Combination Therapy for NIDDM With Biosynthetic Human Insulin and Glyburide

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OBJECTIVE— To investigate the effects of the addition of glyburide to the regimen of insulin-treated non-insulin-dependent diabetes mellitus (NIDDM) patients with regard to their overall insulin requirement and dosage schedule and to assess persistence of these effects.

RESEARCH DESIGN AND METHODS— A double-blind randomized parallel-group, placebo-controlled, 20-wk outpatient trial at the Clinical Research Unit (CRU) at St. Luke's/Roosevelt Hospital (New York). Subjects were 20 insulin-dependent NIDDM patients previously managed on insulin alone. After a baseline period of satisfactory diabetes control on biosynthetic human insulin alone, insulin dosage was halved, and patients were placed on a combination with either glyburide or placebo. Diabetes control equivalent to baseline was reestablished by adjusting insulin as required on subsequent visits to the CRU.

RESULTS— Insulin requirements in the glyburide group decreased by 29 U at 14 wk compared with 9 U in the placebo group ($P < 0.05$). At 20 wk, the decreases remained significant (25 vs. 11 U, respectively; $P < 0.05$). The mean ± SD reduction in insulin requirement in the glyburide group was relatively constant (25 ± 10 U) and was not related to premedication insulin requirement. Successful response to glyburide was inversely correlated with initial serum alkaline phosphatase level.

CONCLUSIONS— Glyburide reduces insulin requirements for 20 wk of combination therapy in NIDDM patients. Patients whose initial insulin requirement is ≤25 U have a 50% chance of achieving equivalent glycemic control on glyburide alone.

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Insulin therapy in non-insulin-dependent diabetes mellitus (NIDDM) frequently requires dosages much in excess of all estimates of β-cell response in nondiabetic individuals. There are concerns regarding the role of hyperinsulinemia in the pathogenesis of atherosclerosis (1), retinal neovascularization (2), sodium and water retention (3), and weight gain (4–7). Moreover, tight control, a goal of contemporary diabetes management, usually requires multiple injections daily, a combination of short- and intermediate- or long-acting insulin preparations, and frequent skin punctures for self–blood glucose monitoring, all of which undermine patient compliance. An orally administered drug that could simplify a patient's insulin regimen, although achieving similar results, would be a welcome adjunct.

Conflicting results in previous trials indicated a need for a long-term, parallel-group, placebo-controlled trial to investigate the effects of the addition of glyburide to the regimen of insulin-treated NIDDM patients with regard to their overall insulin requirement and dosaging schedule and to assess the persistence of these effects.

RESEARCH DESIGN AND METHODS

— Twenty subjects with NIDDM who had been managed with insulin alone for at least 1 yr before recruitment were studied. Subjects ranged in age from 46 to 68 yr and were between 91 and 166% of ideal body weight. Women were postmenopausal. All subjects completed the study and were included in all analyses, except for C-peptide levels as specified below.

Exclusion criteria were *1*) endocrinologic disease other than diabetes mellitus, *2*) a history of allergies to sulfonamides and/or insulin, *3*) a history of impaired gastric emptying, *4*) active hepatic disease, *5*) renal disease significantly impairing creatinine clearance

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Table 1—*Glycemic control during 20 wk of combination therapy*

	Week				
	0	4	9	14	20
Glyburide					
Peak glucose (mM · L^{-1})	11.8	13.5	14.0	12.9	13.1
Area under glycemic curve (mM · L^{-1} · 3h)	29.7	33.1	35.4	31.5	32.9
Placebo					
Peak glucose (mM · L^{-1})	12.3	17.3	14.7	14.8	14.6
Area under glycemic curve (mM · L^{-1} · 3h)	30.4	43.8	36.4	36.8	36.7

Values at wk 4 and 9 are significantly ($P < 0.05$) higher than those at baseline (wk 0) by Dunnett's test. Values at weeks 14 and 20 were no longer significantly different from week 0, indicating that equivalent glycemic control had been reestablished.

