Acarbose in the Treatment of Type I Diabetes

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OBJECTIVE — This 36-week multicenter double-blind placebo-controlled study was designed to assess the safety and efficacy of acarbose, administered in conjunction with diet and insulin therapy, for the treatment of patients with type I diabetes.

RESEARCH DESIGN AND METHODS — Acarbose was administered using a forced titration protocol in dosages ranging from 50 to 300 mg t.i.d.

RESULTS — Treatment with acarbose was associated with a mean reduction in postprandial glucose levels (60 min after the administration of a test meal) of 59 mg/dl and a mean reduction in HbA_{1c} levels of 0.48%. There was no difference in the incidence of hypoglycemia between treatment groups. Gastrointestinal events, including flatulence, diarrhea, and abdominal pain, were reported more frequently in acarbose-treated patients than in placebo-treated patients.

CONCLUSIONS — Acarbose was found to be a safe and effective agent, when used in combination with diet and insulin therapy, for the treatment of type I diabetes.

There is a growing body of evidence that demonstrates a link between hyperglycemia and the development of microvascular complications (1–4). The Diabetes Control and Complications Trial (DCCT) has demonstrated that reductions in glycated hemoglobin levels are associated with concomitant reductions in the incidence of retinopathy, nephropathy, and neuropathy (5). Other studies in both animals and humans also support the concept that well-controlled blood glucose levels may prevent or slow the progression of microvascular disease (4,6,7). Since these complications are a major source of the morbidity and mortality associated with diabetes, the ability to define therapeutic approaches that enable the achievement of the best possible glycemic control is a primary goal for the treatment of diabetic patients.

Acarbose represents a novel therapeutic approach for the treatment of hyperglycemia in diabetic patients. This complex oligosaccharide is a potent competitive inhibitor of intestinal brush border α-glucosidases that are required for the breakdown of starches, dextrins, maltose, and sucrose into absorbable monosaccharides. After the administration of acarbose, the resulting delay in the digestion and the subsequent absorption of intestinal carbohydrates has been shown to improve glycemic control in both type I and type II diabetic patients (8–13). Taken with each meal, acarbose attenuates the rise in postprandial plasma glucose in both type I and type II diabetic individuals and is associated with a reduction in postprandial serum insulin levels in type II diabetic patients.

This paper reports the results of a multicenter placebo-controlled study designed to determine the long-term safety and efficacy of acarbose, in conjunction with diet and insulin therapy, for the treatment of patients with type I diabetes.

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DCCT, Diabetes Control and Complications Trial.

RESEARCH DESIGN AND METHODS

Patient population

The study population consisted of male and female patients aged ≥18 years with an established diagnosis of type I diabetes and a stable body weight. Patients were excluded from the study if they had any disease or condition that significantly complicated the diabetic state or adherence to the protocol, including gastrointestinal disease associated with abnormal gut motility and/or absorption. Approval from the institutional review board was obtained for all centers, and written informed consent was obtained from all patients before enrollment in the study.

Study design

This study consisted of a screening visit, a 6-week pretreatment (run-in) period, a 24-week double-blind randomized parallel (acarbose versus placebo) treatment period, and a 6-week posttreatment (follow-up) period. During the pretreatment period, each patient was instructed to follow a diabetic diet designed to maintain a stable body weight throughout the study. Patients were randomized to receive either acarbose or placebo three times daily and were instructed to take the study medication at the beginning of each main meal.

A standard insulin protocol was not used for the study. Patients were on a variety of insulin regimens ranging from two to four injections of insulin per day and including various combinations of regular/NPH and regular/ultralente insulins. Stabilization of the patient's prestudy insulin regimen was done during the 6-week run-in to the start of the study drug. Following randomization, the insulin dosage was adjusted based on hypoglycemic events and was done at the discretion of the individual investigator. A hypoglycemic event was defined by the investigator on the basis of patients' reported clinical symptoms and/or self-monitored blood glucose.

