attributable to slower absorption of glyburide (8). Similar results have been obtained in a randomized short-term study published previously (22) and in an open long-term study of glipizide (33). These findings suggest that the insulinotropic effect of SU can be maintained for a long period of time (2). However, although the insulinotropic effect of insulin was maintained both in this and the open study (33), no correspondingly sustained effect on glucose control was maintained in this study. This may be attributable to increased insulin resistance.

The postprandial insulin levels increased substantially on treatment in the SU groups and did not change significantly from 3 to 15 months. However, this does not signify that insulin secretion was unchanged during treatment. Because the glucose levels were higher at 15 months, glucose stimulation of insulin secretion must have been stronger. The feed-back interplay of glucose and insulin concentrations makes it difficult to assess the relative contributions of impaired insulin secretion and increased insulin resistance over time. However, the concurrent increases in fasting blood glucose, HbA_{1c} levels, and basal insulin secretion are in keeping with progressive insulin resistance. In addition, the reduced postprandial increase of insulin secretion in the presence of increasing glucose levels may reflect glucose toxicity (34) or loss of glucose through urine breaking the feedback loop between glucose levels and insulin secretion (2). However, it might also relate to reduced SU sensitivity of the β-cells during chronic exposure (23).

In conclusion, treatment with glipizide or glyburide gave better glycemic control during 15 months of treatment compared with placebo, but it did not stop progression of the disease.

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