(<1.3 ml/s), and 6) current treatment with steroids, estrogens, progestogens, β-blockers, Ca^{2+}-channel antagonists, diuretics, monoamine oxidase inhibitors, clonidine, probenecid, anticoagulants, or nonsteroidal antiinflammatory agents.

Candidates who met the selection criteria received detailed instructions regarding their diet and diabetes management over the next 20 wk. Study participants monitored their diurnal glucose profile with Chemstrips BG and Accuchek II. Study medication and placebo were provided by Upjohn (Kalamazoo, MI).

The study was double blind with random assignment to equal-sized parallel groups and with repeated determinations of insulin requirement, urinary C-peptide, HbA_1, serum lipids, and glycemic profiles in response to standard test meals over 20 wk. A preliminary phase on insulin monotherapy with biosynthetic human insulin to achieve satisfactory diabetes control preceded the clinical trial.

On study days (wk 0, 4, 9, 14, 20), subjects reported fasting to the Clinical Research Unit (CRU) at 0900 for a standard test meal (464 kcal: 19% protein, 58% carbohydrate, 23% fat). Capillary fingerstick samples were drawn at 30-min intervals for 180 min. Subjects remained in the CRU for 8 h, during which all urine was collected for C-peptide determinations (radioimmunoassay kit, Serono, Norwell, MA). At the completion of the week 0 tests in the CRU, subjects were randomized into two groups and sent home with instructions to begin taking study medication 7 days later (week 1). At that time, their insulin dosage was halved, although retaining the administration schedule. They were instructed to take one tablet of medication twice a day for 3 days and then to double the medication dosage for the remainder of the study if no side effects were noted. All subjects implemented the full dosage of study drug without complications. Throughout the trial, subjects were required to come to the CRU on scheduled follow-up study days (weeks 4, 9, 14, and 20) and on additional days as required, at which times the insulin dosage was adjusted by whatever number of units was deemed appropriate to reestablish and maintain glycemic control equivalent to that at week 0. HbA_1 determinations were made on weeks 0, 9, and 20.

Student's *t* test was used to compare initial screening values of pa-

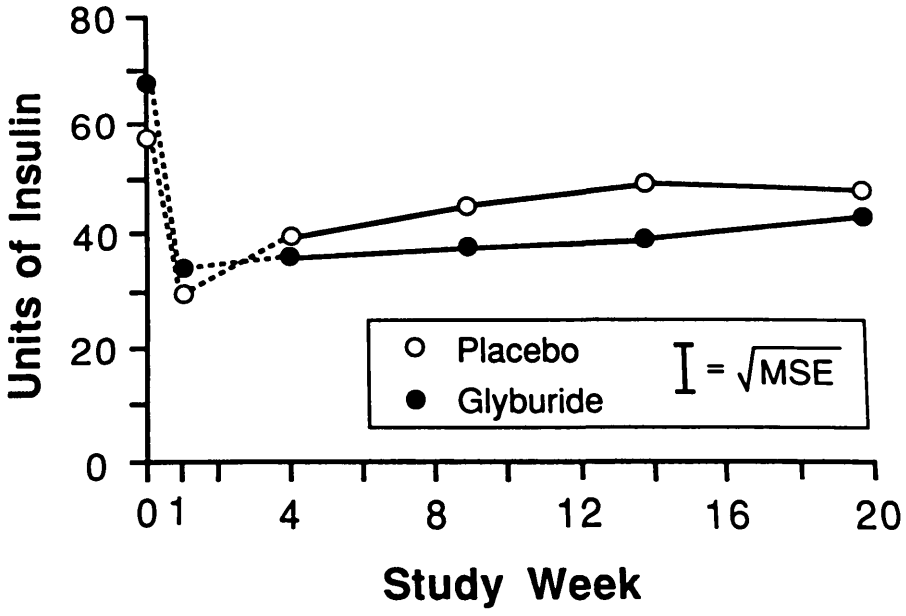

Figure 1—*Mean insulin dosage at 0, 1, 4, 9, 14, and 20 wk. Values for week 1 represent an arbitrary reduction from week 0 level. Subsequent dosages were prescribed on basis of home fingerstick blood glucose tests.* $\sqrt{MSE}$ *is a measure of variability in change within a group. Changes from week 0 >1.1×* $\sqrt{MSE}$ *are statistically significant.*

