# Maintenance of Sulfonylurea Responsiveness in NIDDM

## Randomized Double-Blind Study of Intermittent Glyburide Therapy

GEORGE GRUNBERGER, MD

**OBJECTIVE** — To assess the effectiveness of intermittent administration of sulfonylurea (glyburide) to patients with non–insulin-dependent diabetes mellitus (NIDDM).

**RESEARCH DESIGN AND METHODS** — A randomized, double-blind, prospective trial compared daily administration with intermittent administration of glyburide to patients who initially responded to the drug. Twenty-eight of 60 patients with NIDDM achieved the predetermined improvement in plasma glucose concentration on glyburide therapy. These 28 responders were enrolled into a 16-wk trial of daily versus intermittent (2 wk on, 2 wk off) glyburide treatment. Laboratory assessment of glycemic control and insulin secretion in fasting and 2-h postprandial states was done every 2 wk.

**RESULTS** — Patients on continuous glyburide therapy maintained their glycemic control throughout the study. In contrast, patients on the intermittent schedule lost their glycemic control immediately after being placed on placebo. Despite a significant response to each sulfonylurea pulse, these subjects never regained their baseline glycemic levels. Their fructosamine and $HbA_{1c}$ concentrations deteriorated and remained significantly higher than those of the continuously treated subjects.

**CONCLUSIONS** — Results suggest that administration of glyburide on an intermittent basis after a 2-wk drug-free period to patients initially rendered responsive to sulfonylurea therapy is without clinical merit.

The detailed mechanism of action of oral sulfonylurea agents remains unclear. These drugs normalize blood glucose levels on a long-term basis only in a few patients with NIDDM. Sulfonylureas acutely increase plasma insulin concentration and decrease peripheral insulin resistance to eventually achieve a new steady state of decreased plasma glucose and insulin levels. The insulinotropic effects of sulfonylureas are initiated by activation of specific plasma membrane receptors (1). Continuous exposure of these receptors to sulfonylurea could downregulate them and impair insulin release. This study was designed to ascertain whether an intermittent administration of glyburide would produce the same effects as continuous drug therapy in patients with NIDDM who initially respond to the drug.

## RESEARCH DESIGN AND METHODS

— Patients with NIDDM without a history of insulin use or oral hypoglycemic agent therapy within 2 mo of the study were screened. In the prerandomization phase, the subjects were placed on a weight-maintaining American Diabetes Association (ADA) diet. Patients whose fasting plasma glucose fell to <8.9 mM within 1 mo of diet alone were excluded. The remaining patients were started on 2.5–5 mg glyburide (Micronase, Kalamazoo, MI) daily (before breakfast). Dose was adjusted weekly until 20 mg/d was reached or fasting plasma glucose fell to <7.8 mM. "Response" was defined as fasting plasma glucose <7.8 mM or a fall of at least 25% from the baseline while on 20 mg/d glyburide. Of the 60 patients placed on glyburide, 28 showed response (Table 1); the mean fasting glucose among the 28 participants was 7.8 ± 0.4 mM. Phase II consisted of a 16-wk randomized, double-blind trial of glyburide given on a daily or intermittent basis. The intermittent schedule was 2 wk of daily placebo followed by 2 wk of glyburide, repeated over the 16-wk trial. At each biweekly visit, fasting and 2-h post-Sustacal (Mead Johnson Pharmaceutical, Evansville, IN) plasma glucose and serum insulin levels and $HbA_{1c}$ and fructosamine concentrations were determined. Patients continued on the same glyburide dose except when hyperglycemia (>20% increase of fasting plasma glucose on 2 consecutive visits) occurred; glyburide

FROM THE DIABETES SECTION, DEPARTMENT OF INTERNAL MEDICINE, WAYNE STATE UNIVERSITY SCHOOL OF MEDICINE, DETROIT, MICHIGAN.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO GEORGE GRUNBERGER, MD, UNIVERSITY HEALTH CENTER–4H, 4201 ST. ANTOINE, DETROIT, MI 48201.

RECEIVED FOR PUBLICATION 9 MAY 1991 AND ACCEPTED IN REVISED FORM 12 SEPTEMBER 1991.

**Table 1—*Patient characteristics***

| | CONTINUOUS | INTERMITTENT | *P* |
|---|---|---|---|
| *N* (M/F) | 10/4 | 9/5 | 0.69 |
| AGE (YR) | 58.8 ± 2.1 | 56.6 ± 1.9 | 0.46 |
| DURATION OF DIABETES (YR) | 8.8 ± 1.7 | 6.6 ± 1.0 | 0.27 |
| IDEAL BODY WEIGHT (%) | 129.1 ± 4.9 | 139.6 ± 6.8 | 0.23 |
| RACE (BLACK/WHITE) | 2/12 | 5/9 | 0.19 |

Values are means ± SE.

was increased by 5 mg/d in that event. The subjects' weights did not deviate by >5% from their baseline values.