Acarbose was administered using a forced titration protocol with the dosage titrated at 6-week intervals in the following increments: 50 mg t.i.d. (baseline, week 0),

Table 1—*Demographic characteristics of patients valid for efficacy analysis*

	Treatment group	
	Placebo	Acarbose
n	122	114
Mean age (years)	36.8 ± 1.1	37.7 ± 1.1
Sex (% M/F)	65/35	66/34
Mean body weight (kg)	73.2 ± 1.2	73.1 ± 1.3
Mean BMI (kg/m^2)	24.9 ± 0.3	24.6 ± 0.3
Caucasian (%)	86	89
Black (%)	8	4
Hispanic (%)	6	6
Asian (%)	0	1
Mean duration of diabetes (years)	13.4 ± 1	15.8 ± 1

100 mg t.i.d. (week 6), 200 mg t.i.d. (week 12), and 300 mg t.i.d. (week 18). Reduction of the dose to a previously tolerated level was permitted at any time if intolerable adverse effects other than hypoglycemia developed. If hypoglycemia developed, the insulin dosage was reduced at the discretion of the investigator.

During the 24-week treatment period, patients were evaluated at 6-week intervals for dose titration, clinical and laboratory assessment, reporting of any side effects, adjustment of insulin dosage, and assessment of protocol compliance. During the 6-week follow-up period, patients continued to follow their prescribed dietary and insulin regimens.

At each study visit, a full-meal tolerance test was performed. Plasma glucose measurements were taken before the test meal (fasting) and at 60, 90, and 120 min after the test meal was served. The test meal consisted of a 600-calorie breakfast containing 50% carbohydrate, 30% fat, and 20% protein ingested over a 15- to 20-min period. Acarbose was administered with the first bite of the test meal. Additional clinical data collected at study visits included body weight and other vital signs, HbA_{1c} levels, fasting blood chemistry (including total cholesterol and total triglycerides), urinalysis, and hematology counts. HDL cholesterol was measured at baseline and at the end of the treatment period. All efficacy and safety laboratory measurements were analyzed at a central laboratory (SmithKline), with the exception of the plasma glucose values, which were analyzed at individual centers. Glycated hemoglobin levels were assayed using the Daiichi method (SmithKline), which has a normal range of 3.6–4.9%.

The primary criteria of efficacy were the mean change from baseline in HbA_{1c} levels, the mean percentage change in total daily insulin requirements from baseline, and the mean change from baseline in the number of hypoglycemic episodes at the treatment endpoint. The treatment endpoint was defined as the last valid observation for each patient during the double-blind phase of the study. Secondary efficacy analyses included the mean change from baseline in meal tolerance test variables (fasting, postprandial blood glucose levels, glucose area-under-curve [from 0 {fasting} to 120 min], glucose C_{max} [maximal postprandial glucose concentration], and glucose rise [1-h postprandial glucose rise above the fasting level]), serum lipid levels, HbA_{1c} levels, and total daily insulin requirements at each of the scheduled visits.

The safety evaluation consisted of a complete medical history taken at visit 1 and a complete physical examination, 12-lead electrocardiogram, and laboratory evaluation performed at visits 1, 4, 6, 8, and 9. Vital signs were measured, and adverse events were recorded at all visits.

Statistical analyses

All significance tests were performed at an alpha level of 0.05. Continuous data were analyzed using an analysis of variance model. The analysis of variance model included effects for drug, center, and stratum. In addition, for those variables and visits where the drug-by-center or by-stratum interaction effects were significant, the respective interaction term was included in the model. In this study, there was little indication of drug-by-stratum interaction, and therefore, the intended analysis by stratum was deemed unnecessary.

Pairwise comparisons for all during-treatment visits were performed via one-tailed tests for HbA_{1c}, meal tolerance test variables, total cholesterol, total triglycerides, and LDL cholesterol. Pairwise comparisons were performed via two-tailed tests for the number of hypoglycemic episodes, daily insulin requirements, HDL cholesterol, and all variables when analyzed for baseline comparability. Within-group changes from baseline were tested via one-tailed or two-tailed Student's *t* tests, as determined by whether the corresponding between-group comparison was one-tailed or two-tailed. All comparisons were based on the least squares method estimated by the model.

Changes from baseline in HbA_{1c} levels and daily insulin requirements at the double-blind endpoint were also analyzed categorically. An "improvement" was defined as a decrease of at least 1% in HbA_{1c} levels or a ≥20% decrease in the total daily insulin requirement from baseline. A "worsening" was defined as an increase of at least 1% in HbA_{1c} levels or a ≥20% increase in the total daily insulin requirement from baseline. Comparisons between treatment groups of percent of patients showing improvement versus no change or worsening were made based on a one-tailed test using Mantel-Haenszel method with the center as a covariate. In addition, a combined response variable based on both variables was defined. A "success" was defined as an improvement in either HbA_{1c} or insulin as defined above, without a worsening in the other response. A "failure" was defined as a worsening of either response. Comparisons between treatment groups of success (versus no change or failure) were made similarly.