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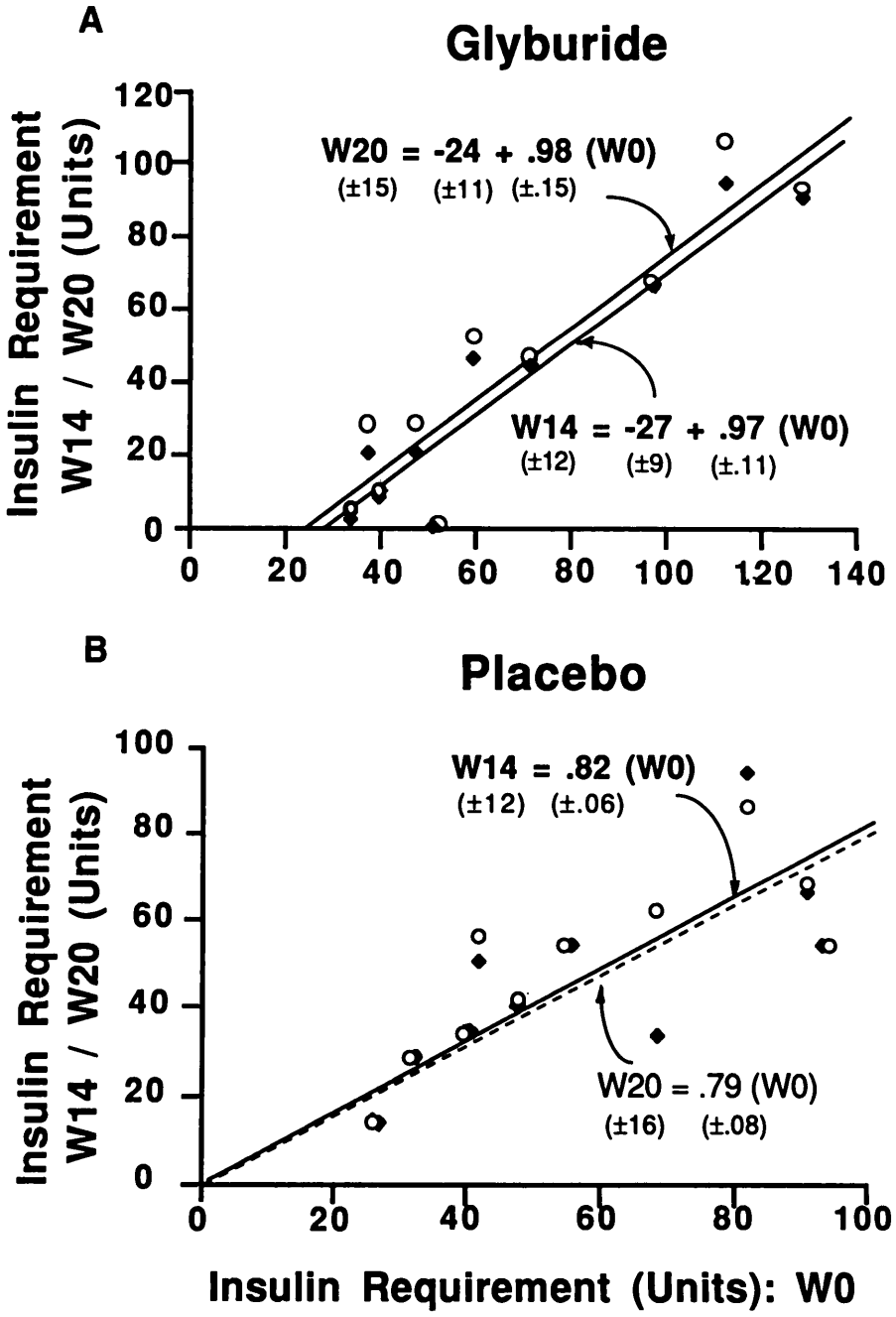