Laboratory analyses were performed at the Upjohn Clinical Research Laboratories (Kalamazoo, MI) under blinded conditions. $HbA_{1c}$ values were measured with ion-exchange high-performance liquid chromatography (normal mean ± SD $HbA_{1c}$ 4.98 ± 0.49%). *t* Test was done for efficacy variables; statistical analyses were by GLM (type III SS) tests.

**Table 2—*Outcome variables at randomization***

| | CONTINUOUS | INTERMITTENT | *P* |
|---|---|---|---|
| GLUCOSE (MM) | | | |
| FASTING | 7.39 ± 0.28 | 8.33 ± 0.44 | 0.09 |
| 2-H POSTPRANDIAL | 10.89 ± 0.94 | 12.39 ± 0.72 | 0.22 |
| INSULIN (PM) | | | |
| FASTING | 186.6 ± 25.2 | 152.4 ± 12.6 | 0.23 |
| 2-H POSTPRANDIAL | 473.4 ± 64.8 | 443.4 ± 57.6 | 0.73 |
| $HbA_{1c}$ (%) | 7.04 ± 0.37 | 7.59 ± 0.28 | 0.24 |
| FRUCTOSAMINE (MM) | 2.94 ± 0.31 | 3.02 ± 0.22 | 0.82 |

Values are means ± SE.

**RESULTS**— Six outcome variables were identified before the study: fasting and postprandial plasma glucose, fasting and postprandial serum insulin, $HbA_{1c}$, and fructosamine. There were no significant differences in any of these variables or other laboratory data at the time of randomization (Table 2). Fasting glucose levels remained relatively constant (wk 0 7.39 ± 0.28 mM, wk 16 8.0 ± 0.61 mM) among patients on the continuous glyburide treatment (Fig. 1). In contrast, the intermittently treated subjects showed marked fluctuations of the fasting plasma glucose with improvements during the active drug therapy and deteriorations while on placebo. The nadir glucose concentrations of the intermittently treated subjects (at 4, 8, 12, and 16 wk) were significantly higher than their baseline concentrations and were also higher than the glucose levels of continuously treated patients at each time point. Furthermore, each nadir glucose level was higher than the preceding one. The mean 2-h post-Sustacal glucose levels followed the same pattern among the patients in the two groups (Fig. 2). The continuously treated patients demonstrated essentially constant fructosamine values throughout the study, reflecting stable glycemic values (Fig. 3). Patients who received glyburide intermittently showed rises and declines in fructosamine that correlated with the deterioration and improvement of their glycemic control. Similar results were obtained for longer-term glycemic control as indicated by $HbA_{1c}$. $HbA_{1c}$ values (Fig. 4) gradually improved among the daily treated patients over the first 8 wk and remained constant thereafter. However, in the intermittently treated group, a gradual increase in $HbA_{1c}$ was observed that correlated with the deterio-

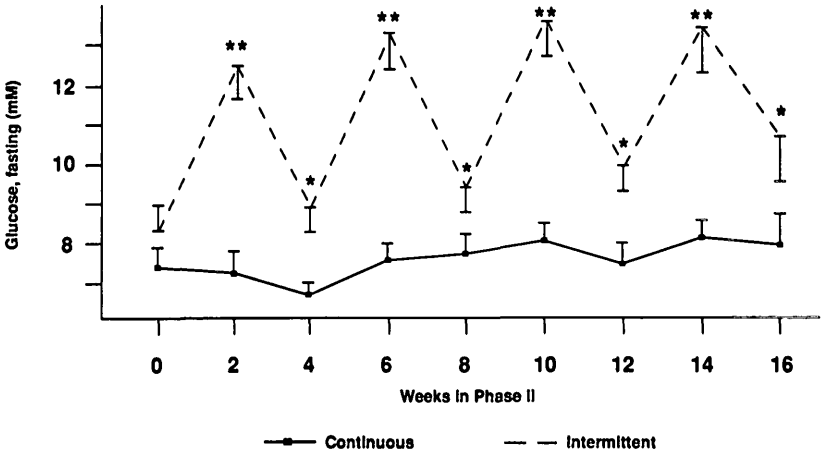


**Figure 1**—*Fasting plasma glucose levels during the 16 wk of the randomized double-blind phase II of the study. Data are means ± SE.* *$P < 0.05$. **$P < 0.001$.