Safety data (dropout rates, incidence of adverse events, and clinical laboratory results) were analyzed by χ^2 or Fisher's exact tests.

RESULTS

Efficacy

A total of 264 patients were randomized to receive either placebo (n = 132) or acarbose (n = 132). Data from 122 patients in the placebo group and 114 patients in the acarbose group were valid for the efficacy analysis. The treatment groups were comparable at baseline with respect to all demographic and disease characteristics analyzed (Table 1). Baseline metabolic variables and insulin dose were also similar between treatment groups (Table 2).

Treatment with acarbose was associated with a statistically significant reduction in mean HbA_{1c} levels (placebo subtracted) of 0.48%. A time course depicting the mean change in HbA_{1c} levels (from baseline) for each treatment visit indicates significant reductions in the acarbose-treated patients at all timepoints examined (weeks 6, 12, 18, and 24) (Fig. 1). In contrast, in placebo-treated patients, HbA_{1c} levels increased during the double-blind treatment period.

Treatment with acarbose was also associated with significant reductions in all

Table 2—*Baseline and mean change from baseline at the double-blind endpoint for all efficacy variables for all valid patients*

	Placebo		Acarbose		Difference in mean change from baseline between treatment groups
	Baseline	Change	Baseline	Change	
HbA_{1c} (%)	6.59 ± 0.09	0.18 ± 0.08*	6.58 ± 0.09	−0.30 ± 0.08†	−0.48
Total daily insulin dose‡	49.8 ± 1.8	−0.5 ± 1.6	46.6 ± 1.9	−3.4 ± 1.6†	−2.9
Number of hypoglycemic episodes	4.9 ± 1	−2.9 ± 0.8†	7.0 ± 1.0	−2.2 ± 0.8†	0.7
Fasting plasma glucose (mg/dl)	197.6 ± 8.6	−0.4 ± 10.8*	207.8 ± 8.7	−26.8 ± 11.0†	−26.4
60-min plasma glucose (mg/dl)	294.0 ± 9.8	0.6 ± 11.4*	298.1 ± 9.9	−58.0 ± 11.5†	−58.6
90-min plasma glucose (mg/dl)	308.6 ±10.3	−11.7 ± 13.3*	312.9 ± 10.5	−58.6 ± 13.0†	−46.9
120-min plasma glucose (mg/dl)	293.4 ± 10.5	−12.4 ± 13.4*	301.8 ± 10.7	−53.6 ± 13.1†	−41.2
Plasma glucose C_{max} (mg/dl)	319.2 ± 10.1	−6.3 ± 12.9*	326.0 ± 10.2	−60.4 ± 12.6†	−54.1
Plasma glucose rise (mg/dl)	96.5 ± 6.2	−3.4 ± 7.4*	90.3 ± 6.3	−26.2 ± 7.2†	−22.8
Plasma glucose area under the curve (mg · min · dl $^{-1}$)	36,478 ± 1,231	−446 ± 1,479*	37,577 ± 1,251	−7,948 ± 1,503†	−7,502.0
Fasting triglyceride (mg/dl)	110.0 ± 7.1	11.3 ± 10.0	95.0 ± 7.3	1.5 ± 10.2	−9.8
HDL cholesterol (mg/dl)	49.2 ± 1.4	1.4 ±1.1	47.3 ± 1.5	1.9 ± 1.1	0.5
LDL cholesterol (mg/dl)	133.2 ± 4.8	−2.1 ± 2.9	130.7 ± 4.9	1.0 ± 3.0	3.1
Total cholesterol (mg/dl)	204.7 ± 5.0	0.5 ± 3.0	199.7 ± 5.7	4.7 ± 3.0	4.2
Body weight (kg)	73.0 ± 1.2	0.1 ± 0.2	73.2 ± 1.2	0.2 ± 0.2	0.1

Data are means ± SE. Acarbose dosage was 100–300 mg t.i.d. Endpoint represents the final double-blind assessment after 6–24 weeks of therapy. Change is the percentage change from baseline. *Significant difference from acarbose. †Significant change from baseline. ‡Baseline values are expressed in units.

plasma glucose variables that were measured (Table 2). Fasting plasma glucose levels were reduced by 26 mg/dl (relative to placebo) and postprandial plasma glucose levels were reduced by 59 mg/dl, 47 mg/dl and 41 mg/dl at 60, 90, and 120 min following administration of a standardized test meal (Fig. 2). There were also significant reductions in plasma glucose C_{max}, glucose rise, and the area under the curve in acarbose-treated patients, compared with placebo control subjects.

