A Double-Blind Placebo-Controlled Trial Evaluating the Safety and Efficacy of Acarbose for the Treatment of Patients With Insulin-Requiring Type II Diabetes

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OBJECTIVE — To determine whether a forced titration of acarbose (from 50 to 300 mg three times daily) administered over a 24-week period, in conjunction with diet and insulin therapy, improves glycemic control and reduces daily insulin requirements in insulin-requiring type II diabetes.

RESEARCH DESIGN AND METHODS — This multicenter, randomized, double-blind, placebo-controlled trial was 36 weeks in duration. The trial consisted of a 6-week pretreatment period, a 24-week double-blind treatment period, and a 6-week post-treatment follow-up period. The primary efficacy variables were the mean change from baseline in HbA_{1c} levels and the mean percentage change from baseline in total daily insulin dose.

RESULTS — Treatment with acarbose was associated with significant reductions in HbA_{1c} levels of 0.40% ($P = 0.0001$) and in total daily insulin dose of 8.3% ($P = 0.0015$). There were also significant reductions in all plasma glucose variables measured, including a 0.9 mmol/l reduction in fasting glucose ($P = 0.0440$), a 2.6 mmol/l reduction in glucose C_{max} ($P = 0.0001$) and a 270 mmol · min^{-1} · l^{-1} reduction in glucose area under the curve ($P = 0.0002$). Although acarbose treatment was associated with a greater incidence of adverse events than was placebo treatment, primarily flatulence and diarrhea, these events did not generally prevent patients from completing the study.

CONCLUSIONS — The results of this study suggest that acarbose is a safe and effective adjunct to diet and insulin therapy for the management of insulin-requiring type II diabetes.

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AUC, area under the curve; DCCT, Diabetes Control and Complications Trial; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum pyruvic-oxaloacetic transaminase.

In many type II diabetes patients, adequate metabolic control is often difficult to achieve, despite intensive therapeutic efforts with diet and/or sulfonylureas. Satisfactory management of the disease frequently requires the administration of daily insulin injections. The insulin regimens used, however, often fail to adequately control postprandial glucose elevations. Furthermore, the insulin therapy itself may be associated with increased appetite, weight gain, and hypoglycemia (1–3).

Acarbose, an orally administered complex oligosaccharide, is a potent competitive inhibitor of intestinal brush-border α-glucosidases. It delays the hydrolysis and subsequent absorption of ingested carbohydrates, causing a reduction in postprandial increments in blood glucose and insulin. A number of clinical trials have been conducted in the U.S. and Europe in which acarbose was administered to type I and type II diabetic patients in combination with diet modification, sulfonylurea drugs, or insulin (4–7). These trials have demonstrated that acarbose is effective in reducing postprandial excursions in blood glucose levels and in improving long-term glycemic control. However, to date, there have been no adequate and well-controlled trials that address the safety and effectiveness of acarbose for the treatment of insulin-requiring type II diabetic patients.

This study was designed to determine whether acarbose, administered in a forced titration fashion, from 50 to 300 mg t.i.d., in conjunction with diet and insulin therapy, could further improve metabolic control (as measured by a reduction in HbA_{1c}) and reduce daily insulin requirements in insulin-requiring type II diabetic patients.

RESEARCH DESIGN AND METHODS

— This double-blind, randomized, multicenter, placebo-controlled study was 36 weeks in duration and included a 6-week pretreatment run-in period, a 24-week double-blind

treatment period, and a 6-week post-treatment follow-up period. At the beginning of the pretreatment period, patients were placed on a diet designed to maintain a stable body weight. The composition of the diet conformed to the American Diabetes Association recommendations at that time (8). Any necessary adjustments to the insulin regimen were made after implementation of the diet. HbA_{1c} and a standardized 600-kcal meal tolerance test were performed at the initial visit. The morning dose of insulin was given 30 min before the test meal, and study medications were administered with the first bite of the test meal. The patients' diet, weight, blood glucose level, insulin regimen, and general medical condition were closely monitored during the pretreatment period. At the end of the pretreatment period, baseline efficacy and safety data were collected.