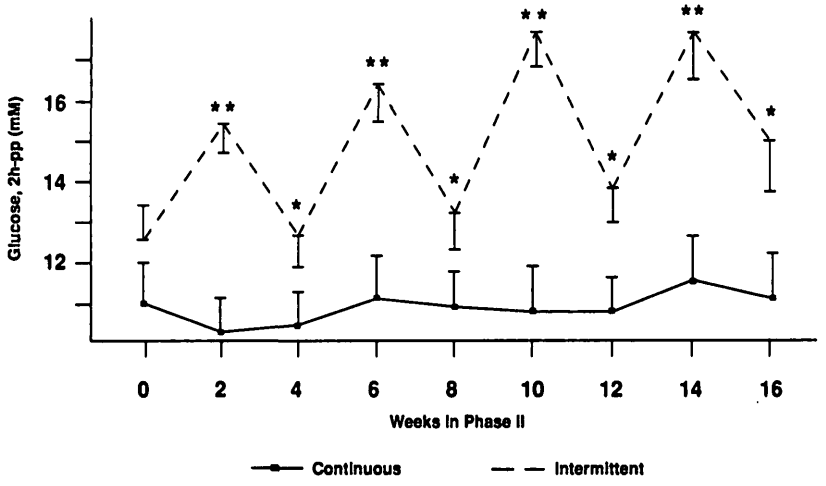


**Figure 2**—*Plasma glucose concentrations 2 h after ingestion of Sustacal during phase II of the study. Data are means ± SE. *P < 0.05. **P < 0.001.*

rating glycemic control. There was a statistically significant difference between $HbA_{1c}$ of the two groups at every point of the study. The fasting and 2-h post-Sustacal serum insulin levels were higher among the continuously treated patients; however, this difference was statistically significant only at wk 10 and 14. The absolute insulin secretory response to Sustacal was generally diminished while the patients were on the placebo.

**CONCLUSIONS**— This study tested the hypothesis that daily administration of sulfonylurea agent would not be necessary in those patients with NIDDM in whom a satisfactory response to the drug was established. The optimized diet and initial hypoglycemic response would lead to an improved state of in vivo insulin sensitivity, which would not require a continuous exposure to the sulfonylurea. Sustained levels of sulfonylureas induced a state of refractoriness of pancreatic islet β-cells to acute stimulation with sulfonylureas but not to another secretagogue (2). In that study, this refractory state was induced rapidly and was reversible. Therefore, it seemed reasonable that patients with NIDDM would benefit from repeated short exposures to sulfonylureas once their initial response was assured. Such an approach would reduce the frequency of secondary drug failure, decrease the cost of therapy, and minimize the necessity of insulin treatment. The hypothesis, in the manner it was tested, was not confirmed. Given the design limitations, the study showed an inability to maintain glycemic control by an intermittent administration of glyburide. To eliminate potential confounding factors, we excluded those patients who showed a fair response to dietary management alone. We concentrated on establishing a response to glyburide in those patients with NIDDM resistant to diet alone. Only 47% of subjects met our criteria for response under idealized conditions of frequent contact with a dietician or physician. Several studies have assessed effects of placebo after administration of sulfonylureas. Approximately one-third of the patients who initially responded to sulfonylurea treatment remained in good control when placed on placebo (3–6). These results could indicate both the inappropriate use of the oral hypoglycemic therapy in some NIDDM patients and the possibility that the drug-induced improvement of insulin action persists for some length of time.

In this study, there was a uniform deterioration of glycemic control in all of the patients in the intermittent glyburide arm of the protocol. Each new exposure to glyburide after a 2-wk period on placebo in our subjects resulted in improved insulinotropic effect. Importantly, the intermittently treated group showed a significant deterioration of integrated glycemic control over the brief duration of the study when assessed by

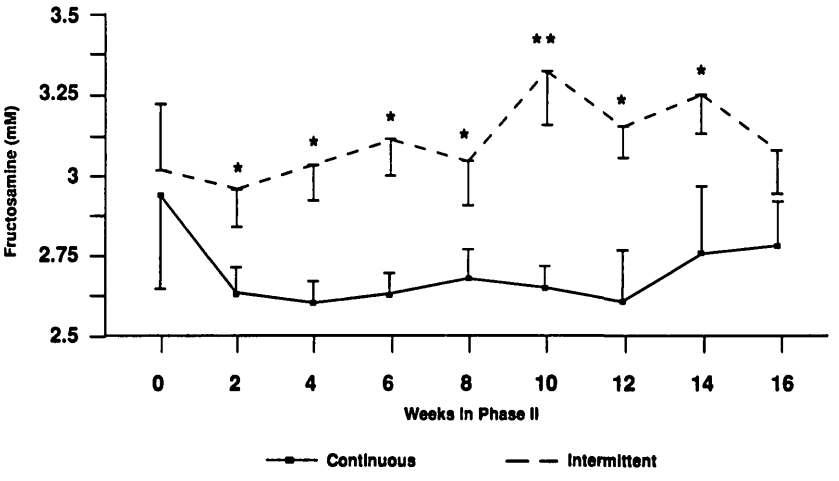


**Figure 3**—*Serum fructosamine levels during the randomized double-blind phase of the study. Data are means ± SE. *P < 0.05. **P < 0.001.*

