The Synergistic Effect of Miglitol Plus Metformin Combination Therapy in the Treatment of Type 2 Diabetes

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OBJECTIVE — To investigate the efficacy and safety of miglitol in combination with metformin in improving glycemic control in outpatients in whom type 2 diabetes is insufficiently controlled by diet alone.

RESEARCH DESIGN AND METHODS — In this multicenter, double-blind, placebo-controlled study, 324 patients with type 2 diabetes were randomized, after an 8-week placebo run-in period, to treatment with either placebo, miglitol alone, metformin alone, or miglitol plus metformin for 36 weeks. The miglitol was titrated to 100 mg three times a day and metformin was administered at 500 mg three times a day. The primary efficacy criterion was change in HbA_{1c} from baseline to the end of treatment. Secondary parameters included changes in fasting and postprandial plasma glucose and insulin levels, serum triglyceride levels, and responder rate.

RESULTS — A total of 318 patients were valid for intent-to-treat analysis. A reduction in mean placebo-subtracted HbA_{1c} of −1.78% was observed with miglitol plus metformin combination therapy, which was significantly different from treatment with metformin alone (−1.25; P = 0.002). Miglitol plus metformin also resulted in better metabolic control than metformin alone for fasting plasma glucose (−44.8 vs. −20.4 mg/dl; P = 0.0025), 2-h postprandial glucose area under the curve (−59.0 vs. –18.0 mg/dl; P = 0.0001), and responder rate (70.6 vs. 45.52%; P = 0.0014). All therapies were well tolerated.

CONCLUSIONS — In type 2 diabetic patients, miglitol in combination with metformin gives greater glycemic improvement than metformin monotherapy.

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Maintaining normal plasma glucose levels is a key factor in reducing the risk of developing diabetes complications (1,2). Current recommendations supported by recent data from the U.K. Prospective Diabetes Study data emphasize life-style management, diet, and exercise as the first-line approach, followed by therapy with hypoglycemic or antihyperglycemic agents, either alone or in combination. The biguanide metformin is a frequent first-line choice of antidiabetic medication (3,4). However, monotherapy with any hypoglycemic agent eventually necessitates the use of increasing doses because type 2 diabetes worsens over time with declining pancreatic β-cell function (5) and eventually requires addition of a second antidiabetic medication.

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Abbreviations: AUC, area under the curve; ITT, intent to treat.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The recently developed class of α-glucosidase inhibitors has a unique mode of action; it blocks oligosaccharide catabolism, delays carbohydrate digestion and absorption, and smooths and lowers postprandial plasma blood glucose peaks (6–9). Substantial evidence supports their use as monotherapy or adjunct therapy for poorly controlled type 2 diabetes (5,10–14). Miglitol is the first pseudomonosaccharide α-glucosidase inhibitor derived from 1-deoxynojirimycin and is structurally a glucose analog (15,16). Its efficacy in monotherapy (13,17) and in combination with sulfonylureas (11) as a glucose-lowering agent in type 2 diabetes has been shown in a number of clinical studies. A study of miglitol in combination with metformin has been reported previously in elderly type 2 diabetic patients (18). However, it is still unclear whether miglitol can enhance glycemic control when given in combination with metformin in middle-aged type 2 diabetic patients and whether the safety and tolerability profile of miglitol and metformin as monotherapy is affected by such a combination. Therefore, this study was performed to investigate the efficacy and safety of miglitol in combination with metformin in improving glycemic control, compared with metformin monotherapy, in middle-aged outpatients in whom type 2 diabetes was insufficiently controlled by diet alone. The primary control group in this study was the metformin arm. Comparisons with miglitol monotherapy and placebo were also performed.

RESEARCH DESIGN AND METHODS

— This was a multicenter, double-blind, randomized, placebo-controlled parallel group study. Eligible patients were type 2 diabetic patients (men and women) >40 years of age in whom diabetes was inadequately controlled by diet alone, i.e., in whom HbA_{1c} level was ≥7.2 and ≤9.5%. The major exclusion criteria included type 1 diabetes, the presence of major debilitating diseases, recent cardiovascular

