Comparative Efficacy of a Once-Daily Controlled-Release Formulation of Glipizide and Immediate-Release Glipizide in Patients With NIDDM

MICHAEL BERELOWITZ, MD
CHRISTINE FISCHETTE, PHD
WILLIAM CEFALU, MD
DAVID S. SCHADE, MD
TAMARA SUTFIN, PHD
IONE A. KOURIDES, MD

OBJECTIVE — To compare the efficacy and safety of controlled-release glipizide (glipizide-GITS [gastrointestinal therapeutic system]) and immediate-release glipizide in patients with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS — In a multicenter, open-label, randomized, two-way crossover study, 132 patients with NIDDM received daily doses of 5, 20, or 40 mg of either glipizide-GITS or immediate-release glipizide for 8 weeks followed by 8 weeks of the alternate formulation. Plasma glucose, serum insulin, C-peptide, and plasma glipizide levels were measured at fasting and post-Sustacal challenge at the end of 1 and 8 weeks of each treatment phase. HbA_{1c} was measured at the end of weeks 7 and 8 of each treatment phase.

RESULTS — Both formulations of glipizide yielded similar mean HbA_{1c} values. However, mean fasting plasma glucose (FPG) levels were significantly lower with glipizide-GITS treatment than with immediate-release glipizide at the end of week 1 (11.0 vs. 11.6 mmol/l; $P < 0.01$) and at the end of the 8-week treatment phase (10.9 vs. 11.7 mmol/l; $P < 0.001$). Fasting insulin and C-peptide levels were lower after 5 mg glipizide-GITS vs. immediate-release glipizide. Glucose responses to Sustacal were similar after both formulations of glipizide; however, serum insulin ($P < 0.01$) and C-peptide responses ($P < 0.05$) were lower with glipizide-GITS than with immediate-release glipizide treatment at the end of the 8-week treatment phase. Mean plasma glipizide concentrations were stable by the end of week 1, and the concentrations increased proportionately with dose. Once-daily Glipizide-GITS provided effective mean glipizide concentrations (>50 ng/ml) 24 h after dosing, even at the lowest (5 mg) dose level. Both formulations were well tolerated.

CONCLUSIONS — Glipizide-GITS was significantly more effective than immediate-release glipizide in reducing FPG levels. Both formulations reduced postprandial plasma glucose levels equally; however, glipizide-GITS exerted its control in the presence of lower plasma glipizide concentrations in addition to significantly lower insulin and C-peptide levels. This suggests that glipizide-GITS improves insulin sensitivity.

From the Division of Endocrinology and Metabolism, SUNY at Stony Brook, Stony Brook, New York; Bowman Gray School of Medicine, Winston-Salem, North Carolina; University of New Mexico School of Medicine, Albuquerque, New Mexico; and Pfizer, New York, New York.

Address correspondence and reprint requests to Michael Berelowitz, MD, Division of Endocrinology and Metabolism, HSC 15th Floor, Room 060, SUNY at Stony Brook, Stony Brook, NY 11794.

Received for publication 4 April 1994 and accepted in revised form 7 July 1994.

NIDDM, non-insulin-dependent diabetes mellitus; GITS, gastrointestinal therapeutic system; FBG, fasting blood glucose; CV, coefficient of variation; HPLC, high-performance liquid chromatography; FPG, fasting plasma glucose; AUC, area under the curve.

Pathogenesis of non-insulin-dependent diabetes mellitus (NIDDM) involves both inadequate insulin secretion and insulin resistance (1). Treatment has been aimed at correcting the metabolic abnormalities with diet and exercise so as to restore insulin sensitivity and to reduce hyperglycemia. Pharmacological agents are administered only if diet and exercise fail.

Oral hypoglycemic agents represent the most commonly used pharmacological approach to the treatment of NIDDM. Glipizide, a second generation sulfonylurea, is rapidly absorbed, achieves high peak blood concentrations within 1–3 h after administration, and has a half-life of 2–4 h. It is administered two to three times daily in ~45% of patients (2). To provide a once-daily formulation, the controlled-release technology of the gastrointestinal therapeutic system (GITS) (Alza, Mountain View, CA) has been applied to glipizide (3).