At the start of the 24-week, double-blind treatment period, patients received 50 mg t.i.d. of acarbose or matched placebo. The dosage of study medication was increased at 6-week intervals in the following increments: 50, 100, 200, and 300 mg t.i.d. Study medication was administered with meals and was discontinued at week 24. Patients were instructed to continue with the same insulin regimen that was being used at the end of the run-in period. The dosage of study medication could be decreased at any time if intolerable adverse events other than hypoglycemia occurred. If hypoglycemia occurred (as determined by the investigator), the insulin dosage was reduced. At the end of each 6-week interval, before the dosage titration, vital signs, body weight, HbA_{1c}, and changes (if any) in insulin regimen and diet were recorded, and a standard meal tolerance test was administered. The number of hypoglycemic episodes, adverse experiences, or intercurrent illnesses and compliance with the study protocol were also assessed at this time. At 12 and 24 weeks after the start of study medication, a full safety evaluation was conducted.

During the 6-week post-treatment follow-up (weeks 24–30), patients discontinued the study medication but continued their diets and insulin regimens. At the end of the follow-up period, patients were again evaluated using the same battery of efficacy and safety tests performed at weeks 12 and 24.

Patient population

The study population consisted of 219 men and women with a primary diagnosis of type II diabetes of at least 6 months duration. These patients had a stable body weight (±5 kg for at least 3 months), had been receiving insulin therapy for at least 2 months, and had not received sulfonylurea drugs for at least 4 weeks before the initiation of the study. Lipid-lowering agents, glucocorticoids, and drugs that could significantly alter gastrointestinal (GI) motility and/or absorption were not prescribed during the study. Each patient gave written informed consent before enrollment.

Analysis of efficacy

Analyses of primary efficacy variables were based on a mean change from baseline in HbA_{1c} and a mean percentage change from baseline in daily insulin requirements at the double-blind endpoint. The double-blind endpoint was defined as the last valid observation for each patient. Secondary analyses of efficacy included change from baseline in the following meal tolerance test variables: fasting, 60-, 90-, and 120-min plasma glucose concentrations; postprandial plasma glucose area under the curve (AUC) (0–120 min); and maximal postprandial glucose concentration (C_{max}).

Also included were serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride levels, and the number of hypoglycemic episodes. To minimize variability in laboratory determinations, a central laboratory was used for all biochemical test determinations, except for plasma glucose measurements, which were taken after the meal tolerance test at each center.

Statistical analysis

Continuous efficacy variables were analyzed using an analysis of variance model. Between-group comparisons for all during-treatment visits were performed using one-tailed tests for HbA_{1c}, total and LDL cholesterol, total triglycerides, and all meal tolerance test variables. Two-tailed tests were used for during-treatment pairwise comparisons of HDL cholesterol, number of hypoglycemic episodes, body weight, and percentage change relative to baseline in total daily insulin requirement. All variables were analyzed for baseline comparability and changes from baseline during follow-up periods using two-tailed tests. All comparisons were based on the least-square means estimated by the model. All significance tests were performed at an α-level of 0.05.

The incidence of adverse events and high and low laboratory abnormalities was analyzed using two-tailed χ^2 or Fisher's exact tests, as appropriate.

RESULTS — Of the 219 patients randomly assigned to receive the study drug, 207 were valid for the efficacy analyses: 103 were in the acarbose group, and 104 were in the placebo group. The treatment groups were comparable with respect to all demographic and disease characteristics that were analyzed (e.g., age, weight, body mass index, sex, and ethnicity).

Efficacy

The mean change from baseline in HbA_{1c} at the end of the treatment period was −0.57% for the acarbose group and −0.17% for the placebo group (P = 0.0001) (Table 1). Total daily insulin dose was reduced by 7.1% in acarbose-treated patients (from 56.8 to 52.8 U) and was increased by 1.2% in the placebo-treated patients (from 62.2 to 62.9 U) (P = 0.0015) (Table 1). Acarbose treatment was associated with a net reduction in HbA_{1c} of 0.40% and a net reduction in insulin dose of 8.3%.

A time course plotting HbA_{1c} levels and total daily insulin dosage over the 24-week course of treatment is shown in

Table 1— *Mean baseline and change from baseline in efficacy variables at endpoint*

