DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2004; **20**: 225–231.
Published online 10 February 2004 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.443

RESEARCH ARTICLE

Effects of glipizide GITS and glibenclamide on metabolic control, hepatic glucose production, and insulin secretion in patients with type 2 diabetes

Eugene H. Go[1]*
Marinella Kyriakidou-Himonas[2]
Michael Berelowitz[3]

[1]*Midwestern Endocrinology, P.A., Overland Park, Kansas, USA*

[2]*Larnaca, Cyprus*

[3]*Pfizer, Inc., New York, New York, USA*

*Correspondence to: Eugene H. Go, Midwestern Endocrinology, P.A. 5520 College Blvd, Suite 330, Overland Park, KS 66211, USA.
E-mail: goendoc@yahoo.com

Received: 12 June 2003
Revised: 14 November 2003
Accepted: 28 November 2003

Abstract

Objective Evaluation of effects of glipizide gastrointestinal therapeutic system (GITS) administered once daily (AM or PM) and glibenclamide on glycemic control, insulin secretory response, and hepatic glucose production (HGP) in patients with type 2 diabetes.

Methods In a randomized, double-blind, and placebo-controlled study, subjects (HbA_{1c} between 8.6 and 10.0%) received a titrated daily dose (5–20 mg) of either glipizide GITS AM ($n = 11$), glipizide GITS PM ($n = 10$), glibenclamide ($n = 11$), or placebo ($n = 10$) for eight weeks. Fasting and 24-h glucose and insulin, HGP, fructosamine, and HbA_{1c} were measured at baseline and at study conclusion; glucose and insulin were also evaluated after Sustacal® challenge.

Results Fasting and 24-h glucose were significantly reduced by glipizide GITS AM (33%, $p < 0.001$; 39%, $p < 0.0001$), glipizide GITS PM (33%, $p < 0.0001$; 32%, $p < 0.0001$), and glibenclamide (37%, $p < 0.05$; 37%, $p < 0.0001$). Fasting insulin was not significantly increased by any treatment; 24-h insulin was not increased by glipizide GITS AM, but was elevated by glipizide GITS PM (39%, $p < 0.05$) and glibenclamide (23%, $p < 0.05$). Fructosamine and HbA_{1c} were significantly reduced by glipizide GITS AM (28%, $p < 0.001$; 22%, $p < 0.0001$), glipizide GITS PM (25%, $p < 0.005$; 24%, $p < 0.005$), and glibenclamide (17%, $p < 0.001$; 14%, $p < 0.05$). Glipizide GITS AM and glibenclamide significantly reduced HGP by approximately 19% ($p < 0.05$) and 17% ($p < 0.01$) respectively. Glipizide GITS and glibenclamide significantly ($p < 0.0001$) decreased the glucose excursion after Sustacal challenge. The reductions in glucose excursions were accompanied by significant ($p < 0.05$) increases in the insulin response, suggesting an improvement in meal-related insulin secretion.

Conclusions Glipizide GITS and glibenclamide treatment are effective agents for improving fasting plasma glucose and HbA_{1c}. Each possessed a suppressive effect on basal HGP and improved postprandial glycemia, but only glipizide GITS AM was effective without causing a persistent elevation in insulin. This profile of glipizide GITS AM is therapeutically attractive, as it is consistent with the potential for a reduced risk of hypoglycemia. Copyright © 2004 John Wiley & Sons, Ltd.

Keywords diabetes; glipizide; glibenclamide; glycemic control; hepatic glucose production; insulin secretory response

Introduction

Both insulin resistance and decreased insulin secretion are major features of the pathophysiology of type 2 diabetes [1–3]. Insulin resistance is evident in skeletal muscle, liver, and adipose tissue, the major target tissues of insulin action [1,2,4–6]. Skeletal muscle insulin resistance leads to postprandial hyperglycemia, while hepatic insulin resistance is a causative factor in the subsequent development of fasting hyperglycemia [1]. The development of insulin resistance in peripheral tissues is exacerbated by chronically elevated free fatty acids [7–9]. Initially, insulin resistance is compensated for by hyperinsulinemia, thus preserving normal glucose tolerance. However, over time, hepatic insulin resistance worsens and β-cell compensation deteriorates, culminating in fasting hyperglycemia [1].

Pharmacological agents that reduce hepatic glucose production (HGP) exhibit a beneficial effect on fasting plasma glucose (FPG) and overall metabolic control in patients with type 2 diabetes [10–14]. Owing to the importance of the early insulin response in suppressing postprandial HGP, pharmacological approaches that enhance early insulin secretion also represent a critical component in improving glycemic control in patients with type 2 diabetes [15].