Sulfonylureas exert their effects by improving insulin secretion, particularly after meals. Extrapancreatic effects of sulfonylureas on metabolically responsive tissues remain controversial. The present study compares the actions of controlled-release glipizide (glipizide-GITS) with immediate-release glipizide in patients with NIDDM previously maintained on low-, intermediate-, or high-dose second generation sulfonylurea therapy. End points were fasting and post-Sustacal glucose, insulin, C-peptide levels, and HbA_{1c} as a measure of overall metabolic control.

RESEARCH DESIGN AND METHODS

— The efficacy of glipizide-GITS (Glucotrol XL, Pfizer) and immediate-release glipizide was compared in nine centers throughout the U.S. (see APPENDIX) in 132 patients: 64 women and 68 men, 31–75 years of age, with a diagnosis of NIDDM made at least 6 months before study entry. All patients had previously been maintained on immediate-release glipizide or glyburide at a stable dose for at least 2 months (Tables 1 and 2).

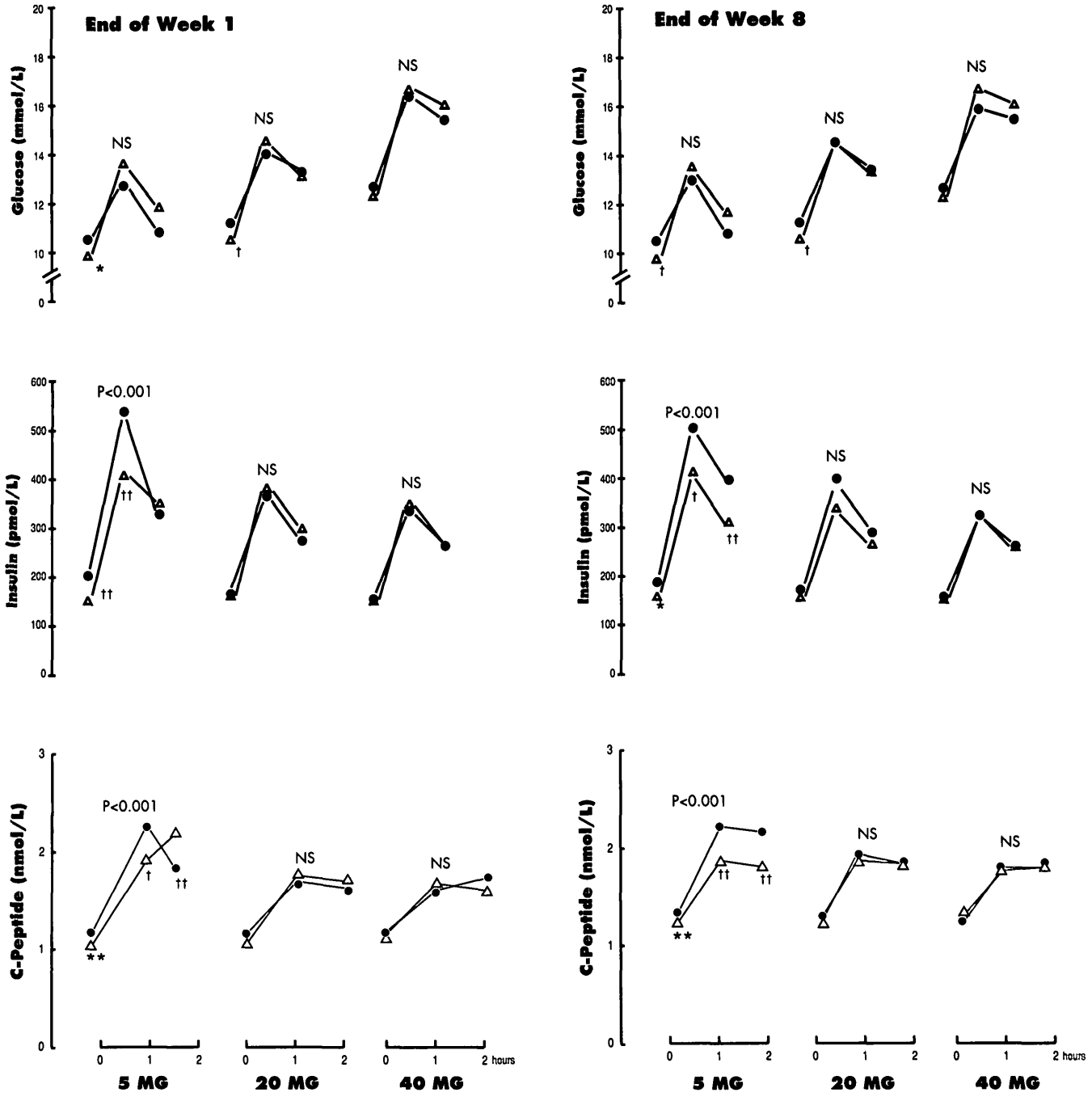

Figure 1—*Mean plasma glucose (top), serum insulin (middle), and serum C-peptide (bottom) levels before, 1 h, and 2 h post-Sustacal after 1 and 8 weeks of immediate-release glipizide (●) or glipizide-GITS (△) therapy. FPG concentrations were lower in glipizide-GITS–treated subjects after 5 and 20 mg. There was no significant difference in the glucose levels post-Sustacal between treatments by dose or overall. Insulin and C-peptide levels were significantly lower at all time points after 1 and 8 weeks of treatment with 5 mg glipizide-GITS than after immediate-release glipizide.* *P < 0.05; †P < 0.005; ††P < 0.001; **P < 0.01.

Upon entering the study, patients were randomly assigned to either immediate-release glipizide or glipizide-GITS treatment for 8 weeks and then crossed over to the other drug for an additional 8 weeks. Patients were assigned to one of three dose groups (low: 5 mg, previous dosing <7.5 mg glyburide or <10 mg immediate-release glipizide; intermediate: 20 mg, previous dosing 7.5–15 mg glyburide or 10–20 mg glipizide; high: 40 mg, previous dosing >15 mg glyburide

