Efficacy, Safety, and Dose-Response Characteristics of Glipizide Gastrointestinal Therapeutic System on Glycemic Control and Insulin Secretion in NIDDM

Results of two multicenter, randomized, placebo-controlled clinical trials

DONALD C. SIMONSON, MD
IONE A. KOURIDES, MD
MARK FEINGLOS, MD
HARRY SHAMOON, MD
CHRISTINE T. FISCHETTE, PHD
THE GLIPIZIDE GASTROINTESTINAL THERAPEUTIC SYSTEM STUDY GROUP

OBJECTIVE — To investigate the efficacy, safety, and dose-response characteristics of an extended-release preparation of glipizide using the gastrointestinal therapeutic system (GITS) on plasma glucose, glycosylated hemoglobin (HbA_{1c}), and insulin secretion to a liquid-mixed meal in NIDDM patients.

RESEARCH DESIGN AND METHODS — Two prospective, randomized, double-blind, placebo-controlled, multicenter clinical trials were performed in 22 sites and 347 patients with NIDDM (aged 59 ± 0.6 years; BMI, 29 ± 0.3 kg/m^2; known diabetes duration, 8 ± 0.4 years) were studied. Each clinical trial had a duration of 16 weeks with a 1-week washout, 3-week single-blind placebo phase, 4-week titration to a fixed dose, and 8-week maintenance phase at the assigned dose. In the first trial, once-daily doses of 5, 20, 40, or 60 mg glipizide GITS were compared with placebo in 143 patients. In the second trial, doses of 5, 10, 15, or 20 mg of glipizide GITS were compared with placebo in 204 patients. HbA_{1c}, fasting plasma glucose (FPG), insulin, C-peptide, and glipizide levels were determined at regular intervals throughout the study. Postprandial plasma glucose (PPG), insulin, and C-peptide also were determined at 1 and 2 h after a mixed meal (Sustacal).

RESULTS — All doses of glipizide GITS in both trials produced significant reductions from placebo in FPG (range −57 to −74 mg/dl) and HbA_{1c} (range −1.50 to −1.82%). Pharmacodynamic analysis indicated a significant relationship between plasma glipizide concentration and reduction in FPG and HbA_{1c} over a dose range of 5–60 mg, with maximal efficacy achieved at a dose of 20 mg for FPG and at 5 mg for HbA_{1c}. PPG levels were significantly lower, and both postprandial insulin and C-peptide levels significantly higher in patients treated with glipizide GITS compared with placebo. The percent reduction in FPG was comparable across patients with diverse demographic and clinical characteristics, including those with entry FPG ≥250 mg/dl, resulting in greater absolute decreases in FPG and HbA_{1c} in patients with the most severe hyperglycemia. Despite the forced titration to a randomly assigned dose, only 11 patients in both studies discontinued therapy because of hypoglycemia. Glipizide GITS did not alter lipids levels or produce weight gain.

CONCLUSIONS — The once-daily glipizide GITS *1)* lowered HbA_{1c}, FPG, and PPG over a dose range of 5-60 mg, *2)* was maximally effective at 5 mg (using HbA_{1c}) or 20 mg (using FPG) based on pharmacokinetic and pharmacodynamic relationships, *3)* maintained its effectiveness in poorly controlled patients (those with entry FPG ≥250 mg/dl), *4)* was safe and well tolerated in a wide variety of patients with NIDDM, and *5)* did not produce weight gain or adversely affect lipids.

From the Department of Medicine (D.C.S.), Joslin Diabetes Center, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; Pfizer Inc. (I.A.K., C.T.F), New York, New York; the Department of Medicine (M.F.), Duke University Medical Center, Durham, North Carolina; and the Department of Medicine (H.S.), Albert Einstein College of Medicine, Bronx, New York.

Address correspondence and reprint requests to D.C. Simonson, MD, Chief, Section of Diabetes and Metabolism, Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115.

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FPG, fasting plasma glucose; GITS, gastrointestinal therapeutic system; HPLC, high-performance liquid chromotography; PPG, postprandial plasma glucose.

NIDDM is a heterogeneous metabolic disorder characterized by a relative deficiency in insulin secretion, resistance to the action of insulin in muscle and in other peripheral tissues, and increased rates of hepatic glucose production (1,2). Although nonpharmacological measures such as diet and exercise are clearly the cornerstone of diabetes management, most patients are unable to achieve adequate glucose control with these interventions alone.

When pharmacological therapy becomes necessary, most physicians initially use sulfonylurea medications, because they have a long history of proven efficacy and safety (3–7). Although the sulfonylureas act primarily by stimulating endogenous insulin secretion, numerous in vitro and in vivo studies (8–15), including those using glipizide gastrointestinal therapeutic system (GITS) (16,17), suggest that they also may enhance peripheral insulin sensitivity (either directly or indirectly as a result of a reduction in plasma glucose) and reduce hepatic glucose production (16,18–22,40). Thus, sulfonylurea agents partially ameliorate each of the major metabolic defects that characterize the diabetic state.

Differences in the pharmacokinetic and pharmacodynamic characteristics of the various sulfonylurea compounds produce different therapeutic and side-effect profiles (23). Longer-acting agents like glyburide (taken once or twice per day) or chlorpropamide (taken once per day) are efficacious but tend to produce more sustained hyperinsulinemia and have higher rates of hypoglycemia during routine clinical use (24–26). Conversely, shorter-acting sulfonylureas such as immediate release glipizide or tolbutamide are thought to be more efficacious in enhancing meal-stimulated insulin secretion and generally have a lower risk of hypoglycemia (14,27–31), but often need to be taken more than once per day, which may decrease compliance (32,33) and produce greater excursions in

plasma drug levels both above and below the therapeutic range.

Thus, from several perspectives it would be desirable to have a drug with an intrinsically short duration of action be available at an effective therapeutic plasma level throughout a 24-h period. To achieve this goal, the short-acting sulfonylurea glipizide was formulated as an extended-release preparation using the GITS, which delivers drug by a membrane-controlled osmotic process (34), resulting in effective plasma drug concentrations over the 24-h period with once-daily administration. We report here the results of the first two randomized multicenter clinical trials examining the efficacy, safety, and dose-response characteristics of this controlled release delivery system for glipizide on indexes of glycemic control and insulin secretion in patients with NIDDM.

RESEARCH DESIGN AND METHODS

Patients

For the study, 347 patients with NIDDM were randomized in two parallel-design clinical trials described below. Volunteers were recruited from 22 clinical diabetes and endocrinology practices based at university medical centers, community hospitals, and private offices throughout the U.S.

Eligibility criteria included: *1)* men or women ≥30 years of age; *2)* diagnosis of NIDDM for ≥6 month before study entry; *3)* fasting plasma glucose (FPG) ≥140 and <300 mg/dl at the end of week 2 of the placebo phase, or if FPG was <140 mg/dl, a 2-h postprandial plasma glucose (PPG) ≥200 mg/dl was required; *4)* glycosylated hemoglobin (HbA_{1c}) >6% at the end of week 2 of placebo administration; and *5)* treatment with oral sulfonylureas and/or diet for a minimum of 3 months before entry into the study. Women were included if they were postmenopausal, surgically sterile, or using adequate contraception.

Patients were excluded if they: *1)* were <80% or >160% of ideal body weight (1983 Metropolitan Life Insurance Tables), *2)* had IDDM, *3)* were currently taking insulin or had been treated with insulin for more than 1 week during the previous 3 months, *4)* had a history of ketoacidosis during the past year, *5)* had labile glycemic control (i.e., frequent episodes of severe hyperglycemia or hypoglycemia), *6)* had proliferative retinopathy or proteinuria >1 gm/day, *7)* had significant hepatic, renal, or cardiovascular dysfunction, *8)* had a history of gastrointestinal dysfunction or chronically used laxatives or cathartics, *9)* had a history of cancer or drug abuse, *10)* had known intolerance to sulfa drugs, or *11)* were pregnant or intended to become pregnant during the trial.