Sulphonylureas were initially developed in the 1950s and have remained the cornerstone of pharmacological therapy for type 2 diabetes [16,17]. Sulphonylureas are insulin secretagogues: they control blood glucose levels by directly stimulating early (first-phase) insulin secretion in the pancreatic β-cells. Sulphonylureas are high-affinity ligands for the sulphonylurea receptor type 1 (SUR1) subunit of the ATP-sensitive potassium channel (K_{ATP}) located on plasma membranes of β-cells [18]. K_{ATP} channels are also expressed in extrapancreatic tissue, including liver tissue [18–20]. The K_{ATP} channel comprises two subunits (SUR1 and KIR6.2, an inward rectifier), both of which are required for channel functionality. An increase in the ATP/ADP ratio, which occurs during oxidative glucose metabolism, or ligand binding to SUR1 results in the closure of the K_{ATP} channel and insulin secretion [17].

In addition to their primary effect on early insulin secretion, extrapancreatic effects of sulphonylureas have been reported, including increasing glucose utilization and suppression of HGP [21–28]. Although previous studies have established the clinical efficacy and excellent safety profile of glipizide GITS, a once-daily, extended release formulation of glipizide [29–32], they were not designed to evaluate the potential effect of this agent on HGP. In this double-blind, placebo-controlled study, we have compared the effects of glipizide GITS and glibenclamide on metabolic control and HGP glucose production in patients with type 2 diabetes.

Design and methods

Subjects and study design

Men and women between the ages of 30 and 80 years with a documented diagnosis of type 2 diabetes (according to American Diabetes Association criteria) at least 6 months before the study and who were treated with diet alone and/or sulphonylureas (for a minimum of 2 months) were eligible for this study. Women who were pregnant were ineligible for enrollment. Of the 50 patients screened, 42 were enrolled in this study.

This randomized, double-blind, placebo-controlled study was conducted at the Stony Brook University Hospital, affiliated with the State University of New York at Stony Brook. The study protocol was approved by the Institutional Review Board at the University Hospital. Patients were informed about the purpose and risks of the study and gave their written consent to participate. Once enrolled, patients were removed from previous sulphonylurea therapy (if applicable) and placed on a weight-maintenance diet ($\geq$200 g of carbohydrate) and placebo for four weeks.

Patients who qualified for randomization (FPG $\geq$ 7.8 mmol/L and $\leq$13.9 mmol/L, and $HbA_{1c} > 7\%$ and $<11\%$) were admitted for in-patient evaluation consisting of two days of metabolic testing. On day 1, a sample of blood was drawn for assay control for drug levels at zero hour (after an overnight fast). Subsequently, patients were given a Sustacal® (Mead Johnson, Evansville, IN) challenge test (240 mL delivered in place of breakfast), followed by 24-h sampling (hourly intervals) for glucose and insulin using an intravenous (iv) catheter in the antecubital vein. During the 24-h period after Sustacal challenge (hour 0), patients were provided with a predetermined lunch, dinner, and evening snack (at hour 4, 10, and 13 respectively). On day 2 (at 8 : 00 AM), HGP was assessed using the stable isotope [6,6-^{2}H]-glucose [10,11,33,34]. Patients received a priming dose of [6,6-^{2}H]-glucose followed by a continuous IV infusion of [6,6-^{2}H]-glucose (0.034 mg/kg/min) for 3 h. Blood samples for the determination of plasma [6,6-^{2}H]-glucose-specific activity were drawn (via a catheter inserted in the retrograde direction into the wrist vein) at 5-min intervals during the last 30 min of the equilibrium period. Hepatic glucose production was calculated by dividing the [6,6-^{2}H]-glucose infusion rate by the steady state plateau of [6,6-^{2}H]-glucose-specific activity achieved during the last 30 min of the 3-h basal tracer infusion period. At the conclusion of assessing HGP and immediately before lunch, patients were randomly assigned to one of four treatment groups: glipizide GITS administered in either AM or PM (5 mg p.o. daily; Glucotrol XL®, Pfizer, Inc., New York, NY), glibenclamide administered in the AM (5 mg po. daily; Diaβeta®, Aventis Pharmaceuticals NJ, Bridgewater, NJ), or placebo.

The dose of each drug was titrated in 5-mg increments every week, according to the results of plasma glucose

values. The objective of dose titration was to keep the FPG between 4.4 and 7.8 mmol/L and postprandial glucose at or below 10.0 mmol/L, or to continue until the patient reached a dose of 20 mg per day. Glipizide GITS and placebo were taken daily before breakfast (AM) and before dinner (PM). Glibenclamide was administered in the AM. Group 1 (placebo; $n = 10$) received a placebo tablet for both glipizide GITS and glibenclamide in the morning and evening. Group 2 (glipizide GITS AM; $n = 11$) received a morning dose of glipizide GITS with a glibenclamide placebo, and an evening dose of both placebos. Group 3 (glipizide GITS PM; $n = 10$) received a morning dose of both placebos and an evening dose of glipizide GITS with glibenclamide placebo. Group 4 (glibenclamide; $n = 11$) received glipizide GITS placebo and glibenclamide in the AM, and placebo for both medications in the PM.