events, gastrointestinal diseases, medications likely to affect intestinal motility or the absorption of nutrients, hypersensitivity to miglitol or metformin, and a history of lactic acidosis. Patients who were taking either sulfonylurea or metformin below the maximum dose could be eligible as long as the antidiabetic drug was discontinued. Before starting any study procedures, patients who fulfilled the eligibility criteria gave their written informed consent and entered a single-blind, 8-week placebo run-in period. All subjects were seen by a dietitian before the run-in period and were advised regarding a well-balanced weight-reducing diet (19). They were also advised regarding exercise, mainly walking 20–30 min at least three times per week. The diet was reinforced after 1 month, and if the HbA_{1c} was still ≥7.2% by 2 months, they were considered dietary failure. Patients with HbA_{1c} levels ≥7.2 but ≤9.5% (110–146% above the upper limit of the normal range) at the end of the run-in period were eligible for randomization to matching placebo or to active treatment with either miglitol plus placebo, metformin plus placebo, or metformin plus miglitol for 36 weeks. The miglitol dosage was force-titrated as follows: administration of the drug was started at 25 mg three times a day for 4 weeks, increased to 50 mg three times a day for 8 weeks, and then increased to 100 mg three times a day until the end of the study. Administration of metformin was started and maintained at 500 mg three times a day throughout the study. All patients were given an Elite Glucometer and were advised regarding regular home blood-glucose monitoring.

Efficacy and safety evaluation

The primary efficacy criterion was the change in HbA_{1c} level from baseline to the end of the double-blind treatment for the intent-to-treat (ITT) population, which included any patient who had both a baseline value and at least one postrandomization efficacy value.

Secondary efficacy parameters included the change in fasting and postprandial plasma glucose and insulin levels and serum triglyceride levels from baseline to the end of treatment, measured at 0, 60, 90, and 120 min after a standardized liquid test breakfast (55% carbohydrate, 30% fat, and 15% protein; providing ~450 kcal). The study medications were given with the tolerance test meal. The proportion of responders in the different treatment groups was also evaluated, in which a clinically significant response was defined as either a ≥15% reduction in HbA_{1c} from baseline or an HbA_{1c} level <7.0%.

HbA_{1c} was measured during screening, at week –2 and baseline, and thereafter at each visit (weeks 4, 8, 12, 16, 20, 28, and 36) after randomization. Routine fasting plasma glucose was measured at week −2 and at every subsequent visit. Fasting and postprandial (60, 90, and 120 min) glucose and insulin levels as well as triglyceride levels were specifically measured at baseline and at weeks 12, 16, and 36 or at premature termination.

Safety and tolerability were investigated by the occurrence of adverse events; hypoglycemic events; changes in vital signs; and changes in laboratory values, including biochemical parameters, hematology, vitamins (thiamine-dependent transketolase, folate, vitamin B_{12}, vitamin A, and retinol protein binding), and standard urinalysis. Adverse events were monitored and documented at week –2 and at all visits thereafter. Routine biochemistry, hematology, and urinalysis were performed at screening, baseline, and weeks 12, 20, and 36 or at premature termination; vitamin assays were performed at baseline and at the final visit. Physical examinations were conducted at screening, week –2, baseline, week 12, and the end of the study, whereas vital signs and weight were recorded at each visit. Routine laboratory determinations were performed using standard methodology by local laboratories, whereas the preprandial and postprandial efficacy measurements and vitamin evaluations were performed at a central laboratory.

Statistical analysis

To detect a mean difference of 0.6% in the change in HbA_{1c} between treatment groups from baseline to the end of treatment, with $\alpha = 0.05$ and a power $(1-\beta)$ of at least 90%, a minimum of 60 patients per treatment group were required. To account for multicenter variability, this was increased by 20% to 75 patients per treatment arm.

Treatment groups were compared at baseline for demographic variables and other prognostic factors, such as family history of type 2 diabetes, medical history, vital signs, and concomitant medications. The primary efficacy parameter was the change in HbA_{1c} from baseline to the end of treatment and was analyzed by analysis of variance techniques. All four treatment groups were included in the primary comparisons, which used orthogonal contrasts.

The primary analysis of efficacy was performed on the ITT population, which included all patients who had both baseline and postrandomization efficacy values. For end-of-treatment analysis, the last-observation-carried-forward method was used. All patients who received at least one dose of trial medication were included in the safety analysis. Adverse events and other safety parameters were analyzed in terms of the percentage of patients in whom they occurred.

RESULTS — A total of 324 patients were randomized in the study: 83 to placebo, 82 to miglitol monotherapy, 83 to metformin monotherapy, and 76 to metformin/miglitol combination therapy. Six patients (one each from the placebo and metformin/miglitol combination therapy groups and two each from the miglitol and metformin monotherapy groups) were excluded from the ITT analysis because of the absence of recorded HbA_{1c} values after randomization. A total of 318 patients (98%) were valid for the ITT analysis. Selected demographic parameters and clinical data for all randomized patients are shown in Table 1. Treatment groups were comparable for number of patients, age, race (predominately Caucasian), weight and BMI, sex ratio, duration of diabetes, and baseline HbA_{1c}. The mean durations of treatment exposure by treatment group were as follows: placebo 200.3 ± 93.3 days; miglitol 190.9 ± 90.5 days; metformin 231.6 ± 70.1 days; metformin plus miglitol combination 203.3 ± 94.6 days.