Study design

Studies were conducted as two prospective, randomized, double-blind, placebo-controlled, parallel design, multicenter clinical trials. With the exception of the differences in the doses of glipizide GITS tested, the protocols for the two studies were identical. After a 1-week washout from current sulfonylurea therapy, patients were administered placebo for 3 weeks. After 2 weeks on placebo, patients were evaluated for entry into the double-blind phase. Those patients who met all of the above-described criteria were randomly assigned to a fixed dose of glipizide GITS (5, 20, 40, or 60 mg in the first study and 5, 10, 15, or 20 mg in the second study) or placebo. During weeks 4–7, the doses of glipizide GITS were titrated at weekly intervals to the preassigned level. At the end of this period, patients were maintained at their assigned dose for 8 weeks (weeks 8–15) and no further dosage changes were permitted. All medication was taken once daily with 8 ounces of fluid immediately before breakfast.

Efficacy and safety measurements

Levels of HbA_{1c} were determined at the screening visit and at the end of study weeks 2, 3, and 15 using ion exchange high-performance liquid chromatography (HPLC). Concentrations of FPG, serum insulin, and C-peptide were determined at the end of study weeks 1, 2, 3, 9, 12, and 15. FPG was measured by the glucose oxidase method using an Hitachi 737 apparatus, and serum insulin and C-peptide were measured by radioimmunoassay (Hazelton, Vienna, VA) using commercial kits (INCSTAR, Stillwater, MN) (coefficient of variation = 8.9% for insulin and 13.1% for C-peptide). Patients were challenged with 8 ounces of Sustacal (a liquid mixed meal) in the morning at the end of weeks 2, 9, 12, and 15. Levels of plasma glucose, serum insulin, and serum C-peptide were determined 0, 1, and 2 h after challenge using the above-described methods.

All observed or volunteered adverse experiences and study-emergent illnesses were recorded at each visit. Laboratory safety data were obtained at baseline and at the end of the study. Laboratory results falling outside the normal range were reviewed for clinical significance and relation to study medication. In addition, mean laboratory values at baseline and at the final visit, plus the mean change from baseline to the final visit, were calculated for glipizide GITS and placebo, and the mean changes were compared. Vital signs and body weight were obtained at baseline and at regular intervals during the study, and electrocardiograms were obtained at baseline and final visit. Finally, patients were instructed to measure their blood glucose twice daily—in the morning (having fasted from 8:00 P.M. the previous night) and at bedtime—three times per week.

Patients were discontinued from the study if they had intolerable adverse experiences, an episode of hypoglycemia, or excessive hyperglycemia (lack of efficacy). Hypoglycemia was defined as either *1)* presence of symptoms of hypoglycemia alone, *2)* a blood glucose level <60 mg/dl by home blood glucose monitoring regardless of the presence of symptoms, or *3)* blood glucose <80 mg/dl when tested in the clinic. Excessive hyperglycemia was defined as FPG >330 mg/dl in the clinic on two consecutive visits.

Glipizide assays

Samples were collected for analysis of plasma glipizide levels at the end of weeks 9, 12, and 15. The samples were collected just before and 1, 2, and 24 h after dosing and Sustacal administration. The concentration of glipizide for an individual patient was defined as the average of the values obtained at 24 h postdosing at weeks 9, 12, and 15. Plasma samples were assayed for glipizide, using HPLC with ultraviolet absorbance detection at 275 nm (35). The method is linear over a glipizide concentration range of 10–1,000 ng/ml, and the limit of quantification was 10.0 ng/ml in 1.0 ml of plasma. The pharmacokinetic/pharmacodynamic relationship was determined by plotting the concentration of glipizide versus the change in FPG from baseline to last value within weeks 9, 12, and 15 and the change in HbA_{1c} from baseline to week 15.

Statistical analysis

The primary outcome measures were HbA_{1c} and FPG levels. Levels of fasting and post-Sustacal serum insulin and C-peptide also were analyzed. Baseline values for each of these measures were determined at the end

Table 1—*Demographic characteristics of patients randomized to double-blind treatment*

Variable	Glipizide GITS dose (mg)						Placebo
	5	10	15	20	40	60	
n	68	42	42	69	28	29	69
Sex							
Men	40	25	26	47	17	23	53
Women	28	17	16	22	11	6	16
Race							
White	50	32	30	54	25	24	50
Black	10	4	4	7	1	1	8
Other	8	6	8	8	2	4	11
Age (years)	57.4 (33–81)	58.7 (34–78)	55.5 (31–73)	59.3 (39–84)	61.7 (36–80)	56.9 (32–74)	60.2 (55–76)
Weight (pounds)	185.0 (112–263)	181.0 (123–257)	187.3 (130–271)	186.7 (128–312)	196.2 (144–267)	201.1 (142–270)	191.7 (125–280)
BMI (kg/m^2)	29.0 (18.7–45.4)	28.4 (18.7–42.1)	29.5 (23.0–41.6)	28.8 (20.4–41.5)	29.6 (21.9–39.4)	30.5 (22.3–38.0)	29.7 (22.3–45.2)
Duration of known NIDDM (years)	6.9 (0.5–29.8)	8.8 (0.6–23.4)	6.5 (0.7–26.4)	7.8 (0.9–28.7)	6.6 (0.6–19.6)	5.3 (0.2–18.6)	7.5 (0.5–31.4)

Data are *n* or means (range).

of week 3 (4 weeks after the termination of previous sulfonylurea administration), and endpoint values were determined at the end of week 15 or when the patient left the study (in the case of discontinuation). Results for HbA_{1c}, FPG, serum insulin, and C-peptide were analyzed using analysis of variance. Least-squares means were generated to estimate treatment effects and for pairwise comparisons between treatment groups. Postprandial assessments of plasma glucose, serum insulin, and C-peptide were analyzed using the same methods. The plasma glipizide concentration-response relationship was analyzed by a multiple regression model consisting of the baseline value and linear and quadratic terms of log concentration. All analyses were two-tailed with $P < 0.05$ as the accepted level of significance.

In additional subanalyses, patients from the two studies were stratified according to major demographic or clinical characteristics, including age (<65 or ≥65 years of age), sex, race (black, white, or other), BMI (<30 or ≥30 kg/m^2), duration of known NIDDM (<5, 5–10, or >10 years), and presence of hypertension (diastolic blood pressure ≤90 or 91–105 mmHg). Differences between baseline and endpoint FPG, HbA_{1c}, and PPG were evaluated for each group using the above-described methods.

Because the placebo, 5-mg dose, and 20-mg dose of glipizide were common to both studies, a pooled analysis was performed at these three doses for major outcome variables.

RESULTS

Patient entry, randomization, and withdrawal

The 523 patients were screened, and 347 were randomized into the two trials; 143 were randomized to double-blind treatment with either 5, 20, 40, or 60 mg of glipizide GITS or placebo. Of these, 15 (10.5%) did not complete the study for the following reasons: *1)* insufficient clinical response (three patients in placebo group), hypoglycemia (seven patients in the glipizide GITS groups, usually due to a single blood glucose <60 mg/dl by home glucose monitoring), *3)* an adverse event (one glipizide GITS), *4)* protocol violations (two glipizide GITS), and *5)* noncompliance (two glipizide GITS).

In the second trial, 204 patients were randomized to double-blind treatment with either 5, 10, 15, or 20 mg of glipizide GITS or placebo. Of these patients, 40 (19.6%) did not complete the study. Reasons for discontinuation were: insufficient clinical response (nine glipizide GITS, 15 placebo), hypoglycemia (four glipizide GITS), adverse experiences (four glipizide GITS, three placebo), death (one glipizide GITS), and administrative reasons (three glipizide GITS, one placebo).