The medication dose was stabilized one week after plasma glucose values (fasting and postprandial) achieved target levels (see above), or after four weeks, whichever came first. Treatment continued for an additional four weeks, after which time a Sustacal challenge test and 24-h glucose sampling were performed on day 1 and HGP was assessed on day 2 (conclusion of study), as described above. Home glucose monitoring was required of every patient as follows: in the morning before breakfast after an overnight fast ($\geq$10 h), 2 h after breakfast, before dinner, 2 h after dinner, and at bedtime. The results were recorded in a diary and reviewed at each clinic visit. Samples for FPG were drawn during each visit. Samples for HbA_{1c} and fructosamine were drawn at screening, at the end of week 3, and at the conclusion of the study. Samples for fasting lipid profiles, blood chemistry, and liver function test were drawn at screening, prerandomization, and at the final evaluation.

Assays

Assays for glucose, insulin, and HbA_{1c} were performed as described previously [29]. Briefly, plasma glucose concentrations were determined by the glucose oxidase method using an automated Hitachi 737 glucose analyzer (Hazelton, Vienna, VA); the interassay coefficient of variation (CV) was 1.3%. Serum insulin was measured by radioimmunoassay (Hazelton, Vienna, VA) using commercial kits (INCSTAR, Stillwater, MN); the CV was 9.0%. HbA_{1c} was measured (SciCor, Indianapolis, IN) using ion exchange chromatography; the CV was 1.5%. The other clinical chemistry, hematology, fructosamine assays, and lipid panels were performed in the clinical laboratory at Stony Brook University Hospital. Plasma stable isotope analyses were performed by Metabolic Solutions, Inc. (Nashua, NH) using the method of Bier *et al*. [34].

Safety and tolerability

Safety parameters included physical examination, vital signs, evaluations of electrocardiograms (ECG), and laboratory evaluation before entering the study. Laboratory tests were repeated at the end of week 3 and at study completion. Physical examinations and ECG evaluations were also repeated at study completion. Patients were also monitored on a regular basis for queries about adverse experiences.

Statistical analyses

The primary endpoint was the change from baseline in HGP. The null hypothesis was not an overall treatment effect compared to baseline. Secondary endpoints included fasting and 24-h glucose and insulin, fructosamine, and HbA_{1c}. All values were expressed as the mean $\pm$ SEM, unless otherwise indicated. The normality of the data was confirmed by Chi-square goodness of fit testing, and the homogeneity of variances between groups was confirmed by Bartlett's test. Statistical comparisons were made within treatment groups (baseline versus endpoint) using a *t*-test (paired data), and between each of the groups for the primary and secondary parameters by analysis of variance (ANOVA). In cases where ANOVA indicated a $p < 0.05$, the Bonferroni's Multiple Comparison test was employed to identify which groups were significantly different from each other. This analysis was repeated for each endpoint. Statistical significance was accepted at $p < 0.05$. The sample size of 10 patients per treatment group was sufficient to detect a 15% change in HGP versus baseline with a type 1 error of 0.05, a power of 80% ($\beta = 0.2$), and allowance for an attrition rate of 20%.

Results

Patients

Baseline demographics and glycemic parameters did not differ significantly between the four treatment groups (Tables 1 and 2). Although the body mass index (BMI) of the subjects in the glibenclamide group was 12 to 16% lower than the BMI of subjects in the other groups, this difference was not statistically different. In addition, there was no significant change in body weight during the study (Table 2). All treatments were very well tolerated. There was no significant change in blood pressure or any adverse effect on blood chemistry (data not shown). There was no evidence of fasting hypoglycemia in any of the treatment groups.

Metabolic control

Fasting and 24-h glucose were significantly reduced to a similar degree by glipizide GITS AM (33%, $p < 0.001$; 39%, $p < 0.0001$, respectively), glipizide GITS PM (33%, $p < 0.0001$; 32%, $p < 0.0001$), and glibenclamide (37%, $p < 0.05$; 37%, $p < 0.0001$) (Table 2). For patients who

Table 1. Demographics of study subjects

Characteristics	Placebo	Glipizide GITS AM	Glipizide GITS PM	Glibenclamide	*P*
N	10	11	10	11	
Age (years)	57.1 ± 3.5	53.9 ± 2.4	57.9 ± 3.0	56.9 ± 3.6	0.81
Gender (M, F)	8, 2	6, 5	6, 4	4, 7	0.29
Height (m)	1.71 ± 0.02	1.72 ± 0.04	1.68 ± 0.03	1.63 ± 0.04	0.26
BMI (kg/m^2)	31.9 ± 2.1	33.4 ± 1.5	33.5 ± 2.0	28.2 ± 1.7	0.14
Duration of disease (year)	6.3 ± 2.1	6.6 ± 1.8	6.6 ± 1.8	6.3 ± 2.5	1.0

Data are means ± SEM (n) and were analyzed by ANOVA.