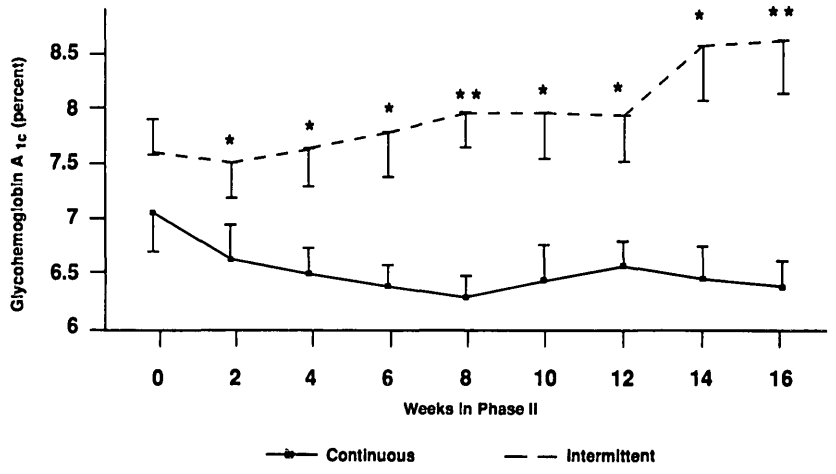


**Figure 4**—*$HbA_{1c}$ during the randomized double-blind phase of the study. Data are means ± SE. *P < 0.05. **P < 0.001.*

fructosamine and $HbA_{1c}$ assays. A troubling dilemma has recently emerged in the management of patients with NIDDM—insulin toxicity versus glucose toxicity (7). Clearly, strategies will be necessary to avoid both of these risks in patients with NIDDM in the future. Data in this study indicate that most of the short-term benefit of glyburide were derived from its stimulation of insulin secretion.

Although the serum insulin levels were higher in the continuously treated subjects, these differences were not statistically significant. Given the clear-cut deterioration of glycemic control, we conclude that in the select group of responders to glyburide, daily administration of the drug is preferred to an intermittent schedule. Other study designs, with shorter duration of the sulfonylurea-free period, might still demonstrate the benefit of intermittent glyburide treatment. Additional placebo-controlled trials could determine whether the consequences of continuous versus episodic exposure of receptors to their ligands also applies to sulfonylureas.

**Acknowledgments**—I gratefully acknowledge the support of Dr. R.F. Carlson, Dr. F.G. Ogrinc and B. Miller (Upjohn), S.W. Brown and K.H. Lantz (Upjohn), and Dr. P. Gorden of the National Institutes of Health (Bethesda, MD) for intellectual stimulation and past support. The excellent work of K. Johnson, T.A. McClendon, RMA, and M. Mann, RD, with study participants is deeply appreciated. Secretarial assistance of P. Fishman is acknowledged.

## References

1. Siconolfi-Baez L, Banerji MA, Lebovitz HE: Characterization and significance of sulfonylurea receptors. *Diabetes Care* 13 (Suppl. 3):2–8, 1990
2. Karam JH, Sanz N, Salamon E, Nolte MS: Selective unresponsiveness of pancreatic β-cells to acute sulfonylurea stimulation during sulfonylurea therapy in NIDDM. *Diabetes* 35:1314–20, 1986
3. Singer DL, Hurwitz D: Long-term experience with sulfonylureas and placebo. *N Engl J Med* 227:450–56, 1967
4. Tomkins GM, Blood A: Assessment of the need for continued oral therapy in diabetics. *Br Med J* 1:649–51, 1971
5. Lev-Ran A: Trial of placebo in long-term chlorpropamide-treated diabetics. *Diabetologia* 10:197–200, 1974
6. Boden G, Master RW, Gordon SS, Shuman CR, Owen OE: Monitoring metabolic control in diabetic outpatients with glycosylated hemoglobin. *Ann Intern Med* 92: 357–60, 1980
7. Spratt IL: Insulin toxicity versus glucose toxicity in elderly patients with NIDDM. *Clin Diabetes* 8:50–51, 1990