Demographic data for all patients randomized to receive treatment are summarized in Table 1. There were no statistically significant differences among the demographic characteristics of patients randomized to the different doses of glipizide GITS or placebo in either study.

Efficacy

HbA_{1c} and FPG, insulin, and C-peptide. Both trials demonstrated that once-daily administration of all glipizide GITS doses resulted in significant reductions in both HbA_{1c} and FPG (Table 2). In the first trial, doses of 5, 20, 40, and 60 mg glipizide GITS resulted in HbA_{1c} reductions from baseline ranging from 1.0 ± 0.2 to 1.2 ± 0.2% ($P <$ 0.0001 versus placebo for all doses), but there were no significant differences among individual doses. In the second trial, decreases from baseline in HbA_{1c} for the 5-, 10-, 15-, and 20-mg doses ranged from 0.5 ± 0.2 to 0.7 ± 0.2% ($P < 0.0001$ versus placebo for all doses) but, again, no significant differences among the various doses were observed. In pooled analysis, the 5- and 20-mg doses of glipizide GITS (which were common to both trials) decreased HbA_{1c} by 0.9 ± 0.1 and 0.9 ± 0.1% from baseline, respectively ($P < 0.0001$ for overall treatment effect, but no significant difference between 5- and 20-mg groups). When glipizide dose was plotted against change in HbA_{1c}, the maximum efficacy was achieved at the 5-mg dose with no further benefit observed at higher doses (Fig. 1).

For FPG, the reductions from baseline ranged from 45 ± 8 to 59 ± 8 mg/dl in the first trial, and from 37 ± 8 to 57 ± 8 mg/dl in the second trial ($P < 0.0001$ versus placebo for all doses in each trial), but no significant differences among doses was observed (Table 2). However, combined results from both trials for patients who received either 5 or 20 mg glipizide GITS did demonstrate a

Table 2—*FPG and HbA_{1c} in all patients at randomization and at final visit in the two studies*

Variable	Glipizide GITS dose (mg)						Placebo
	5	10	15	20	40	60	
FPG (mg/dl)							
n	66	42	41	68	26	29	68
Baseline	229 ± 7	251 ± 8	255 ± 9	243 ± 6	212 ± 11	229 ± 10	235 ± 7
	(129.0–350.0)	(136.0–328.0)	(143.0–336.0)	(163.0–358.0)	(105.0–359.0)	(131.0–329.0)	(141.0–332.0)
Endpoint	189.1 ± 7.7	191.9 ± 9.1	212.9 ± 10.8	182.2 ± 6.5	155.9 ± 11.5	181.0 ± 7.6	252.1 ± 8.4
	(113.0–395.0)	(89.5–331.0)	(89.0–365.0)	(92.0–338.0)	(91.0–331.0)	(91.0–283.0)	(111.0–421.0)
HbA_{1c} (%)							
n	66	42	41	68	26	29	68
Baseline	8.5 ± 0.2	8.8 ± 0.2	8.6 ± 0.2	8.7 ± 0.2	8.4 ± 0.3	8.6 ± 0.3	8.3 ± 0.2
	(6.0–12.6)	(6.6–12.0)	(6.6–12.3)	(6.2–13.0)	(6.5–12.1)	(5.6–12.1)	(6.0–11.6)
Endpoint	7.6 ± 0.2	7.6 ± 0.2	8.11 ± 0.2	7.8 ± 0.2	7.13 ± 0.3	7.5 ± 0.24	9.14 ± 0.2
	(5.6–12.9)	(5.8–11.2)	(5.9–11.8)	(5.0–12.5)	(5.2–12.0)	(5.6–11.4)	(6.0–12.9)

Data are *n* or means ± SE (range).

dose-related effect on FPG (Fig. 2). The 5- and 20-mg doses decreased FPG by 42 ± 6 and 60 ± 6 mg/dl from baseline ($P < 0.0001$ for overall treatment effect), respectively. The reduction in FPG achieved by the 20-mg dose was significantly greater ($P < 0.03$) than that achieved by the 5-mg dose, but no further benefit was achieved at doses above 20 mg per day.

At all doses, maximal changes in fasting blood glucose obtained by fingerstick at clinic visits occurred by approximately the 2nd week of dosing (week 5 in Fig. 3). These decreases in fasting blood glucose were consistent and were maintained throughout the duration of the study (Fig. 3).

A responders' analysis was done to calculate the primary failure rates in pooled data from these studies. Clinical control was operationally defined as a reduction in FPG or 2-h PPG of at least 10% from baseline. The results of this analysis showed that in the placebo group, 85% of patients were primary failures. In the 5-mg group, 12% were primary failures and in the 20-mg group, 9% were primary failures. The percentage of clinically controlled patients in both treatment groups was significantly different from the percentage controlled in the placebo group. However, the percentage of responders in the two treatment groups was not significantly different.

Although there was no significant increase in fasting insulin levels when pooled results in all glipizide GITS-treated patients were compared with placebo, small increases were occasionally observed—typically at doses ≥20 mg/day. In the first study, 5-, 20-, 40-, and 60-mg doses of glipizide GITS increased fasting insulin levels by 5 ± 3, 2 ± 3, 9 ± 3, and 8 ± 3 μU/ml ($P < 0.05$ versus placebo for 40-mg and 60-mg treatment groups), respectively. Fasting C-peptide levels were comparably increased by 0.6 ± 0.2, 0.4 ± 0.2, 0.9 ± 0.2 ($P < 0.05$ versus placebo), and 1.1 ± 0.2 ng/ml ($P < 0.001$ versus placebo), respectively. In the second study, the 5-, 10-, 15-, and 20-mg doses of glipizide GITS changed fasting insulin levels by −1 ± 2, 4 ± 2 ($P < 0.05$ versus placebo), −1 ± 2, and 8 ± 2 μU/ml ($P < 0.001$ versus placebo), respectively. Increases in fasting C-peptide were 0.2 ± 0.2, 0.6 ± 0.2 ($P < 0.05$ versus placebo), 0.6 ± 0.2 ($P < 0.05$ versus placebo), and 1.0 ± 0.2 ng/ml ($P < 0.001$ versus placebo), respectively.

Postprandial assessments. Both studies demonstrated significant effects of glipizide GITS on postprandial glucose, insulin, and C-peptide levels (Fig. 4). In the first trial, the 5-, 20-, 40-, and 60-mg doses significantly decreased the 2-h PPG by 60 ± 10, 58 ± 10, 83 ± 11, and 49 ± 10 mg/dl, respectively ($P < 0.001$ versus placebo for all doses, but no significant differences among doses). Decreases in the 0- to 2-h area under the plasma concentration time curve ($AUC_{0-2\,h}$) for PPG were 105 ± 17, 103 ± 17, 130 ± 19, and 94 ± 17 mg · dl^{-1} · h^{-1}, respectively ($P < 0.001$ versus placebo for all doses, but no significant differences among doses).

In the second trial, the 5-, 10-, 15-, and 20-mg glipizide GITS doses decreased the 2-h PPG by 52 ± 10, 57 ± 10, 38 ± 10, and 57 ± 10 mg/dl, respectively ($P < 0.001$ versus placebo for all doses, but no significant difference among doses). The $AUC_{0-2\,h}$ for PPG was similarly reduced by 103 ± 20, 104 ± 19, 67 ± 18, and 120 ± 19 mg · dl^{-1} · h^{-1}, respectively ($P < 0.001$ versus placebo for all doses, but no significant differences among doses).