Table 2. Effects of treatment with glipizide GITS or glibenclamide on body weight, glycemic control, insulin, and lipids in patients with type 2 diabetes

Parameter	Study interval	Placebo	Glipizide GITS AM	Glipizide GITS PM	Glibenclamide
Body weight (lbs)	Baseline	189.1 ± 12.5 (10)	188.2 ± 14.5 (11)	183.7 ± 16.2 (10)	146.6 ± 15.3 (11)
	change	−0.6 ± 1.1 (9)	14.3 ± 12.3 (10)	8.4 ± 9.0 (10)	6.4 ± 13.6 (10)
Fasting glucose	Baseline	12.2 ± 1.5 (9)	13.5 ± 1.2 (10)	13.0 ± 1.2 (10)	13.6 ± 1.6 (10)
(mmol/L)	change	−2.0 ± 1.4 (9)	−4.4 ± 0.8 (10)*	−4.3 ± 0.6 (10)†	−5.0 ± 1.2 (10)‡
24-h glucose	Baseline	12.2 ± 1.2 (9)	13.5 ± 1.3 (10)	12.6 ± 0.9 (10)	12.4 ± 1.6 (10)
(mmol/L)	change	−0.7 ± 0.2 (9)§	−5.3 ± 0.8 (10)†‖	−4.0 ± 0.4(10)†‖	−4.5 ± 1.0 (10)†‖
Fasting insulin	Baseline	98 ± 16.2 (9)	62 ± 6.6 (10)	104 ± 19.8 (10)	80 ± 13.8 (10)
(pmol/L)	change	−26.4 ± 14.4 (9)	13.2 ± 9.0 (10)	46 ± 32.4 (10)	2 ± 15 (10)
24-h insulin	Baseline	147 ± 35.4 (9)	86 ± 10.8 (10)	155 ± 39.0 (10)	103 ± 28.8 (10)
(pmol/L)	change	−34 ± 25.8 (9)	18 ± 10.2 (10)	61.2 ± 25.2(10)§¶	23.4 ± 9.6 (10)§#
Fructosamine	Baseline	3.4 ± 0.2 (10)	3.6 ± 0.3 (10)	3.6 ± 0.2 (9)	3.4 ± 0.2 (10)
(mmol/L)	change	−0.3 ± 0.1 (9)	−1.0 ± 0.2 (10)*#	−0.9 ± 0.2 (9)‡#	−0.6 ± 0.1 (9)*
HbA_{1c} (%)	Baseline	8.7 ± 0.5 (10)	10.0 ± 0.5 (11)	10.0 ± 0.7 (10)	8.6 ± 0.5 (11)
	change	−0.5 ± 0.5 (9)	−2.2 ± 0.3 (10)†	−2.4 ± 0.6 (9)‡	−1.2 ± 0.4 (10)§
Total cholesterol	Baseline	5.66 ± 0.3 (10)	6.01 ± 0.4 (11)	5.64 ± 0.4 (10)	5.60 ± 0.2 (11)
(mmol/L)	change	−0.79 ± 0.2 (9)*	−1.53 ± 0.3 (10)*#	−0.80 ± 0.3(10)§	−0.88 ± 0.02 (10)‡
LDL cholesterol	Baseline	3.53 ± 0.3 (8)	3.42 ± 0.2 (10)	2.90 ± 0.3 (9)	3.37 ± 0.2 (11)
(mmol/L)	change	−0.50 ± 0.3 (4)	−0.62 ± 0.2 (9)‡	0.03 ± 0.1 (6)	−0.50 ± 0.2 (9)
HDL cholesterol	Baseline	0.99 ± 0.1 (9)	1.12 ± 0.1 (10)	1.02 ± 0.1 (10)	1.09 ± 0.1 (11)
(mmol/L)	change	−0.26 ± 0.1 (8)§	−0.24 ± 0.1 (9)§	−0.17 ± 0.1(10)§	−0.17 ± 0.1 (9)§
Triglycerides	Baseline	3.52 ± 0.6 (10)	3.46 ± 0.1 (11)	3.34 ± 0.6 (10)	2.47 ± 0.3 (11)
(mmol/L)	change	−1.12 ± 0.5 (9)	−1.97 ± 1.1 (10)‡	−0.89 ± 0.5 (10)	−0.62 ± 0.2 (10)§