Figure 2—*Relationship of insulin requirement at 14 (◆) and 20 (○) wk of combination therapy to week 0 requirement. A: intercept of regression line is significantly different from 0 ($P < 0.05$), indicating that patients who, at wk 0, required <24 or <27 U insulin/day may be able to discontinue insulin at 14 and 20 wk. B: decrease in average insulin requirement is significantly smaller compared with decrease in glyburide group ($P < 0.05$) and is in proportion (12 and 18%, respectively) to initial requirement. SE in parentheses.*

tients randomized into the glyburide and placebo groups. Two-way analysis of variance with medication (glyburide or placebo) as a between-subjects factor and test day (0, 4, 9, 14, and 20 wk) as a within-subjects factor was used to test for main effects and interactions. Dunnett's test was used for multiple comparisons of the baseline (week 0) with subsequent test days.

RESULTS — The two study groups were not significantly different on any measured variable at randomization. Body weights did not change significantly during the study. Maximum deviations from initial weight were 2.6 ± 1.2 kg ($n = 20$).

Glycemic control deteriorated transiently when combination therapy was initiated due to the significant reduction (50%) in the insulin dose, according to protocol. Diabetes control equivalent to week 0 was established in both groups by 14 wk and maintained through 20 wk (Table 1).

HbA_1 values at 0, 9, and 20 wk did not change significantly in either group. The initial values (placebo 8.6 vs. glyburide 8.7%) were near the normal range (4.4–8.2%), and the absence of significant change at 9 and 20 wk bespeaks equivalent glycemic control in the two groups during the trial.

The insulin requirement decreased more in the glyburide group than in the placebo group when assessed at 14 wk (placebo 9 U, glyburide 29 U, $P < 0.05$) and at 20 wk (placebo 11 U, glyburide 25 U, $P < 0.05$) (Fig. 2).

The schedule of insulin administration was also influenced. One subject in the control group required one injection less per day at 20 wk compared with week 0, whereas in the glyburide group, two subjects were able to omit their second injection and another discontinued insulin altogether. The best expression for the amount of reduction in insulin requirement achieved by the

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Table 2—*Glyburide subjects' insulin requirement and alkaline phosphatase at week 0 with amount of decrease in insulin dosage at week 20*

Subject	Baseline insulin requirement (U)	Alkaline phosphatase (KAT/L)	Decrease in insulin requirement at week 20 (U)
002	98	0.40	−31
005	40	0.48	−30
007	48	0.43	−20
015	130	0.43	−38
018	114	0.60	−8
021	60	0.72	−8
023	38	0.47	−10
024	72	0.45	−26
026	34	0.40	−30
027	52	0.30	−52

glyburide group at 14 and 20 wk is in terms of a constant number of units (24–27 U), regardless of initial requirement. This suggests that our uniform fixed dosage of glyburide translated into a constant equivalent of insulin units. In contrast, the placebo group's requirement also decreased as a percentage of the initial requirement (18–21%), expressing an improvement in insulin requirement, most likely a consequence of intensive interaction with study personnel. The data and the regression equations are depicted in Fig. 2, A and B. Figure 2A indicates that there is a 50% chance that persons whose daily insulin requirement is ≤25 U may be managed equally well, in terms of glycemic control, on glyburide alone. The amount of decrease in insulin requirement was not related to the degree of compliance, which was >93%.

CHARACTERISTICS OF RESPONDERS— The measure of successful response to glyburide was the amount of decrease in insulin requirement from week 0 to week 14 or from week 0 to week 20. A highly significant correlation with successful response to glyburide was found for only one screening variable: initial alkaline phosphatase ($r = -0.81$; $P < 0.005$), indicating that the greater decreases in insulin requirement were experienced by patients who had lower initial alkaline phosphatase (Table 2). In turn, the higher initial alkaline phosphatase values were associated with several indices of poor glycemic control (screening urinary glucose $r = 0.70$, $P < 0.02$; week 20 HbA_1 $r = 0.62$, $P = 0.05$; week 9 HbA_1 $r = 0.51$, $P = 0.13$; week 0 HbA_1 $r = 0.54$, $P = 0.13$).