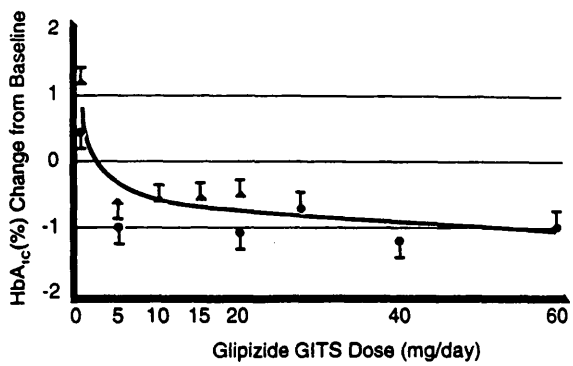

Figure 1—*Dose-response effect of glipizide GITS on mean ± SE change in HbA_{1c} in patients with NIDDM who received 5 mg, 20 mg, 40 mg, or 60 mg glipizide GITS or placebo (study 1, ●) and 5 mg, 10 mg, 15 mg, or 20 mg glipizide GITS or placebo (study 2, ▲). P < 0.0001 for each dose versus placebo; no significant differences among other active doses.*

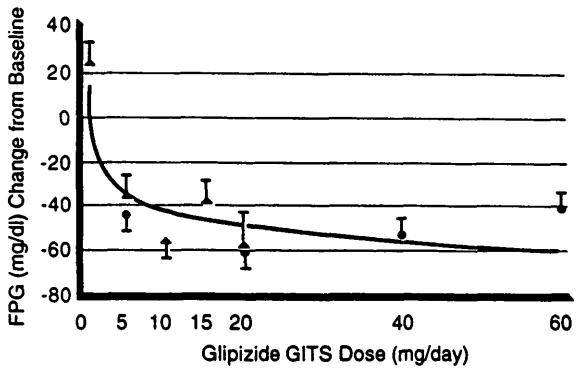

Figure 2—*Dose-response effect of glipizide GITS on mean ± SE change in FPG in patients with NIDDM who received 5 mg, 20 mg, 40 mg, or 60 mg glipizide GITS or placebo (study 1, ●) and 5 mg, 10 mg, 15 mg, or 20 mg glipizide GITS or placebo (study 2, ▲). P < 0.03 for 5-mg dose vs. 20-mg dose; no significant differences among other active doses.*

Nearly all glipizide GITS doses in both studies produced significant increases in postprandial insulin and C-peptide. Combined data showed that the 5-mg dose increased the insulin AUC_{0-2h} by 15 ± 4 μU · ml^{-1} · h^{-1}, whereas the 20-mg dose increased it by 18 ± 4 μU · ml^{-1} · h^{-1} (P = 0.0003 for overall treatment effect, both doses). The respective values for C-peptide were 1.0 ± 0.3 ng · ml^{-1} · h^{-1} and 2.0 ± 0.3 ml/h (P < 0.0001 for overall treatment effect, both doses). The increase in the C-peptide AUC_{0-2h} was significantly greater with the 20-mg dose than with the 5-mg dose (P < 0.01) (Fig. 4).

Pharmacokinetic/pharmacodynamic analyses. In the first study, plasma glipizide concentrations 24 h after dosing at weeks 9, 12, and 15 combined averaged 54 ± 5, 310 ± 38, 537 ± 74, and 698 ± 76 ng/ml for the 5-, 20-, 40-, and 60-mg glipizide GITS doses, respectively. There was no significant dose-response relationship between plasma glipizide concentration and change in HbA_{1c}, but there was a significant (P < 0.05) dose-response relationship between plasma glipizide level and FPG reduction. In the second trial, mean plasma glipizide concentrations 24 h after dosing were 50 ± 5, 158 ± 20, 217 ± 38, and 265 ± 24 ng/ml for the 5-, 10-, 15-, and 20-mg glipizide GITS doses, respectively. There was no significant dose-response relationship between plasma glipizide concentration and change in HbA_{1c}, but again there was a significant (P < 0.01) dose-response relationship between plasma glipizide concentration and FPG reduction.

To reduce between-subject variability and to more easily discern differences in the response curves, patients were divided into quintiles based on mean plasma glipizide concentration. The lowest quintile consisted of all placebo patients. The changes in HbA_{1c} and FPG for each quintile are plotted in Fig. 5. Changes in HbA_{1c} for each quintile were 0.8 ± 0.2, −1.0 ± 0.1, −0.9 ± 0.1, −0.7 ± 0.2, and −1.1 ± 0.1%, respectively. The changes in FPG were 17 ± 6, −36 ± 5, −55 ± 7, −47 ± 6, and −67 ± 6 mg/dl, respectively.

Efficacy of glipizide GITS in specific subpopulations. The number of patients treated with either 5 or 20 mg of glipizide GITS in the two trials permitted assessment of efficacy in subpopulations drawn from the entire patient sample. Analysis demonstrated that glipizide GITS was effective in all patients with NIDDM, regardless of disease severity. Glipizide GITS significantly decreased FPG in patients with FPG <200, 200–249, or ≥250 mg/dl (Fig. 6). At the 5-mg dose, FPG levels decreased by 19 ± 6, 53 ± 8, and 50 ± 13 mg/dl in the three patient groups, respectively (P < 0.0001 versus placebo). At the 20-mg dose, FPG levels decreased by 40 ± 7, 49 ± 8, and 79 ± 7 mg/dl, respectively (P < 0.0001 versus placebo). Moreover, in patients with FPG ≥250 mg/dl, the reduction in FPG with the 20-mg dose was significantly greater than with the 5-mg dose (P < 0.05; Fig. 6).

Similarly, reductions in HbA_{1c} were significantly different (P < 0.0001) from placebo for both the 5- and 20-mg glipizide GITS doses for patients with HbA_{1c} values at baseline <8% and between 8 and 10%. For patients with HbA_{1c} >10%, both doses of glipizide GITS decreased HbA_{1c}, but only the decrease obtained with the 5-mg dose was statistically significant (P < 0.05). Thus, in patients with more severe NIDDM, glipizide GITS in a dose as low as 5 mg still significantly reduced HbA_{1c} levels.

Additional analyses of pooled results from patients treated with either 5 or 20 mg of glipizide GITS demonstrated that it was effective in a number of different demographic patient subpopulations. The drug produced comparable significant reductions in mean FPG and HbA_{1c} levels in patients <65 years and ≥65 years of age; in males and females; in black, white, and patients of other races (primarily Hispanic); in patients with BMI ≤30 or >30 kg/m^2; in patients with NIDDM for <5, 5–10, or >10 years; and in mildly hypertensive patients (diastolic BP 91–105 mmHg).

Glipizide GITS also significantly reduced mean FPG in patients who had

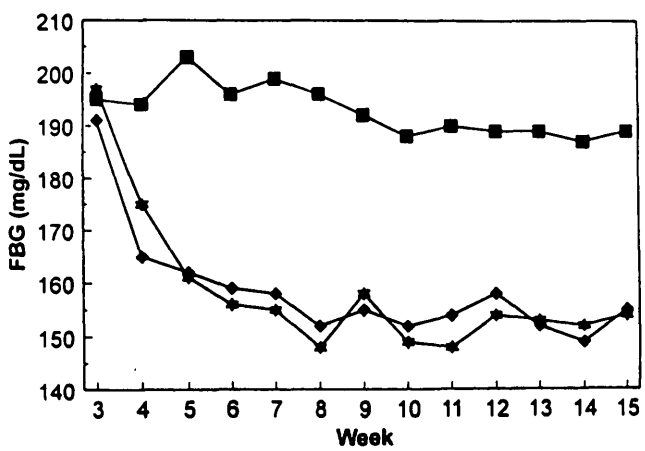

Figure 3—*Mean fasting blood glucose values obtained by fingerstick at weekly clinic visits in patients receiving placebo (■), 5 mg glipizide GITS (◆), or 20 mg glipizide GITS (★). n = 68 for each.*