Table 1—*Patient baseline data*

	5 mg	20 mg	40 mg	Overall
n	50	44	38	132
Age (years)	58.2 ± 11	60.5 ± 9	50.6 ± 11	59.0 ± 10
Weight (kg)				
Men	92.6 ± 13.2	88.8 ± 13.2	91 ± 13.2	90.7 ± 13.2
Women	85.9 ± 16.4	86 ± 20.5	80.1 ± 14.5	83.9 ± 16.8
Duration of diabetes (years)	5.7 ± 6	8.5 ± 6	8.8 ± 5	7.5 ± 6
HbA_{1c} (%)	7.6 ± 1	8.2 ± 1	9.0 ± 1	8.2 ± 1
FPG (mmol/l)	9.8 ± 2.3	10.4 ± 2.1	12.5 ± 2.5	10.8 ± 2.5
Insulin (pmol/l)	166.2 ± 204	164.4 ± 114	148.8 ± 84	160.2 ± 144
C-peptide (nmol/l)	1.1 ± 0.7	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3

Data are means ± SD.

or >20 mg glipizide). The 20- and 40-mg doses of immediate-release glipizide were given twice a day. Plasma glucose, serum insulin, and serum C-peptide levels were measured fasting and after 8 oz. of Sustacal at the end of weeks 1 and 8 of both treatment phases. HbA_{1c} was measured at the end of weeks 7 and 8 of both treatment phases. Plasma glipizide concentrations were measured before, during, and 24 h after Sustacal challenge.

At the end of the second treatment phase, patients whose fasting blood glucose (FBG) differed by >20% from their FBG at the end of the first treatment phase had the option of increasing or decreasing their medication dose by 5 or 10 mg at weekly intervals for 2 weeks, as long as the daily dose of immediate-release glipizide did not exceed 40 mg and that of glipizide-GITS did not exceed 60 mg.

All adverse reactions during the study, whether attributed to study medications or not, were recorded. Blood glucose concentrations were measured by a One Touch glucose monitor (Lifescan, Milpitas, CA) at weekly clinical visits. In addition, patients measured their blood glucose levels at home three times a week in the morning (fasting) and at bedtime.