At completion of study, 11 complete sets of aliquots from 8-h urine collections on study days were available (5 placebo, 6 glyburide). The glyburide group demonstrated a significant increase ($P < 0.05$) in mean urine C-peptide by week 4, and C-peptide values remained significantly higher in the glyburide group throughout the study (Fig. 3).

Successful response to glyburide was associated with low week 0 C-peptide levels ($r = 0.82$, $n = 6$, $P < 0.05$) and with the largest increases in C-peptide during the trial [Δ(week 20 − week 0)] ($r = -0.94$, $n = 6$, $P < 0.01$).

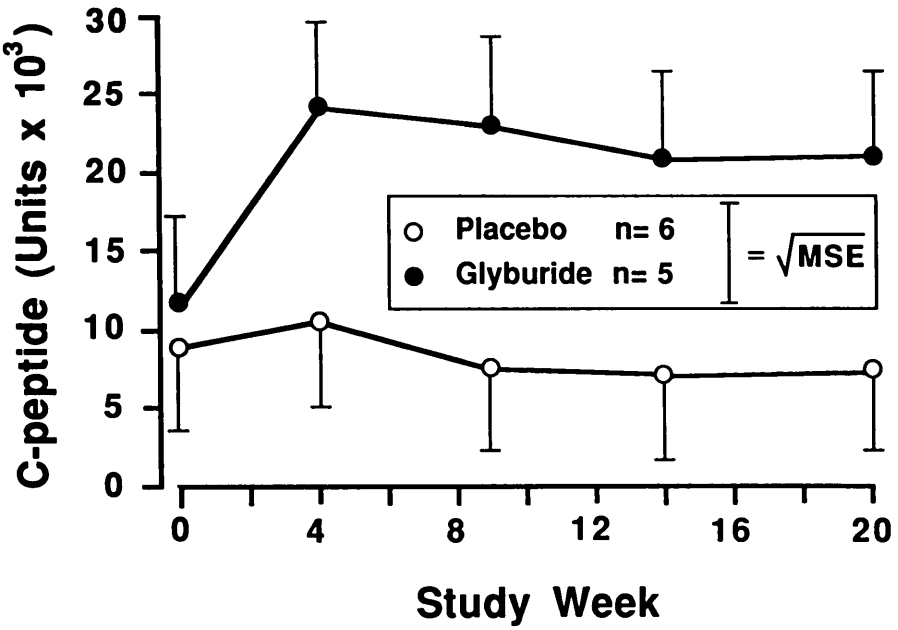

Figure 3—*Urine C-peptide levels at 0, 4, 9, 14 and 20 wk of combination therapy. Complete aliquots were available for 11 of 20 subjects.* $\sqrt{MSE}$ *is a measure of variability in change within group. Changes* $>1.1\times$ $\sqrt{MSE}$ *from week 0 are statistically significant. Error bars show between-group SE based on pooled between-groups variability.*

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CONCLUSIONS— Our results show that the combination of insulin and glyburide in NIDDM significantly reduces the amount of insulin required to maintain satisfactory glycemic control by a mean of 25 U up to 20 wk after initiating therapy. According to our results, there is a 50% chance that persons requiring ≤25 U insulin/day may be managed equally well, in terms of glycemic control, on glyburide alone.

The patients who responded best to combination therapy were characterized by low initial serum alkaline phosphatase levels, absence of glucosuria on screening, and low initial C-peptide levels. Good glycemic control is associated with absence of glucosuria and low alkaline phosphatase levels (8–10). Low initial C-peptide levels in these same patients with good initial glycemic control suggests a greater insulin sensitivity and a more favorable β-cell reserve. This would allow a greater margin for improvement in glucose levels when β-cells are stimulated, enhancing endogenous insulin production.

Although most investigators approached combination therapy with a procedure adding insulin to an unsuccessful sulfonylurea regimen, our study procedure adds a second-generation sulfonylurea to a previously instituted insulin regimen. This sequence approximates the situation of many NIDDM patients in the United States who manage their diabetes with insulin when they present to a subspecialist. A simple way to introduce combination therapy that minimizes the risk of hypoglycemia in the outpatient setting is presented in this paper and may be considered by physicians seeking to implement this therapeutic modality in their patient population.

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