Despite the effect of acarbose on plasma glucose levels, there was no significant difference between treatment groups in either the mean change in total daily insulin dose or in the mean change from baseline in the number of hypoglycemic episodes. In addition, there were no significant differences in the number of injections or the class of insulin administered from baseline to double-blind endpoint. For other variables that were measured, including body weight, fasting triglyceride, and total, HDL, and LDL cholesterol, there were no significant differences between treatment groups.

The percentage of patients exhibiting a positive response to treatment, defined as a decrease from baseline in HbA_{1c} levels of at least 1% or as a ≥20% decrease in total daily insulin dose, is shown in Table 3. HbA_{1c} levels improved in 8% of the placebo-treated patients and 19% of the acarbose-treated patients; 7% of the placebo-treated patients and 15% of the acarbose-treated patients exhibited improvement in their daily insulin requirements. A combined response variable, based on improvement in either HbA_{1c} levels or total daily insulin dose, indicated that 32% of the acarbose-treated patients and 10% of the placebo-treated patients exhibited a positive response to treatment.

Safety

Sixty-three of the 128 placebo-treated patients (49%) and 110 of the 131 acarbose-treated patients (84%) reported one or more adverse events while taking the study medication ($P = 0.01$). These differences between treatment groups were predominantly the result of gastrointestinal symptoms, the most common of which were flatulence, diarrhea (an increase in the number and/or a decrease in the consistency of bowel movements), and abdominal pain. The adverse events that occurred in ≥5% of patients are listed in Table 4.

Five percent (6/132) of the placebo-treated patients and 19% (25/132) of the acarbose-treated patients stopped taking the study medication because of adverse events ($P = 0.0004$). Twenty-four of the acarbose-treated patients discontinued therapy because of gastrointestinal disturbances, and one discontinued therapy because of elevated serum transaminase levels. At the discontinuation of treatment, 17 of these patients were receiving acarbose 50 mg

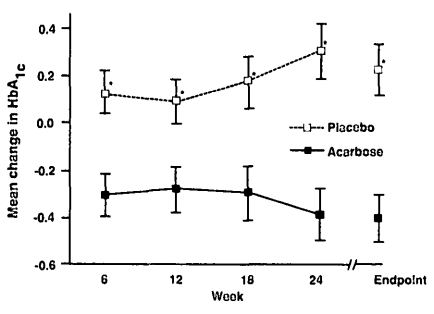

Figure 1—*Mean percentage change from baseline in HbA_{1c} in patients receiving acarbose (■) or placebo (□) at 6, 12, 18, and 24 weeks of treatment and at the double-blind endpoint. *Significantly different from acarbose at P ≤ 0.05.*

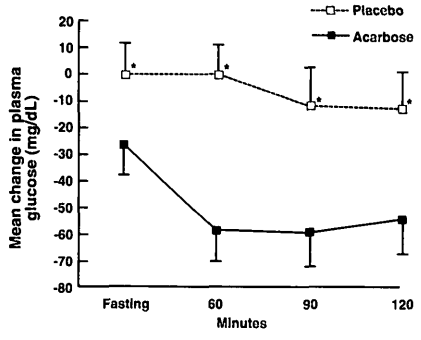

Figure 2—*Mean change from baseline in plasma glucose levels during a standard meal tolerance test in patients receiving acarbose (■) or placebo (□) at the double-blind endpoint. *Significantly different from acarbose at P ≤ 0.05.*

Table 3—*Categorical evaluation of changes from baseline in HbA_{1c}, total insulin dose, and the combined response for patients valid for efficacy*

	Placebo	Acarbose
n	122	114
HbA_{1c} change from baseline		
Improved	10 (8)*	21 (19)
Same	93 (77)	86 (77)
Worse	18 (15)	4 (4)
Percentage change from baseline in total daily insulin dose		
Improved	9 (7)*	17 (15)
Same	102 (84)	91 (80)
Worse	11 (9)	6 (5)
Combined response		
Success	12 (10)*	36 (32)
No change	82 (68)	65 (59)
Failure	27 (22)	10 (9)

Data are *n* (%). HbA_{1c} data were missing for one patient in the placebo group and three patients in the acarbose group. For the HbA_{1c} change from baseline, improvement was defined as a decrease of ≥1%; worsening was defined as an increase of ≥1%. For the percentage change from baseline in total daily insulin dose, improvement was defined as a decrease of 20%, and worsening was defined as an increase of 20%. For the combined response, success was defined as an improvement in either HbA_{1c} or insulin requirement, as defined above, without a worsening in the other response, and failure was defined as a worsening of either response. *Significantly different from acarbose.

t.i.d., four were receiving 100 mg t.i.d., and three were receiving 300 mg t.i.d.