Data are means ± SEM (*n*) and were analyzed using a *t*-test (paired data) within individual treatment groups (endpoint vs baseline), or by ANOVA (between treatment groups) and Bonferroni's multiple comparison test.
*$P < 0.001$, compared to baseline.
†$P < 0.0001$, compared to baseline.
‡$P < 0.005$, compared to baseline.
§$P < 0.05$, compared to baseline.
‖$P < 0.0001$, compared to placebo.
¶$P < 0.001$, compared to placebo.
#$P < 0.05$, compared to placebo.

received glipizide GITS in the AM, the reductions in FPG and 24-h glucose were observed in the absence of a significant change in either fasting or 24-h insulin. In contrast, 24-h insulin was significantly elevated in patients treated with either glipizide GITS PM (39%) or glibenclamide (23%) compared to baseline (both $p < 0.05$) or placebo-treated patients ($p < 0.001$; $p < 0.05$, respectively).

In each treatment group, improved glycemic control resulted in beneficial effects on plasma fructosamine and HbA_{1c}. At the conclusion of the study, glipizide GITS AM treatment significantly decreased plasma fructosamine and HbA_{1c} by 28% ($p < 0.001$) and 22% ($p < 0.0001$) respectively (Table 2). Glipizide GITS PM treatment significantly decreased plasma fructosamine and HbA_{1c} by 25% ($p < 0.005$) and 24% ($p < 0.005$) respectively. In addition, glibenclamide treatment caused significant reductions in plasma fructosamine and HbA_{1c} of 17% ($p < 0.001$) and 14% ($p < 0.05$) respectively. Modest but statistically significant effects on plasma lipids were also noted (Table 2).

Hepatic glucose production

In patients receiving glipizide GITS AM or glibenclamide, HGP was significantly reduced at the conclusion of the study compared to baseline values (Figure 1). Glipizide GITS AM reduced HGP by approximately 19% ($p < 0.05$) and glibenclamide by approximately 17% ($p < 0.01$). The slight reduction in HGP by glipizide GITS PM was not statistically significant. No significant difference was found when comparing glipizide GITS AM, PM, and glibenclamide.

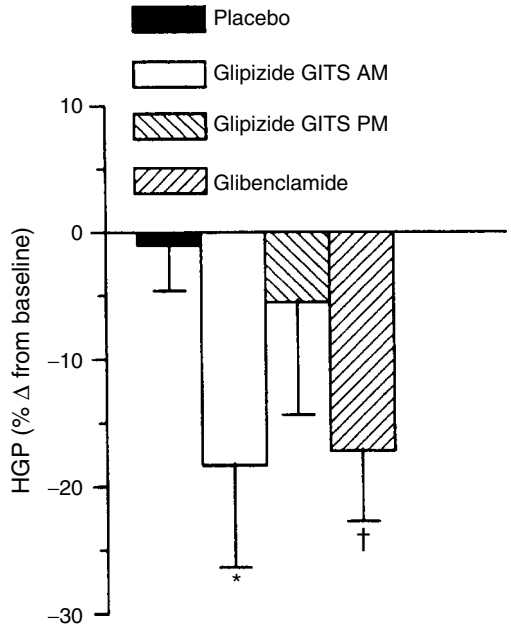

Figure 1. Effect of treatment with glipizide GITS or glibenclamide on HGP in patients with type 2 diabetes. Measurement of HPG is described in 'Research Design and Methods.' The actual rates of HGP (expressed as mg/kg/min) before drug treatment (i.e. at baseline) were as follows: placebo, 2.16 ± 0.22 (9); glipizide GITS AM, 2.44 ± 0.26 (9); glipizide GITS PM, 2.22 ± 0.15 (10); glibenclamide, 2.68 ± 0.20 (10). Data are means ± SEM (n) and were analyzed using a *t*-test (paired data) within individual treatment groups (endpoint vs baseline), or by ANOVA (between treatment groups). *$p < 0.05$, compared to baseline; †$p < 0.01$, compared to baseline

Response to Sustacal challenge

In patients receiving glipizide GITS in either the AM or PM or glibenclamide, the glucose excursion after Sustacal challenge (240 mL) was significantly ($p < 0.005$) decreased compared to placebo-treated patients (Figure 2A). The magnitude of response was approximately 25 to 35% and similar for each group. In each treatment group, the reduction in glucose excursion was accompanied by a significant increase (ranging from 30 to 60%, $p < 0.05$) in the insulin secretory response, suggesting an improvement in meal-related insulin secretion (Figure 2B).