Assays

Plasma glucose concentrations were determined by the glucose oxidase method using an automated Hitachi 737 glucose analyzer (Hazleton, Vienna, VA); the interassay coefficient of variation (CV) was 1.3%. Serum insulin and C-peptide levels were measured by radioimmunoassay (Hazleton, Vienna, VA) using commercial kits (INCSTAR, Stillwater, MN) (CV 8.9% for insulin and 13.1% for C-peptide). HbA_{1c} was measured (SciCor, Indianapolis, IN) using ion exchange high-performance liquid chromatography (HPLC) (CV 1.5%). Plasma glipizide concentrations were determined by HPLC (Hazleton, Madison, WI) (CV 7.6% or better at all concentrations tested).

Statistical analysis

The efficacy variables were analyzed comparatively among treatments and doses using three-way analysis of variance procedures that included study site, treatment, and dose, along with the interactions of these factors in the statistical model and with patients randomized within the site by dose interaction. Separate analyses were performed for the end of weeks 1 and 8. Examination of a preliminary model demonstrated that effects of treatment sequence and study phase were negligible.

RESULTS — All 132 patients who entered the study and received drugs were eligible for safety analysis; 123 patients (93%) completed both treatment phases and were eligible for efficacy analysis. Overall, mean fasting plasma glucose (FPG) levels were significantly lower during glipizide-GITS than during immediate-release glipizide treatment at the end of week 1 (11.0 vs. 11.6 mmol/l; $P < 0.01$) and week 8 (10.9 vs. 11.7 mmol/l; $P < 0.001$). After both week 1 and week 8, FPG was significantly reduced with glipizide-GITS treatment compared with immediate-release glipizide at 5 mg ($P < 0.01$ and $P < 0.005$) and 20 mg ($P < 0.005$ and $P < 0.005$).

There were no significant differences between glipizide-GITS and immediate-release glipizide in overall mean fasting serum insulin or C-peptide concentration or post-Sustacal glucose re-

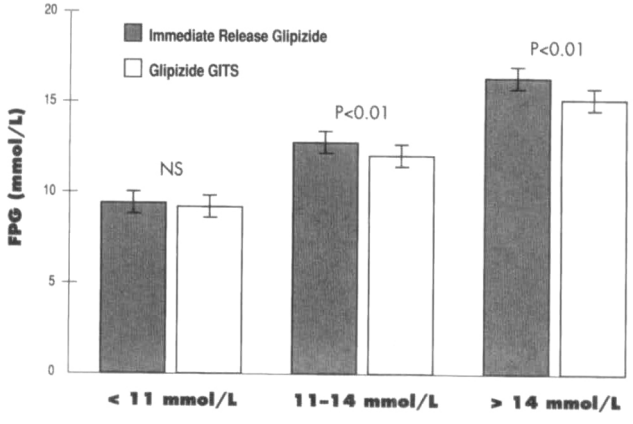

Figure 2—*Subanalysis of mean FPG levels at the end of each phase stratified by FPG after immediate-release glipizide treatments with all patients combined. FPG concentrations were lower in glipizide-GITS–treated patients, significantly so in those with glucose levels ≥11 mmol/l.*

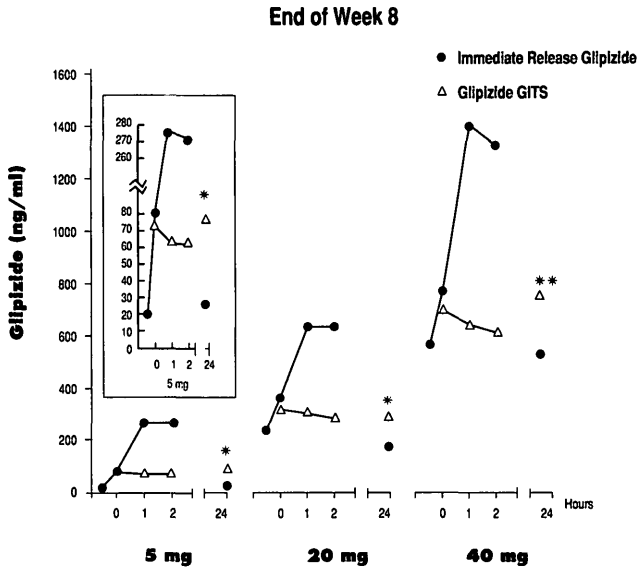

Figure 3—*Mean plasma glipizide concentrations 30 min before, immediately before, and 1 h, 2 h, and 24 h post-Sustacal after 8 weeks of immediate-release glipizide or glipizide-GITS therapy. Sustacal administration in 5, 20, and 40-mg increments is represented on the x-axis. *P < 0.001; **P < 0.01.*