Asymptomatic elevations of aspartate aminotransferase and/or alanine aminotransferase >1.8 times higher than the upper limit of normal were reported in one placebo-treated patient and eight acarbose-treated patients. In those cases where follow-up was conducted, elevated transaminase levels subsided to normal or near normal values after discontinuing the study medication.

CONCLUSIONS — The goal of normal or near normal HbA_{1c} has been difficult to achieve for most patients with type I diabetes with current available therapy. Control of postprandial glucose fluctuations has been especially elusive (14,15). α-glucosidase inhibitors offer an innovative approach for achieving glycemic control in type I diabetic patients by effectively decreasing and delaying the absorption of carbohydrate and smoothing postprandial fluctuations of glucose. In the present study, the treatment with acarbose was associated with a significant improvement in postprandial hyperglycemia and long-term glycemic control, as assessed by the measurement of glycated hemoglobin levels. The treatment with acarbose was associated with a mean reduction in HbA_{1c} levels of 0.48% (relative to placebo).

The magnitude of HbA_{1c} changes measured in this study can be directly compared to the DCCT by indexing the study HbA_{1c} to the DCCT standard.

To enable a conversion of the HbA_{1c} values that were obtained in the present study (using the Daiichi method) to this well-accepted reference method, the HbA_{1c} values were compared with the University of Missouri affinity chromatography assay standardized to their reference high-performance liquid chromatography system (the DCCT control reference assay). A correlation between the two assays was established, and a regression equation was derived (Bayer Clinical Report). The means of the HbA_{1c} levels converted to the standardized affinity assay (Table 5) indicate that the acarbose treatment was associated with a reduction (placebo subtracted) in HbA_{1c} levels of 0.63%.

From the results of the DCCT, a relationship between HbA_{1c} levels and the risk for sustained progression of microvascular complications such as retinopathy was derived, indicating that even moderate elevations in HbA_{1c} are associated with an increased risk of diabetic complications (5). A reduction in HbA_{1c} levels of 0.63% associated with acarbose treatment, as indicated in the present study, would be expected to reduce the risk for sustained progression of retinopathy by ~25%.

Patients with type I diabetes display extremely varied responses to therapy, characterized by idiosyncratic responses to exogenous insulin, diet, exercise, and physical and emotional stress. Clinicians may design a treatment regimen that reduces hyperglycemia, reduces insulin requirements, or both. In the present study, analysis of a combined response variable based on improvements in either HbA_{1c} levels (a reduction of at least 1%) or in insulin requirements (a reduction of at least 20%) indicated that 32% of patients in the acarbose group versus 10% of patients in the placebo group were successfully treated.

Control of postprandial glucose levels is often a major challenge in the treatment of type I diabetic patients. Increasing regular insulin at meals to control high postprandial glucose often leads to hypoglycemia before the next meal. The addition of acarbose at meals can diminish postprandial fluctuations in glucose concentration without subsequent hypoglycemia. The administration of acarbose has also been shown to minimize nocturnal hypoglycemia, presumably by prolonging glucose absorption between meals, especially after the evening meal (16). Although studies have looked at t.i.d. dosing of acarbose for maximum treatment effect, elevations in postprandial glucose may not be a problem with every meal. For some patients on intensified insulin regimens, the problem may be with postbreakfast hyperglycemia and not with other meals. Using acarbose only at breakfast can curtail postbreakfast hyperglycemia and optimize the prenoon glucose level. Alternatively, many individuals consume large amounts of carbohydrate at their evening meal; the addition of acarbose here can help optimize the evening or prebedtime glucose value.