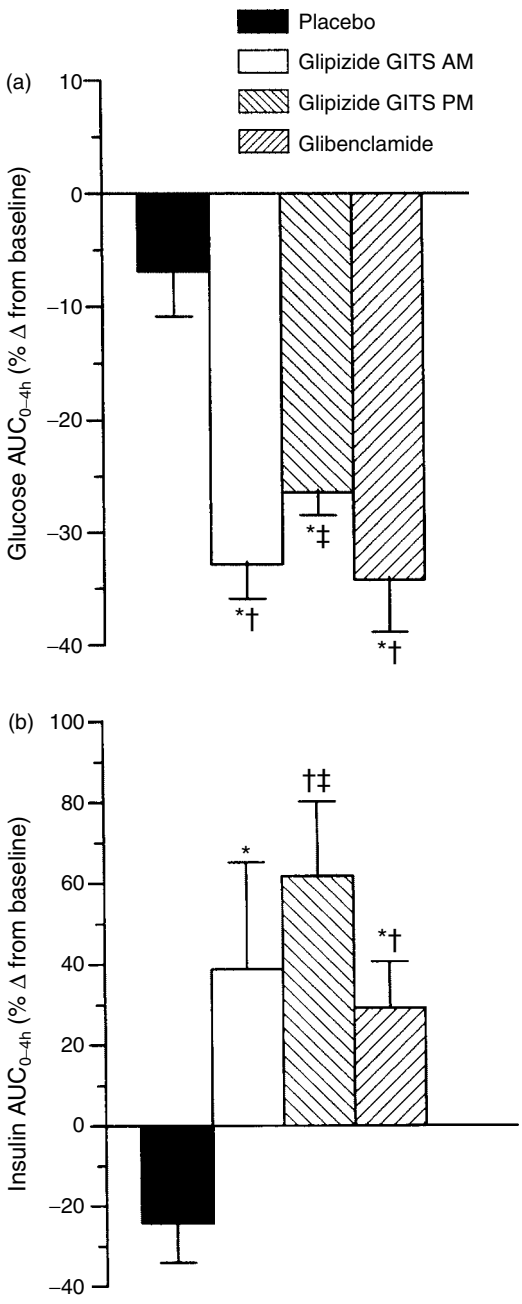

Figure 2. Effects of treatment with glipizide GITS or glibenclamide on glucose tolerance and insulin secretion after Sustacal challenge in patients with type 2 diabetes. The Sustacal challenge and sampling protocol is described in 'Design and Methods.' The actual areas under the curve (AUC_{0-4h}) for glucose (expressed as h x mmol/L) before treatment (i.e. at baseline) were placebo, 14.85 ± 1.25 (9); glipizide GITS AM, 14.84 ± 1.25 (10); glipizide GITS PM, 15.4 ± 1.07 (10); and glibenclamide, 14.75 ± 2.0 (10). The actual AUC_{0-4h} for insulin (expressed as h x pmol/L) before treatment (i.e. at baseline) were placebo, 247.5 ± 63 (9); glipizide GITS AM, 124.5 ± 30 (10); glipizide GITS PM, 223.5 ± 49.5 (10); and glibenclamide, 153 ± 45 (10). Data are means ± SEM (*n*) and were analyzed using a *t*-test (paired data) within individual treatment groups (endpoint vs baseline), or by ANOVA (between treatment groups) and Bonferroni's multiple comparison test. Panel A, *$p < 0.0001$, compared to baseline; †$p < 0.0001$, compared to placebo; ‡$p < 0.005$, compared to placebo. Panel B, *$p < 0.05$, compared to placebo; †$p < 0.05$, compared to baseline; ‡$p < 0.0001$, compared to placebo

Discussion

The present study was performed to compare the effects of glipizide GITS and glibenclamide on glycemic control, insulin secretory response, and HGP in patients with type 2 diabetes. In this study, we report the beneficial effects of both agents on glycemic control, insulin secretory response, and suppression of HGP. Furthermore, glipizide GITS and glibenclamide significantly decreased the glucose excursion and increased the insulin response after Sustacal challenge. Overall, the magnitude of the effects of these agents was similar, as evidenced by significant reductions in the FPG, 24-h glucose, fructosamine, and HbA_{1c}. In addition, glipizide GITS AM and glibenclamide suppressed HGP to a similar degree. It is important that, for glipizide GITS AM, the suppressive effect on HGP was achieved in the absence of significantly increased fasting or 24-h insulin. No significant change in body weight occurred during the study, and each treatment was very well tolerated. These results are consistent with those reported in previous studies evaluating the efficacy of glipizide GITS [29,30,32].