sponses (area under the curve [AUC]); however, the insulin AUC was significantly lower after 5 mg of glipizide-GITS treatment at the end of weeks 1 ($P < 0.001$) and 8 ($P < 0.001$) (Fig. 1). In the 5-mg treatment group, serum insulin levels (during week 1 and week 8, respectively) at fasting ($P < 0.001$ and $P < 0.01$), 1 h ($P < 0.001$ and $P < 0.005$), and 2 h (NS and $P < 0.001$) after Sustacal were lower after glipizide-GITS treatment. After Sustacal, the C-peptide AUC (Fig. 1) was significantly lower after 5 mg of glipizide-GITS treatment both at the end of week 1 ($P < 0.001$) and week 8 ($P < 0.001$). Serum C-peptide levels (during week 1 and week 8, respectively) at fasting ($P < 0.05$ and $P < 0.05$), 1 h ($P < 0.005$ and $P < 0.001$), and 2 h ($P < 0.001$ [week 8 only]) after Sustacal were lower after 5 mg of glipizide-GITS treatment.

A subanalysis to assess whether glipizide-GITS is effective in patients with the most poorly controlled NIDDM showed glipizide-GITS to be more effective than immediate-release glipizide in patients with FPG ≥11 mmol/l, but equivalent in those with FPG <11 mmol/l (Fig. 2).

No significant differences in HbA_{1c} levels were observed between treatments in any dose group or overall at the end of each 8-week treatment phase.

Peak plasma glipizide concentrations occur 1–3 h after dosing with immediate-release glipizide (Fig. 3). After glipizide-GITS, there is a 2- to 3-h lag time before the concentrations begin to increase with maximum plasma glipizide levels 8–12 h after dosing, then a gradual return to pre-dose (Fig. 3). Statistically significant increases in plasma glipizide concentrations were observed 24 h after dosing with glipizide-GITS compared with immediate-release glipizide at the 5-mg dose (74.7 ± 52.3 vs. 28.2 ± 53.1; $P < 0.001$), 20-mg dose (287 ± 190 vs. 183 ± 198; $P < 0.001$), and 40-mg dose (745 ± 748 vs. 575 ± 873; $P < 0.01$).

Only 12 (10%) of the 123 patients who completed the study required a dose adjustment at the end of the second treatment phase because their FBG differed by >20% from the end of the first-phase levels.

Only one patient discontinued the study, because of an episode of hypoglycemia (FPG of 2.44 mmol/l); this patient was receiving 5 mg of glipizide-GITS daily. The incidence of adverse experiences was similar and low during treatment with both glipizide preparations.

CONCLUSIONS — This study compared the efficacy of glipizide in its present immediate-release form with the new, once-daily, controlled-release (GITS) formulation in 132 patients with NIDDM using a two-way crossover design.

Glipizide-GITS lowered FPG to a significantly greater degree than did immediate-release glipizide in the 5- and

Table 2—*Number of patients*

	5 mg	20 mg	40 mg	Overall
Age				
<65 years	34	27	27	88
≥65 years	16	17	11	44
Sex				
Men	24	28	16	68
Women	26	16	22	64
Race				
White	34	30	28	92
Black	7	8	4	19
Other	9	6	6	21
Previous drug				
Glipizide	15	18	15	48
Glyburide	35	26	23	84