One of the major concerns with regard to insulin therapy is the risk of hypo-

Table 4—*Incidence rates of adverse events occurring in 5% of patients*

	Placebo	Acarbose
n	128	131
Abdominal pain	8 (6)*	26 (20)
Pain	4 (3)*	12 (9)
Diarrhea	14 (11)*	43 (33)
Flatulence	50 (39)*	106 (81)
Nausea	7 (5)	7 (5)

Data are *n* (%). *Significant difference between acarbose and placebo at $P \leq 0.05$.

glycemia. Because of its mechanism of action, acarbose, when used as a monotherapy, does not cause hypoglycemia in type II diabetic patients (17), and studies of acarbose in combination with sulfonylureas or with insulin have not demonstrated that there is an increased incidence of hypoglycemia (18,19). The present study in type I diabetic patients also found improved glucose control without an increased incidence of hypoglycemia. However, in the individual patient treated with insulin, improved control on acarbose may lead, in some cases, to a need for less insulin at certain times of the day. An appropriate reduction of basal or prandial insulin may be needed to prevent hypoglycemia.

In the present trial, patients received a variety of different insulin regimens. Despite this variability, acarbose significantly improved glycemic control in these patients. These results may be relevant to the general population of type I diabetic patients who have highly variable insulin regimens.

It is possible that the administration of acarbose in the context of a standardized insulin regimen would result in even greater improvements in glycemic control than seen in this trial. In a small crossover study in which 36 patients received a standardized insulin regimen of regular insulin at each meal and lente insulin administered with acarbose 100 mg t.i.d. in the morning and evening, HbA_{1c} levels were reduced by 1.4% (20).

The incidence of gastrointestinal events was greater in the acarbose-treated patients, compared with the placebo-treated patients. Fermentation of unabsorbed carbohydrate in the colon can result in increased intestinal gas production and, therefore, accounts for the higher incidence of flatulence, abdominal pain, and diarrhea in the acarbose-treated patients. In most instances, these symptoms were mild and not bothersome to the patient, although some patients were initially more sensitive to the side effects even at the low dose. Most of the patients who dropped out in this study because of gastrointestinal side effects did so at the lower dosage level of 50 mg. In patients who were advanced to higher doses when symptoms were severe, decreasing the dose appeared to decrease the number and severity of adverse events. Decreasing the dose of acarbose and the degree of sucrose intake has been shown in other studies to decrease symptoms (21,22). Most long-term studies have demonstrated the tendency of gastrointestinal side effects to decrease with treatment (23). This adaptation to gastrointestinal side effects may be similar to that seen with increasing dietary intake of soluble fiber.

Table 5—*Mean baseline and change from baseline in HbA_{1c} levels at the double-blind endpoint (SmithKline assay and Standard Affinity conversion)*

	SmithKline (normal, 3.6–4.9%)		Standard Affinity (normal, 4–6%)	
	Mean baseline HbA_{1c} (%)	Change from baseline	Mean baseline HbA_{1c} (%)	Change from baseline
Placebo	6.59	0.18	8.81	0.24
Acarbose	6.58	−0.30	8.80	−0.39

Clinically significant changes in serum transaminase levels were more prevalent in acarbose-treated patients than in the placebo-treated patients. The reasons for these elevations are as yet unclear. They were reversible with the cessation of therapy and were not associated with clinical symptoms or with any other laboratory clinical evidence of hepatic dysfunction. Similarly, infrequent elevations in serum transaminase levels have been noted in other acarbose studies; these elevations appear to be dose-related, occurring almost exclusively at doses of 200–300 mg t.i.d. A year-long safety study and other studies have shown no increase in transaminase levels in patients treated with ≤100 mg (data on file, Bayer Corporation).

Although approved for the treatment of type II diabetes, acarbose has not yet been given the indication for treatment of type I diabetes by the Food and Drug Administration. Indications for treatment of both types of diabetes are present in a number of European countries. Based on both efficacy and safety, the current worldwide recommended dose levels for the treatment of either type I or type II diabetes are 50 or 100 mg t.i.d. Studies have shown doses of 100 mg t.i.d. to be equivalent in efficacy to 200 and 300 mg t.i.d. in both types of diabetes (20,24). In this study, the larger doses were used, but in light of other studies, one would expect equal results in terms of efficacy with 100 mg t.i.d.

The study presented here demonstrated that acarbose significantly decreased postprandial glucose and HbA_{1c} with no increase in the incidence of hypoglycemia. With the exception of gastrointestinal symptoms, acarbose was well tolerated. It provides a possible new and useful addition for better treatment of type I diabetes in many patients. Further studies to evaluate its effectiveness in the setting of a structured insulin protocol would be valuable in assessing the drug's maximal therapeutic potential for type I diabetes.

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