Parameter	Baseline		Change from baseline		Difference between treatment groups	*P* value
	Placebo	Acarbose	Placebo	Acarbose		
n	104	103	104	103		
Primary criteria						
HbA_{1c} (%)	6.58 ± 0.09	6.44 ± 0.09	−0.17 ± 0.08	−0.57 ± 0.08	0.40	0.0001
Total daily insulin dose (U)	62.2 ± 3.3	56.8 ± 3.4	1.2 ± 1.9	−7.1 ± 2.0	8.3	0.0015
Secondary criteria						
Weight (kg)	87.9 ± 1.9	87.8 ± 2.0	0.7 ± 0.3	0.3 ± 0.3	0.3	NS
Meal tolerance test variables						
Fasting plasma glucose (mmol/l)	9.8 ± 0.3	9.5 ± 0.4	0.7 ± 0.4	−0.3 ± 0.4	0.9	0.044
60-min plasma glucose (mmol/l)	15.3 ± 0.4	14.4 ± 0.4	0.3 ± 0.4	−1.9 ± 0.4	2.2	<0.0001
90-min plasma glucose (mmol/l)	15.6 ± 0.4	14.8 ± 0.4	0.4 ± 0.4	−2.6 ± 0.4	3.0	<0.0001
120-min plasma glucose (mmol/l)	15.3 ± 0.5	14.2 ± 0.5	0.3 ± 0.4	−2.5 ± 0.5	2.8	<0.0001
Plasma glucose AUC ($mmol \cdot l^{-1} \cdot min^{-1}$)	1,950 ± 50	1,850 ± 60	70 ± 50	−200 ± 60	270	0.0002
Plasma glucose C_{max} (mmol/l)	16.4 ± 0.4	15.3 ± 0.5	0.2 ± 0.4	−2.3 ± 0.4	2.6	<0.0001
No. of hypoglycemic episodes	2.7 ± 0.6	19 ± 0.6	−1.6 ± 0.6	−0.3 ± 0.6	−1.3	0.0812

Data are means ± SE. Change from baseline is expressed as percentage change from baseline.

Fig. 1. Throughout the treatment period, there was a significant reduction in HbA_{1c} levels and insulin dose at all time points examined (weeks 6, 12, 18, and 24) ($P < 0.05$) in the acarbose treatment group, with the magnitude of the reduction increasing with the duration of treatment. In contrast, in the placebo group, there was a slight decrease in HbA_{1c} levels during the first 6 weeks of treatment, followed by a plateau. Total daily insulin dose remained relatively constant during treatment. Six weeks after discontinuation of treatment (week 30), acarbose-treated patients exhibited a deterioration in glycemic control.

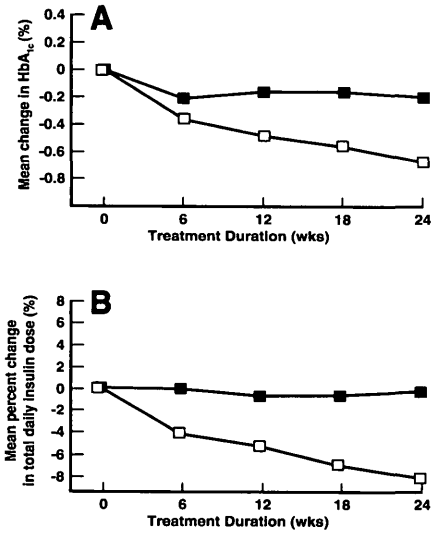

Figure 1—*Time course during treatment period plotting changes in mean HbA_{1c} levels (A) and mean percentage change in total daily insulin dose (B) for acarbose (□) and placebo (■) groups for those patients included in the efficacy analyses.*

At the end of the treatment period, all plasma glucose variables were significantly reduced in the acarbose-treated patients (Table 1). Fasting plasma glucose levels increased in the placebo-treated patients by 0.7 mmol/l and decreased in the acarbose-treated patients by 0.3 mmol/l (Table 1). There were statistically significant (placebo-subtracted) reductions in postprandial glucose levels at 60, 90, and 120 min (after administration of a test meal challenge) of 2.2, 3.0, and 2.8 mmol/l, respectively (Table 1). In the acarbose-treated patients, glucose AUC and glucose C_{max} were also substantially reduced by 270 $mmol \cdot min^{-1} \cdot l^{-1}$ and 2.6 mmol/l, respectively, relative to placebo. After discontinuation of treatment, postprandial plasma glucose variables returned to baseline levels.

Despite the lowering of postprandial glucose concentration that was associated with acarbose treatment, the number of reported hypoglycemic episodes was not significantly different between treatment groups ($P = 0.08$). Plasma lipid levels (i.e., triglycerides and cholesterol) were also comparable between treatment groups.

A response variable based on the combined changes in HbA_{1c} and daily insulin requirements was defined (before breaking the random code), with treatment being considered either successful (improvement in one primary parameter without worsening of the other), having no effect, or a failure (worsening of one or both parameters). By these definitions, treatment was considered successful in 45% of the acarbose patients and in 14% of the placebo patients ($P = 0.0001$). Treatment was considered a failure in 4% of acarbose patients and in 12% of placebo patients ($P = 0.0245$).