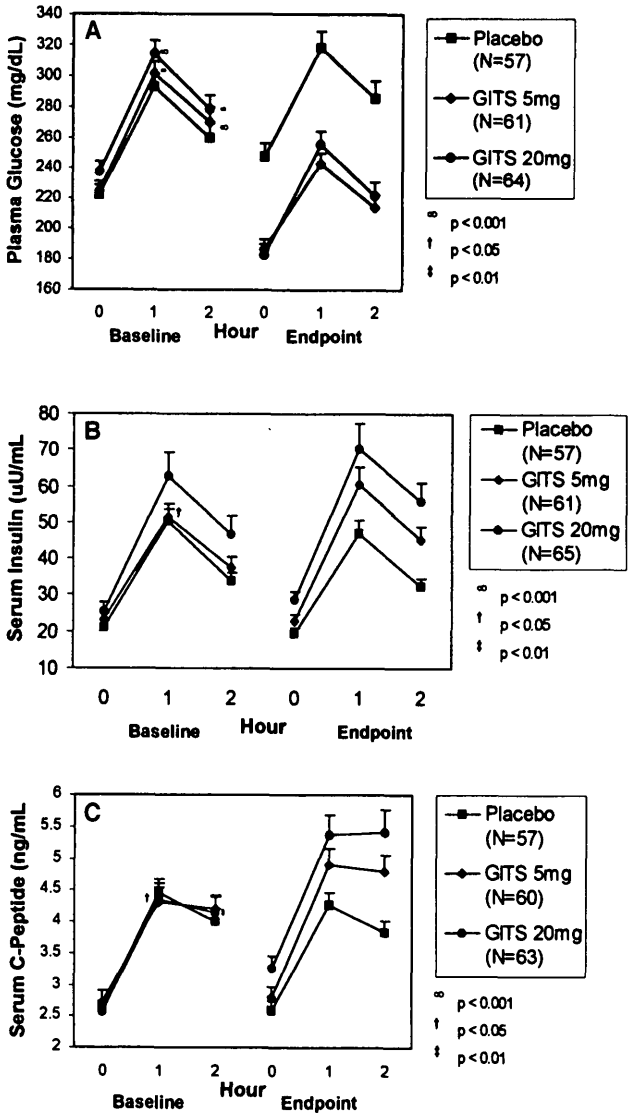

Figure 4—*Mean ± SE plasma glucose* (A), *serum insulin* (B), *and serum C-peptide* (C) *levels during Sustacal challenge at randomization and at the end of treatment for placebo* (■), *5-mg* (◆), *and 20-mg* (●) *doses of glipizide GITS.*

been treated with dietary therapy only and with immediate-release glipizide at entry. Compared with placebo, glipizide GITS significantly reduced mean FPG in patients whose prior therapy had been diet only (51 ± 31 vs. −42 ± 8 mg/dl in the placebo and glipizide GITS treatment groups, respectively; $P < 0.05$). In patients whose prior therapy had been immediate-release glipizide, the extended-release GITS formulation also significantly reduced mean FPG (65 ± 19 vs. −7 ± 9 mg/dl in the placebo and glipizide GITS treatment groups, respectively, $P < 0.01$) and mean HbA_{1c} (0.5 ± 0.2 vs. −1.2 ± 0.5% in the placebo and glipizide GITS treatment groups, respectively, $P < 0.01$).

Safety

The adverse events reported most often for glipizide GITS and placebo-treated patients, respectively, were: asthenia (10.1 vs. 13.0%), headache (8.6 vs. 8.7%), dizziness (6.8 vs. 5.8%), and diarrhea (5.4 vs. 0.0%). None were statistically significantly different from baseline except diarrhea ($P < 0.05$). Only eight of the 278 patients (2.9%) treated with glipizide GITS and none of the 69 patients receiving placebo experienced symptoms of hypoglycemia during the trial. There was no trend toward a higher incidence of adverse events, including hypoglycemia, with increasing glipizide GITS doses. Moreover, the overall incidence of adverse events for the glipizide GITS-treated patients was not significantly higher than that for the patients who received placebo.

The number of patients withdrawn from treatment due to adverse reactions was similar among all doses of glipizide GITS [5 mg ($n = 8$), 10 mg ($n = 3$), 15 mg ($n = 4$), 20 mg ($n = 4$), 40 mg ($n = 4$), and 60 mg ($n = 3$)]. By comparison, 21 (34%) of the placebo-treated patients discontinued treatment, most frequently because of excessive hyperglycemia.

Analysis of plasma lipid levels revealed no significant differences between placebo and pooled glipizide GITS–treated patients in the two trials. Total cholesterol decreased from 219 mg/dl at baseline to 214 mg/dl at final visit in the placebo group, and from 203 to 201 mg/dl in the glipizide GITS group. HDL cholesterol remained essentially unchanged during the study in the placebo groups (37 vs. 37 mg/dl) and in the pooled glipizide GITS group (37 vs. 36 mg/dl). Finally, triglycerides decreased from 168 to 154 mg/dl in the placebo group and from 178 to 176 mg/dl during glipizide GITS treatment.

There was no significant change in body weight during the course of the study in the pooled glipizide GITS–treated patients in the two trials (mean changes = −0.7 ± 0.6 and −0.3 ± 0.4 pounds, respectively. In contrast, body weight changed by −7.9 ± 1.3 and −6.9 ± 0.8 pounds in the placebo groups in the two trials ($P <$ 0.0001 versus pooled glipizide GITS), probably due to inadequate glycemic control.

CONCLUSIONS — The two multicenter trials reported here demonstrate that glipizide GITS produces and maintains significant reductions in FPG, HbA_{1c}, and PPG over a dose range of 5 mg to 60 mg in patients with NIDDM with very low rates of hypoglycemia. In addition to demonstrating the efficacy and safety of this new sustained release preparation of glipizide, these studies provide several important insights into the mechanism of action and clinical application of the drug.

First, dose-response analyses demonstrated a significant relationship between glipizide dose and the decrease in FPG and HbA_{1c}, with maximal efficacy achieved at 20 mg for FPG and at 5 mg for HbA_{1c}. Not only did higher doses fail to produce further therapeutic benefit, but the 60-mg dose actually produced moderately less improvement in HbA_{1c} and FPG than did the 20-mg dose. These results also were supported by phar-

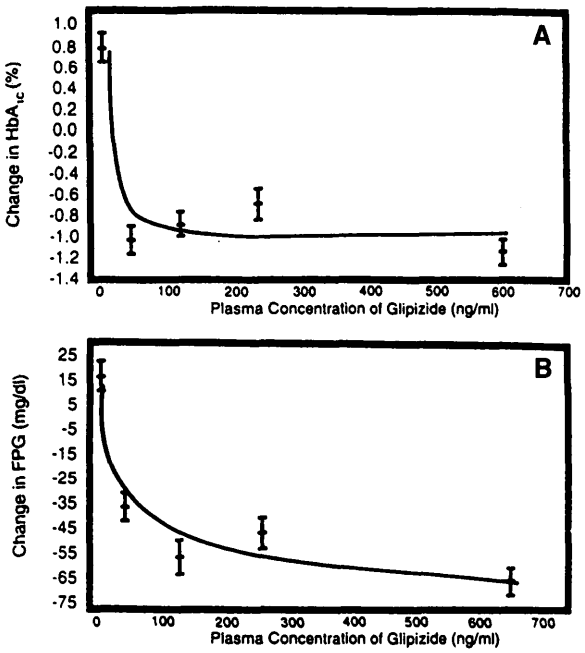

Figure 5—A: *Concentration-response curve for mean (± SE) change in HbA_{1c} within quintiles of plasma glipizide concentration for all patients in both studies. Plasma concentrations are the geometric means of each quintile. Observed and fitted mean changes in HbA_{1c} are adjusted for study and baseline differences.* n = *62, 59, 60, 63, and 63 for the lowest to highest quintile.* P < *0.0001 for overall treatment effect.* B: *Concentration-response curve for mean (± SE) change in FPG within quintiles of plasma glipizide concentration for all patients in both studies. Plasma concentrations are the geometric means of each quintile. Observed and fitted mean changes in FPG are adjusted for study and baseline differences.* n = *68, 62, 63, 63, and 63 for the lowest to highest quintile.* P < *0.0001 for overall treatment effect.*