20-mg dosage groups. This was associated with higher fasting plasma glipizide levels after glipizide-GITS and likely reflects the effect of its altered pharmacokinetics. Lower FPG could result from decreased hepatic glucose production or increased glucose disposal. Lower FPG occurred in the presence of lower (5 mg) or unchanged (20 mg) insulin and C-peptide levels, suggesting that glipizide-GITS may have an insulin-sensitizing effect compared with immediate-release glipizide. The exact mechanisms await clarification. The glucose response to Sustacal challenge was similar after glipizide-GITS and immediate-release glipizide; however, the 5-mg glipizide-GITS group demonstrated significantly lower concomitant insulin and C-peptide secretory responses, suggesting the possibility of greater sensitivity to the action of insulin. Equivalent glucose control with lower circulating insulin levels is considered to be a goal of therapy in NIDDM, since an association of hyperinsulinemia and insulin resistance with cardiovascular disease has been noted (4).

HbA_{1c} levels were equivalent after glipizide-GITS and immediate-release glipizide, despite improved FPG in the patients receiving 5 and 20 mg of glipizide-GITS. This can be attributed to the 8-week duration of the study and the well-described lag in the decline of HbA_{1c} levels following reduction in plasma glucose (5).

Once-daily dosing with the GITS formulation provides effective plasma concentrations (6,7) throughout the 24-h dosing interval with less peak to trough fluctuation than is observed with immediate-release glipizide. The lower FPG observed after 5 and 20 mg of glipizide-GITS rather than after immediate-release glipizide is likely related to the higher basal (fasting) plasma glipizide concentrations maintained with the GITS formulation and suggests that dose-related effects of plasma glipizide can be distinguished up to at least 300 ng/ml but not >500 ng/ml (40-mg dose). Despite the threefold higher plasma glipizide concentrations after immediate-release glipizide, similar post-Sustacal glucose responses were observed with both formulations at all dose levels, suggesting threshold concentration of plasma glipizide (~300 ng/ml) above which no additional glucose-lowering effect is likely to be achieved.

In this study, patients were switched safely from the immediate-release form to glipizide-GITS on a milligram-for-milligram basis without a loss of efficacy. In conclusion, this study comparing the efficacy and safety of two formulations of glipizide, conventional immediate release and the GITS controlled-release forms, has shown an improved metabolic profile for the glipizide-GITS formulation at the 5- and 20-mg doses.

Acknowledgments— This work was supported by a grant from Pfizer.

This study was reported in part at the 54th annual meeting of the American Diabetes Association, New Orleans, Louisiana, June 11–14, 1994.

APPENDIX— Study investigators and sites included the following: Michael Berelowitz, MD, SUNY at Stony Brook, Stony Brook, NY; William Cefalu, MD, Bowman Gray School of Medicine, Winston-Salem, NC; David S. Schade, MD, University of New Mexico School of Medicine, Albuquerque, NM; Samuel Miller, MD, University of Texas Health Science Center, San Antonio, TX; David Kelley, MD, University of Pittsburgh School of Medicine, Pittsburgh, PA; Miguel Roura, MD, The Diabetes and Thyroid Center, Jacksonville, FL; Stephen Clement, MD, Walter Reed Army Medical Center, Washington, DC; Philip Raskin, MD, Southwestern Medical School, University of Texas Health Science Center, Dallas, TX; Corbin Roudebush, MD, Joslin Diabetes Clinic, Indianapolis, IN.

References

1. Dinneen S, Gerich J, Rizza R: Carbohydrate metabolism in non-insulin-dependent diabetes mellitus. *N Engl J Med* 327: 707–713, 1992
2. Gerich JE: Oral hypoglycemic agents. *N Engl J Med* 321:1231–1245, 1989
3. Swanson DR, Barclay BL, Wong PSL, Theeuwes F: Nifedipine gastrointestinal therapeutic system. *Am J Med* 83:3–9, 1987
4. Reaven GM: Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med* 44:121–131, 1993
5. Tahara Y, Shima K: The response of GHb to stepwise plasma glucose change over time in diabetic patients. *Diabetes Care* 16:313–1314, 1993
6. Groop L, Groop P-H, Stenman S: Comparison of pharmacokinetics, metabolic effects and mechanisms of action of glyburide and glipizide during long-term treatment. *Diabetes Care* 10:671–678, 1987
7. Groop L, Barzilai N, Ratheiser K, Luzi L, Wahlin-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