Using direct radioisotopic measurement of HGP, we found that sulphonylurea therapy suppressed HGP in patients with type 2 diabetes. The degree of suppression was similar for each treatment, but there was a distinct and possibly important difference exhibited by glipizide GITS AM. Glipizide GITS AM suppressed HGP in the absence of a sustained increase in plasma insulin. These data support the idea that glipizide GITS AM exerts a direct peripheral action on HGP, as opposed to an effect mediated indirectly by the elevation of plasma insulin. In contrast, although glibenclamide suppressed HGP, it did so in the context of significantly increased 24-h plasma insulin, suggesting a possible indirect effect mediated by insulin. However, it is also possible that the suppression of HGP in response to both glipizide GITS and glibenclamide was a consequence of reduced glucose toxicity. Previous studies have reported that chronic sulphonylurea therapy leads to a reduction in HGP in healthy individuals and patients with type 2 diabetes [21–24,27]. Whether sulphonylureas exert a direct suppressive effect on HGP cannot be answered by these published studies or the data presented here. However, a large number of studies have consistently reported direct effects of sulphonylureas on liver glucose metabolism *in vitro* [28,35].

There is a growing appreciation of the association of mortality with postprandial hyperglycemia [36–38]. Thus, treatments directed at reducing postprandial glucose excursions could be important additions to clinical therapy. In addition to their ability to reduce FPG and 24-h glucose, glipizide GITS and glibenclamide improved postprandial glucose excursions, as judged by a reduction in the glucose AUC_{0-4h} after Sustacal challenge. By the end of the study, the reductions in each group were of similar magnitude: 33% for glipizide GITS AM, 26% for glipizide GITS PM, and 34% for glibenclamide. Coincident with their ability to reduce the glucose AUC_{0-4h}, glipizide GITS AM, PM, and glibenclamide produced significant increases in the insulin secretory response (approximately 40, 65, and 27%, respectively). Taken together, these data indicate an overall improvement in meal-related insulin secretion after each treatment regimen; however, only glipizide GITS AM provided this benefit in the absence of persistently elevated circulating insulin. This feature of glipizide GITS AM is therapeutically attractive, being consistent with a reduced risk of hypoglycemia.

Conclusions

In summary, this study found that glipizide GITS and glibenclamide treatment reduced FPG and HbA_{1c}, exerted a suppressive effect on basal HGP, and improved postprandial glycemia; however, only glipizide GITS AM was effective without causing a persistent elevation in insulin. None of the treatments significantly increased body weight and each exhibited a modest beneficial effect on plasma lipids. In view of the potential risks associated with chronic hyperinsulinemia, including increased adiposity and weight gain, morning administration of glipizide GITS appears to offer a beneficial approach to reduce these risks. However, any potential benefit of less weight gain would require a study of longer duration. The profile of glipizide GITS AM is also consistent with the potential for a reduced risk of hypoglycemia.

Acknowledgments

The expert assistance of Ms. Nancy Wyllie (study coordinator) and Elissa Feldman (registered dietician) is gratefully acknowledged. Funding for this study was provided by Pfizer, Inc.

References

1. DeFronzo RA. Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes. *Diabet Rev* 1997; **5**: 177–269.
2. Reaven GM. Insulin resistance and its consequences: type 2 diabetes mellitus and coronary heart disease. In *Diabetes Mellitus: A Fundamental and Clinical Text*, LeRoith D, Taylor SI, Olefsky JM (eds). Lippincott Williams & Wilkins: Philadelphia, 2000; 604–615.
3. Porte D Jr. Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications. *Diabetes Metab Res Rev* 2001; **17**: 181–188.
4. Bergman RN, Van Citters GW, Mittelman SD, *et al*. Central role of the adipocyte in the metabolic syndrome. *J Investig Med* 2001; **49**: 119–126.
5. Abbasi F, McLaughlin T, Lamendola C, Reaven GM. Insulin regulation of plasma free fatty acid concentrations is abnormal in healthy subjects with muscle insulin resistance. *Metabolism* 2000; **49**: 151–154.
6. Arner P. Insulin resistance in type 2 diabetes: role of fatty acids. *Diabetes Metab Res Rev* 2002; **18**(Suppl. 2): S5–S9.
7. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* 2002; **51**: 7–18.
8. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.

9. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Invest* 2002; **32**(Suppl. 3): 14–23.
10. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 1991; **73**: 1294–1301.
11. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1996; **81**: 4059–4067.
12. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; **333**: 550–554.
13. Foley JE. Rationale and application of fatty acid oxidation inhibitors in treatment of diabetes mellitus. *Diabetes Care* 1992; **15**: 773–784.
14. Moller DE. New drug targets for type 2 diabetes and the metabolic syndrome. *Nature* 2001; **414**: 821–827.
15. Pratley RE, Weyer C. The role of impaired early insulin secretion in the pathogenesis of Type II diabetes mellitus. *Diabetologia* 2001; **44**: 929–945.
16. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; **131**: 281–303.
17. Lebovitz HE. Insulin secretagogues: sulphonylureas and meglitinides. In *Diabetes Mellitus: A Fundamental and Clinical Text*, LeRoith D, Taylor SI, Olefsky JM (eds). Philadelphia: Lippincott Williams & Wilkins: 2000; 769–778.
18. Aguilar-Bryan L, Bryan J. Molecular biology of adenosine triphosphate-sensitive potassium channels. *Endocr Rev* 1999; **20**: 101–135.
19. Gribble FM, Ashcroft FM. Sulphonylurea sensitivity of adenosine triphosphate-sensitive potassium channels from beta cells and extrapancreatic tissues. *Metabolism* 2000; **49**(Suppl. 2): 3–6.
20. Malhi H, Irani AN, Rajvanshi P, *et al*. KATP channels regulate mitogenically induced proliferation in primary rat hepatocytes and human liver cell lines. Implications for liver growth control and potential therapeutic targeting. *J Biol Chem* 2000; **275**: 26 050–26 057.
21. Best JD, Judzewitsch RG, Pfeifer MA, Beard JC, Halter JB, Porte D Jr. The effect of chronic sulphonylurea therapy on hepatic glucose production in non-insulin-dependent diabetes. *Diabetes* 1982; **31**: 333–338.
22. Simonson DC, Ferrannini E, Bevilacqua S, *et al*. Mechanism of improvement in glucose metabolism after chronic glibenclamide therapy. *Diabetes* 1984; **33**: 838–845.
23. DeFronzo RA, Simonson DC. Oral sulphonylurea agents suppress hepatic glucose production in non-insulin-dependent diabetic individuals. *Diabetes Care* 1984; **7**(Suppl. 1): 72–80.
24. Groop L, Luzi L, Melander A, *et al*. Different effects of glibenclamide and glipizide on insulin secretion and hepatic glucose production in normal and NIDDM subjects. *Diabetes* 1987; **36**: 1320–1328.
25. McGuinness OP, Cherrington AD. Effect of glibenclamide on hepatic glucose metabolism. *Am J Med* 1990; **89**: 51S–53S; discussion 26S-37S.
26. Schmitz O, Lund S, Bak JF, *et al*. Effects of glipizide on glucose metabolism and muscle content of the insulin-regulatable glucose transporter (GLUT 4) and glycogen synthase activity during hyperglycaemia in type 2 diabetic patients. *Acta Diabetol* 1994; **31**: 31–36.
27. Tayek JA. Low-dose oral glibenclamide reduces fasting blood glucose by decreasing hepatic glucose production in healthy volunteers without increasing carbohydrate oxidation. *Am J Med Sci* 1995; **309**: 134–139.
28. Del Prato S, Vigili dK, Riccio A, Tiengo A. Hepatic sensitivity to insulin: effects of sulphonylurea drugs. *Am J Med* 1991; **90**(Suppl. 6A): 29S–36S.
29. Berelowitz M, Fischette C, Cefalu W, Schade DS, Sutfin T, Kourides IA. Comparative efficacy of a once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care* 1994; **17**: 1460–1464.
30. Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT. The Glipizide Gastrointestinal Therapeutic System Study Group. Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycaemic control and insulin secretion in NIDDM. Results of two multicenter, randomized, placebo-controlled clinical trials. *Diabetes Care* 1997; **20**: 597–606.
31. Foster RH, Plosker GL. Glipizide. A review of the pharmacoeconomic implications of the extended-release formulation in type 2 diabetes mellitus. *Pharmacoeconomics* 2000; **18**: 289–306.
32. Chung M, Kourides I, Canovatchel W, Sutfin T, Messig M, Chaiken RL. Pharmacokinetics and pharmacodynamics of extended-release glipizide GITS compared with immediate-release glipizide in patients with type II diabetes mellitus. *J Clin Pharmacol* 2002; **42**: 651–657.
33. Wolfe RR. Glucose metabolism. *Radioactive and Stable Isotope Tracers in Biomedicine: Principles and Practice of Kinetic Analysis*, New York: Wiley: 1992; 283–315.
34. Bier DM, Leake RD, Haymond MW, *et al*. Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 2003; **26**: 1016–1023.
35. Adams MD, Raman P, Judd RL. Comparative effects of englitazone and glibenclamide on gluconeogenesis and glycolysis in the isolated perfused rat liver. *Biochem Pharmacol* 1998; **55**: 1915–1920.
36. Donahue RP, Abbott RD, Reed DM, Yano K. Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu heart program. *Diabetes* 1987; **36**: 689–692.
37. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ. Isolated postchallenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 1999; **42**: 1050–1054.
38. The DECODE Study Group. (European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe). Glucose tolerance and mortality: comparison of WHO and American diabetes association diagnostic criteria. *Lancet* 1999; **354**: 617–621.