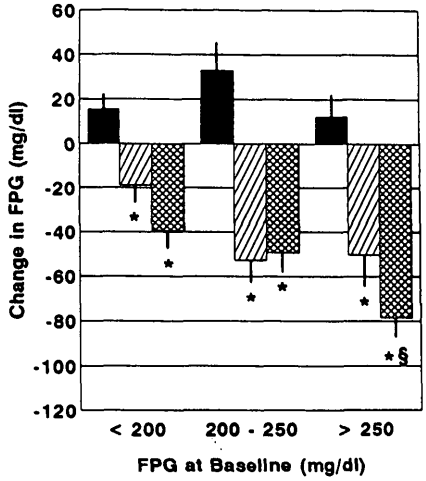

Figure 6—*Mean (± SE) change in FPG level from randomization to final visit in patients treated with placebo (solid bars), 5 mg (striped bars), and 20 mg (crosshatched bars) glipizide GITS stratified by baseline FPG.* *P < *0.001 versus placebo;* §P < *0.05 versus 5-mg dose.*

macodynamic analyses of plasma glipizide levels versus these indexes of glycemic control and are consistent with a previous observation for immediate-release glipizide (36,37), suggesting an optimal dosing "window" for oral sulfonylurea agents.

Whereas immediate-release glipizide has a maximum recommended dose of 40 mg per day in divided doses, the GITS preparation is maximally effective at 5–20 mg once daily, depending on the therapeutic parameter being measured. It is likely that the lower doses required with the GITS formulation are the result of the use of the extended-release system, which provides effective plasma concentration of glipizide over 24 h. In fact, plasma glipizide concentrations 24 h after administration of the 5-mg doses were ~50 ng/ml, well within the therapeutic range (25–100 ng/ml) previously proposed (21,38). Mean plasma glipizide levels 24 h after administration of the 20-mg dose were 250-300 ng/ml, which approximates the maximal therapeutic level of the drug (21,38). In addition, plasma levels of glipizide measured 24 h after dosing are significantly higher after glipizide GITS administration versus immediate release glipizide when using comparable total daily doses (39). On the basis of these results, glipizide GITS was approved for use in the U.S. for the treatment of NIDDM at a dose range of 5-20 mg.

It is important to emphasize that the process of delivering a shorter acting sulfonylurea like glipizide through a controlled release preparation does not make it therapeutically equivalent to a longer acting agent like glyburide. In previous studies, we directly compared intravenous infusions of glipizide and glibenclamide (glyburide) at comparable drug levels (~100–200 ng/ml) to demonstrate this pharmacodynamic difference between these agents (21). In that study, insulin secretion peaked within 10 min after glipizide administration and declined thereafter; however, glyburide produced a sustained elevation of insulin and C-peptide over the 2-h period of study (21). This is consistent with our findings in the current study in which postprandial insulin or C-peptide secretion was enhanced at most glipizide GITS doses levels up to 20 mg, whereas fasting plasma insulin levels were generally not significantly different from placebo in this dose range.

In this study, the maximal benefit in HbA_{1c} was achieved at the lowest dose studied (5 mg), whereas a dose-response relationship up to 20 mg was observed for FPG. We believe that our inability to detect a greater dose-response relationship in HbA_{1c} was probably due to the relatively short time period of treatment (8 weeks) at each assigned dose. These results were not unexpected. FPG primarily measures hepatic glucose production, which is reduced over a short period by glipizide GITS (40). Therefore, a dose-response relationship can be generated with regard to this parameter over a short time period. In contrast to this, HbA_{1c} reflects the mean average glycemia over a 3- to 4-month period and incorporates both fasting and postprandial measurements. Therefore, changes in HbA_{1c} that correspond to the changes in FPG may not have been measurable given the study duration and design.

Comparison of the present results with those from a 1990 study by Jaber et al. (43) also suggests that glipizide GITS may provide glycemic control superior to that achieved with immediate-release glipizide. These investigators showed that administration of immediate-release glipizide (up to 20 mg b.i.d.) significantly reduced PPG and bedtime blood glucose but did not significantly decrease fasting preprandial glucose, whereas glyburide reduced all three at the same doses. In the two trials we report here, 5-mg or higher doses of glipizide GITS administered once daily signifi-

cantly decreased both FPG and HbA_{1c}. Thus, glipizide GITS may be more potent on a dose-for-dose basis than immediate release glipizide. This question was recently addressed more directly in a study by Berelowitz et al. (39) who compared immediate-release glipizide with glipizide GITS in a 16-week 2-way crossover trial that included 132 randomized patients. After 8 weeks of treatment on each drug, FPG was significantly lower with once-daily glipizide GITS than with once- or twice-daily immediate-release glipizide administered in the same total daily dose, whereas HbA_{1c} levels were comparable. Fasting insulin and C-peptide levels were either comparable or statistically lower with glipizide GITS versus immediate-release glipizide. Glipizide GITS also produced the same reduction in PPG as immediate-release glipizide with a significantly lower increase in postprandial insulin and C-peptide. These findings are supported by the results of another study in which glipizide GITS produced comparable reductions in FPG to those seen following glyburide therapy at the same doses, with lower fasting insulin levels in glipizide GITS–treated patients (42).

Several other aspects of the results obtained in the present trials suggest important differences between the efficacy of glipizide GITS and immediate-release glipizide. Lebovitz (28) summarized results from three studies in which immediate-release glipizide was used for the treatment of patients with NIDDM. His analysis of the combined results indicated that glipizide was less effective in patients with severe NIDDM (prestudy FPG >250 mg/dl) than in patients with milder degrees of fasting hyperglycemia. However, in the present trials, glipizide GITS produced a greater absolute reduction (and a comparable percentage reduction) in both FPG and HbA_{1c} in patients with the most severe fasting hyperglycemia, suggesting that the controlled release formulation may be of particular benefit in these poorly controlled patients. Thus, with regard to therapeutic efficacy, glipizide GITS exhibits characteristics similar to the biguanide, metformin, which also has been reported to produce the greatest reductions in FPG levels and HbA_{1c} in the patients with the most severe hyperglycemia (44).

Glipizide GITS also demonstrated efficacy in patients of varying demographic characteristics. Although previous studies have shown that immediate-release glipizide and other sulfonylureas may be less effective in patients <60 years of age than in older patients (45), the present trial suggests that the GITS formulation is comparably effective in reducing FPG and HbA_{1c} in younger (<65 years of age) and older (≥65 years of age) individuals with NIDDM without increasing the risk of hypoglycemia. Safe and effective treatment for NIDDM in older patients is an important issue, because it has been estimated that 12–15% of the population in the U.S. >60 years old has NIDDM, and this population may be at the greatest risk for the adverse consequences of hypoglycemia (46–51).

It is widely believed that sulfonylurea treatment is less likely to be effective in patients with long-standing NIDDM than in recently diagnosed patients. This most likely results from progressive decline in β-cell function with advancing disease, although some investigators have suggested that desensitization of the insulin secretory response to repeated exposure to the sulfonylurea also may contribute (52–54). Although the current study was not of sufficient duration to address these questions, preliminary data from a long-term extension of the present trial indicate that significant reductions in FPG and HbA_{1c} are maintained over the course of 1 year (Pfizer Inc., unpublished observations). In addition, the results of this study clearly indicate that glipizide GITS produced comparable and significant reductions in both HbA_{1c} and FPG in patients with NIDDM for <5 years, 5–10 years, and >10 years duration.