Safety

Most of the adverse events involved the digestive system, with 76% of the acarbose patients reporting flatulence and 33% reporting diarrhea compared with

35 and 13% of placebo patients, respectively. There were no significant differences between treatment groups in the incidence of adverse events related to other body systems.

There was a trend toward a higher incidence of treatment-emergent serum glutamic-oxaloacetic transaminase (SGOT) elevations (5% for acarbose and 2% for placebo; NS) and serum glutamic-pyruvic transaminase (SGPT) elevations (7% for acarbose and 5% for placebo; NS) in acarbose-treated patients than in the placebo control subjects. Of those patients with serum transaminase elevations, three had elevations greater than three times the upper limit of normal for SGOT and/or SGPT. These elevations were asymptomatic and became normalized after discontinuation of the study medication. There were no differences between treatment groups in any other clinical laboratory tests or vital signs. The frequencies of premature study termination were comparable between treatment groups.

CONCLUSIONS — In this study, we have demonstrated that the treatment of insulin-requiring type II diabetic patients with acarbose was associated with improved long-term glycemic control, as indicated by a reduction in HbA_{1c} of 0.40% and a decrease in the total daily insulin dose of 8.3% relative to placebo control subjects. During the course of treatment, there was a steady decline in HbA_{1c} values in acarbose-treated patients. Of the patients treated with acarbose, 45% showed a positive clinical response, which was defined as a reduction in HbA_{1c} concentration of at least 1% and/or a reduction in total daily insulin requirement of 20%, compared with a 14% response rate in the placebo-treated patients.

The HbA_{1c} values reported in this study were obtained using the Daiichi assay (SmithKline). Because this assay has a different normal range (3.6–4.9%) than the University of Missouri high-performance liquid chromatography reference system used in the Diabetes Control and Complications Trial (DCCT) (9), experiments were performed to enable a conversion of the Daiichi values to University of Missouri values (unpublished data on file, Miles). When the mean values of HbA_{1c} were converted using the derived regression equation, acarbose was found to reduce HbA_{1c} levels by 0.53% relative to placebo. Extrapolating from the results reported in the DCCT, a reduction of this magnitude would be expected to reduce the risk of microvascular complications (i.e., sustained progression of retinopathy) by 20–25%, from 4.7/100 patient-years to 3.6/100 patient-years.

In addition to reducing HbA_{1c} levels, acarbose also significantly reduced postprandial glucose levels. After a test meal challenge, acarbose was shown to reduce 60-, 90-, and 120-min plasma glucose levels and glucose AUC compared with placebo. The role of postprandial elevations of glucose in the pathogenesis of long-term diabetic complications has not been extensively studied. While HbA_{1c} may be representative of glycation of long-lived proteins, it may not accurately reflect the effects of glycation of short-lived proteins. Proteins with a rapid turnover may be susceptible to modification by postprandial excursions of glycemia, and these short-lived glycated proteins may be involved in the etiology of diabetic microvascular complications.

Although acarbose-treated patients reported more adverse events than did placebo control subjects, the majority of patients completed the study and received the maximal dose of study medication. Most of the adverse events that were reported affected the GI system (e.g., flatulence and diarrhea) and were relatively mild in nature, as indicated by comparable rates of study withdrawal (due to adverse events) in the placebo and the acarbose groups (4 vs. 9%, respectively). The greater incidence of GI disturbances in acarbose-treated patients was not unexpected, since inhibition of α-glucosidases results in greater quantities of undigested carbohydrates reaching the large bowel, leading to increased bacterial fermentation and gas production. Because of the forced-titration design of this study, however, the effects of dose and duration on the incidence of adverse events were difficult to ascertain.

A trend toward serum transaminase elevations was noted in this study. In all cases, the transaminase elevations were completely reversed with cessation of acarbose therapy and were not associated with any other clinical or laboratory evidence of hepatic dysfunction.

Acarbose represents a novel therapeutic approach for the treatment of insulin-requiring type II diabetic patients. This study demonstrates that the addition of acarbose to insulin and dietary therapy results in significant improvement in overall glycemic control, as is manifest by a reduction in HbA_{1c} of 0.40% and a reduction in 1-h postprandial glucose of 3.0 mmol/l, despite the significantly lower dosages of insulin that are administered to these patients. With the exception of GI disturbances (i.e., flatulence and soft stools or diarrhea), acarbose is a well-tolerated agent. These findings strongly suggest a beneficial role for acarbose, in combination with diet and insulin, for the treatment of insulin-requiring patients with type II diabetes.

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