Certain ethnic and racial groups in the U.S.—including African-Americans, Hispanics, and Native Americans—have a particularly high prevalence of NIDDM. In the present study, 23% of the population was comprised of racial and ethnic minority groups, and there was no difference in efficacy when compared with white patients. Similarly, obesity is also a well-known risk factor for NIDDM, and the current results suggest that glipizide GITS produces comparable efficacy in both lean and obese patients.

During both clinical trials, glipizide GITS was as well tolerated as the placebo. Most importantly, it was associated with a very low incidence of hypoglycemia, an adverse event that is seen with both immediate-release glipizide and other oral hypoglycemic medications (26,56). Recent studies indicate a lack of hypoglycemic events with glipizide GITS administration in fasting elderly patients (57) as well as in patients who skip breakfast and exercise (58). The tolerability of glipizide GITS may be related to the slow and predictable release of drug from the GITS tablet. This formulation avoids the high peak concentrations associated with immediate-release glipizide tablets and adverse events, most notably hypoglycemia, that have been associated with high plasma drug levels. The tolerability of glipizide GITS is important, since adverse reactions to therapy have been cited as a major reason for failure of oral hypoglycemic agents in patients with NIDDM (59).

In summary, the results of the present trials indicate that glipizide GITS is safe and produces significant reductions in FPG, HbA_{1c}, and PPG in doses as low as 5 mg in patients with NIDDM. The GITS formulation avoids the high plasma drug concentrations associated with immediate-release glipizide. The once-daily dosing of this preparation also may improve patient compliance. Because recent epidemiological and prospective studies suggest that tight control of plasma glucose in patients with NIDDM is likely to have benefits in reducing microvascular complications similar to those observed in patients with IDDM (60–62) and may also reduce the risk of macrovascular disease (63), an oral hypoglycemic agent that can significantly reduce HbA_{1c} and FPG and that does not cause weight gain or adversely effect lipids is a useful adjunct to dietary control and regular exercise in achieving such control in patients with NIDDM.

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APPENDIX

Glipizide GITS Study Group Investigators

Principal Investigator: Donald C. Simonson, MD, Joslin Diabetes Center, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Stephen Aronoff, MD, FACP, Endocrine Associates of Dallas, Dallas, TX; Lawrence Blonde, MD, Ochner Clinic, New Orleans, LA; William Cefalu,

MD, Endocrine Section, Department of Internal Medicine, Bowman Gray School of Medicine, Winston-Salem, NC; Stephen Clement, MD, Endocrine Metabolic Service, Walter Reed Army Medical Center, Washington, DC; Mark Feinglos, MD, Duke University, Durham, NC; Craig Greenberg, MD, Northwest Research Associates, Portland, OR; Seymour Levin, MD, West Los Angeles VA Medical Center, Los Angeles, CA; Charles P. Lucas, MD, Beaumont Hospital, Birmingham, MI; Charles Macy, MD, Lansdale Medical Group, Lansdale, PA; J. Manning, MD, Northwest Research Associates, Portland, OR; Thomas C. Marbury, MD, Orlando Clinical Research Center, Orlando, FL; Dr. Michael J. McAdams, Sacramento, CA; Nicholas H. E. Mezitis, MD, Division of Endocrinology, Diabetes & Nutrition, St. Luke's/Roosevelt Hospital Center, New York, NY; Samuel Miller, MD, Clinical Research Center, San Antonio, TX; Douglas Owens, MD, Greer, SC; Dr. Jeffrey Sandler, Center for Stress Studies, San Diego, CA; Sherwyn L. Schwartz, MD, Diabetes and Glandular Disease Clinic, San Antonio, TX; Harry Shamoon, MD, Montefiore Medical Center, Bronx, NY; Jay Sosenko, MD, Jackson Memorial Hospital, Miami, FL; Laurence Yellen, MD, San Diego, CA.

References

1. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM. *Diabetes Care* 15:318–368, 1992
2. Yki-Järvinen H: Pathogenesis of non-insulin-dependent diabetes mellitus. *Lancet* 343:91–95, 1994
3. Reaven GM: Effect of glipizide treatment on various aspects of glucose, insulin, and lipid metabolism in patients with noninsulin-dependent diabetes mellitus. *Am J Med* 75 (Suppl. 5B):8–14, 1983
4. Feinglos MN, Lebovitz HE: Long-term safety and efficacy of glipizide. *Am J Med* 75 (Suppl. 5B):60–66, 1983
5. Lebovitz HE: Clinical utility of oral hypoglycemic agents in the management of patients with noninsulin-dependent diabetes mellitus. *Am J Med* 75 (Suppl. 5B):94–99, 1983
6. Gerich JE: Oral hypoglycemic agents. *N Engl J Med* 321:1231–1245, 1989
7. Kennedy DL, Piper JM, Baum C: Trends in use of oral hypoglycemia agents 1964–1986. *Diabetes Care* 11:558–562, 1988
8. Greenfield MS, Doberne L, Rosenthal M, Schulz B, Widstrom A, Reaven GM: Effect of sulfonylurea treatment on in vivo insulin secretion and action in patients with non-insulin-dependent diabetes mellitus. *Diabetes* 31:307–312, 1982
9. Pfeifer MA, Halter JB, Judzewitsch RG, Beard JC, Best JD, Ward WK, Porte D Jr: Acute and chronic effects of sulfonylurea drugs on pancreatic islet function in man. *Diabetes Care* 7 (Suppl. 1):25–34, 1984
10. Groop LC, Ratheiser K, Luzi L, Melander A, Simonson DC, Petrides A, Bonadonna RC, Widén E, DeFronzo RA: Effect of sulfonylurea on glucose-stimulated insulin secretion in healthy and non-insulin-dependent diabetic subjects: a dose-response study. *Acta Diabetol* 28:162–168, 1991
11. Ravanam A, Jeffery J, Nehlawi M, Abraira C: Improvement of glucose-primed intravenous glucose tolerance and correction of acute insulin decrement by glipizide in type II diabetes. *Metabolism* 40:1173–1177, 1991
12. Bitzen PO, Melander A, Schersten B, Svensson M, Wåhlin-Boll E: Long-term effects of glipizide on insulin secretion and blood glucose control in patients with non-insulin-dependent diabetes mellitus. *Eur J Clin Pharmacol* 42:77–83, 1992
13. Groop LC: Sulfonylureas in NIDDM. *Diabetes Care* 15:737–754, 1992
14. Groop P-H, Melander A, Groop LC: The acute effect of preprandial exogenous and endogenous sulfonylurea-stimulated insulin secretion on postprandial glucose excursions in patients with type II diabetes. *Diabet Med* 10:633–637, 1993
15. Birkeland KI, Furuseth K, Melander A, Mowinckel P, Vaaler S: Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide. Glycemic control and insulin secretion during 15 months. *Diabetes Care* 17:45–49, 1994
16. Ipp E, Cortez C, Bergner A, Fischette C, Lee W-NP: Glipizide GITS inhibits hepatic glucose production in NIDDM. *Program and Abstracts of the 77th Annual Meeting of the Endocrine Society* 77:545, 1995
17. Cefalu WT, Bell-Farrow AD, Wang ZQ, McBride DG, Stegner J, Dalgleish DC, Morgan TM, Fischette CF: Insulin sensitivity in vivo is improved after glipizide GITS treatment (Abstract). *Diabetes* 44 (Suppl. 1): 107A, 1995
18. Lebovitz HE, Feinglos MN: Mechanism of action of the second-generation sulfonylurea glipizide. *Am J Med* 75 (Suppl. 5B):46–54, 1983
19. DeFronzo RA, Simonson DC: Oral sulfonylurea agents suppress hepatic glucose production in non-insulin-dependent diabetic individuals. *Diabetes Care* 7 (Suppl. 1):72–80, 1984
20. Simonson DC, Ferrannini E, Bevilacqua S, Smith D, Barrett E, Carlson R, DeFronzo RA: Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 33:838–845, 1984
21. Groop L, Luzi L, Melander A, Groop P-H, Ratheiser K, Simonson DC, DeFronzo RA: Different effects of glyburide and glipizide on insulin secretion and hepatic glucose production in normal and NIDDM subjects. *Diabetes* 36:1320–1328, 1987
22. Groop L, Barzilai N, Ratheiser K, Luzi L, Wåhlin-Boll E, Melander A, DeFronzo RA: Dose-dependent effects of glyburide on insulin secretion and glucose uptake in humans. *Diabetes Care* 14:724–727, 1991
23. Wåhlin-Boll E, Alméer L-O, Melander A: Bioavailability, pharmacokinetics and effects of glipizide in type II diabetics. *Clin Pharmacokinet* 7:363–372, 1982
24. Feldman JM: Glyburide: a second generation sulfonylurea hypoglycemic agent. History, chemistry, metabolism, pharmacokinetics, clinical use, and adverse events. *Pharmacotherapy* 5:43–62, 1985
25. Jaspan JB: Monitoring and controlling the patient with non-insulin-dependent diabetes mellitus. *Metabolism* 36 (Suppl. 1):22–27, 1987
26. Drentz AJ, Ferner RE, Bailey CJ: Comparative tolerability profiles of oral antidiabetic agents. *Drug Saf* 11:223–241, 1994
27. Melander A, Wåhlin-Boll E: Clinical pharmacology of glipizide. *Am J Med* 75 (Suppl. 5B):41–45, 1983
28. Lebovitz HE: Glipizide: a second generation sulfonylurea hypoglycemic agent. Pharmacology, pharmacokinetics, and clinical use. *Pharmacotherapy* 5:63–77, 1985
29. Groop L, Wåhlin-Boll E, Groop PH, Totterman KJ, Melander A, Tolppanen EM, Fyhrqvist F: Pharmacokinetics and metabolic effects of glibenclamide and glipizide in type II diabetics. *Eur J Clin Pharmacol* 28:697–704, 1985
30. Ahren B, Lundquist I, Schersten B: Effects of glipizide on various consecutive insulin secretory stimulations in patients with type II diabetes. *Diabetes Res* 3:293–300, 1986
31. Melander A: Clinical pharmacology of sulfonylureas. *Metabolism* 36 (Suppl. 1):12–16, 1987
32. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR: The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 150:1881–1884, 1990
33. Botelho RJ, Dudrak R II: Home assessment of adherence to long-term medication in the elderly. *J Fam Pract* 35:61–65, 1992
34. Swanson DR, Barclay BL, Wong PSL, Theeuwes F: Nifedipine gastrointestinal therapeutic system. *Am J Med* 83 (Suppl. 6B):3–9, 1987
35. Emilsson H: High-performance liquid chromatographic determination of glipizide in human plasma and urine. *J Chromatogr* 421:319–326, 1987
36. Wåhlin-Boll E, Sartor G, Melander A, Scherstén B: Impaired effect of sulfonylurea following increased dosage. *Eur J Clin Phar-*

macol 22:21–25, 1982
37. Stenman S, Melander A, Groop P-H, Groop LC: What is the benefit of increasing the sulfonylurea dose? *Ann Intern Med* 118:169–172, 1993
38. Groop L, Groop P-H, Stenman S, Saloranta C, Tötterman K-J, Fyhrqvist F, Melander A: Comparison of pharmacokinetics, metabolic effects and mechanisms of action of glyburide and glipizide during long-term treatment. *Diabetes Care* 10:671–678, 1987
39. Berelowitz M, Fischette C, Cefalu W, Schade DS, Sutfin T, Kourides I: Comparative efficacy of a once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care* 17:1460–1464, 1994
40. Berelowitz M, Go E: Contrasting influences of glipizide GITS on fasting and post-Sustacal Glycemia, glucose production, and 24-h glucose/insulin profiles in NIDDM. *Diabetes* 45 (Suppl. 2):258A, 1996
41. Tahara Y, Shima K: The response of GHb to stepwise plasma glucose change over time in diabetic patients. *Diabetes Care* 16:1313–1314, 1993
42. Burge MR, Schmitz K, Tive L, Schade DS: Epinephrine is the mechanism of protection against sulfonylurea-induced hypoglycemia in fasted NIDDM patients. *Diabetes* 42 (Suppl. 2):61A, 1996
43. Jaber LA, Wenzloff NJ, Komanicky P: An evaluation of the therapeutic effects and dosage equivalence of glyburide and glipizide. *J Clin Pharmacol* 30:181–188, 1990
44. DeFronzo RA, Goodman AM, and the Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995
45. Kradjan WA, Kobayashi KA, Bauer LA, Horn JR, Opheim DE, Wood FJ: Glipizide pharmacokinetics: effects of age, diabetes, and multiple dosing. *J Clin Pharmacol* 29:1121–1127, 1989
46. Lipson LG, Lipson M: The therapeutic approach to the obese maturity-onset diabetic patient. *Arch Intern Med* 144:135–138, 1984
47. Lipson LG: Diabetes in the elderly: diagnosis, pathogenesis and therapy. *Am J Med* 80 (Suppl. 5A):10–21, 1986
48. Wilson PWF, Anderson KM, Kannel WB: Epidemiology of diabetes mellitus in the elderly. *Am J Med* 80 (Suppl. 5A):3–9, 1986
49. Peters AL, Davidson MB: Use of sulfonylureas in older diabetic patients. *Clin Geriatr Med* 6:903–921, 1990
50. Rosenstock J, Corrao PJ, Goldberg RB, Kilo C: Diabetes control in the elderly: a randomized, comparative study of glyburide versus glipizide in non-insulin-dependent diabetes mellitus. *Clin Ther* 15:1031–1040, 1993
51. Rouff G: The management of non-insulin-dependent diabetes mellitus in the elderly. *J Fam Pract* 36:329–335, 1993
52. Karam JH, Sanz N, Salamon E, Nolte MS: Selective unresponsiveness of pancreatic β-cells to acute sulfonylurea stimulation during sulfonylurea therapy in NIDDM. *Diabetes* 35:1314–1320, 1986
53. Grunberger G: Maintenance of sulfonylurea responsiveness in NIDDM. Randomized double-blind study of intermittent glyburide therapy. *Diabetes Care* 15:696–699, 1992
54. McIntyre HD, Ma A, Bird DM, Patterson CA, Cameron DP: Chronic sulfonylurea therapy augments basal and meal-stimulated insulin secretion while attenuating insulin responses to sulfonylurea per se. *Diabetes Care* 15:1534–1540, 1992
56. Widom B, Simonson DC: Iatrogenic hypoglycemia. In *Joslin's Diabetes Mellitus*. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Lea & Febiger, 1994, p. 489–507
57. Burge MR, Schmitz KL, Reinhardt E, Fischette C, Schade DS: Does fasting cause hypoglycemia in elderly NIDDM patients on glipizide GITS or glyburide? (Abstract). *Diabetes* 44 (Suppl. 1):109A, 1995
58. Riddle M, McDaniel P: Glipizide GITS does not increase the hypoglycemic effect of missing breakfast and mildly exercising (Abstract). *Diabetes* 44 (Suppl. 1):107A, 1995
59. Brodows RG: Benefits and risks with glyburide and glipizide in elderly NIDDM patients. *Diabetes Care* 15:75–80, 1992
60. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
61. Ohkubu Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28: 103–117, 1995
62. Klein R, Klein BEK, Moss SE, Cruickshanks KJ: Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. *Arch Intern Med* 154: 2169–2178, 1994
63. Kuusisto J, Mykkanen L, Pyorala K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994