The primary comparison for all efficacy parameters was between the metformin plus miglitol combination and metformin monotherapy treatment groups. The mean changes in HbA_{1c} values (means ± SEM) in response to the different treatments are shown in Table 2. There was an increase of 0.38 ± 0.12% in the placebo group, virtually no change in the miglitol group (0.02 ± 0.10%), a decrease of −0.85 ± 0.12% in the metformin group, and a decrease of −1.39 ± 0.11% in the metformin plus miglitol

Table 1—*Demographic and clinical data on randomized patients*

Parameters	Placebo	MIG	MET	MIG + MET
n	83	82	83	76
Age (years)	57.7 ± 9.9	57.3 ± 9.0	57.9 ± 8.6	58.9 ± 7.9
Weight (kg)	88.6 ± 14.1	91.0 ± 15.5	89.0 ± 17.8	85.6 ± 13.1
Race				
Caucasian	76 (91.6)	73 (89.0)	73 (88.0)	70 (92.1)
Black	1 (1.2)	0 (0.0)	1 (1.2)	3 (3.9)
Asian	4 (4.8)	4 (4.9)	6 (7.2)	3 (3.9)
Other	2 (2.4)	5 (6.1)	3 (3.6)	0 (0.0)
BMI (kg/m^2)	31.1 ± 4.4	31.1 ± 4.5	30.7 ± 5.1	29.5 ± 3.8
Male/female	56/27	64/18	61/22	59/17
Duration of diabetes (years)	5.1 ± 4.9	5.2 ± 4.7	7.5 ± 7.4	6.1 ± 5.5
Previous use of oral hypoglycemics agents				
None	48 (57.8)	42 (51.2)	55 (66.3)	46 (60.5)
Metformin	22 (26.5)	18 (22.0)	19 (22.9)	16 (21.1)
Sulphonylureas	33 (39.8)	25 (30.5)	43 (51.8)	35 (46.1)
HbA_{1c}(%)	8.1 ± 0.7	8.2 ± 0.9	8.2 ± 0.9	8.3 ± 0.8

Data are means ± SD and *n* (%). MIG, miglitol; MET, metformin.

combination group ($P = 0.002$, comparing miglitol plus metformin and metformin monotherapy). The placebo-substracted mean change in HbA_{1c} or the actual treatment effect is illustrated in Fig. 1. The mean reduction in HbA_{1c} compared with placebo was −0.37% for miglitol treatment, −1.25% for metformin treatment, and −1.78% for metformin plus miglitol treatment. The end-of-treatment mean ± SEM of HbA_{1c} was 8.5 ± 0.1% for placebo, 8.2 ± 0.2% for miglitol, 7.3 ± 0.1% for metformin, and 6.9 ± 0.1% for metformin plus miglitol combination. The latter group achieved the targeted HbA_{1c} level of <7.0% recommended by the American Diabetes Association (20). Furthermore, significantly ($P = 0.0014$) more patients were classified as responders (i.e., showed ≥15% reduction from baseline in HbA_{1c} or achieved HbA_{1c} <7.0%) to metformin plus miglitol combination therapy (70.6%) compared with metformin monotherapy (45.5%); even if only HbA_{1c} <7.0% was used to define responders, combination therapy still maintained a high responder rate (64.0%) compared with metformin monotherapy (34.6%).

Reductions in levels of postprandial plasma glucose were observed in all the active treatment groups, in contrast to an increase in patients taking placebo (Table 2). The reductions in patients receiving metformin plus miglitol combination therapy were significantly greater ($P < 0.0001$) than those in patients on metformin monotherapy. The reduction in fasting plasma glucose was also greater in patients receiving metformin plus miglitol combination therapy than in patients receiving metformin monotherapy ($P = 0.0025$).

Although the mean change in postprandial plasma insulin at 60 min did not reach statistical significance for the comparison between metformin plus miglitol combination therapy and metformin monotherapy, a statistically significant difference was observed in favor of the combination therapy at 90 and 120 min ($P = 0.0143$ and 0.0177, respectively) (Table 2). Postprandial plasma insulin levels decreased more in the placebo group than in the metformin group, which could be caused by bias in the patients' disease status. Because the patients were not newly diagnosed, their duration of disease varied considerably, and some had previously been taking sulfonylurea, which stimulates release of pancreatic insulin. It is clear that lower postprandial plasma insulin levels despite higher postprandial plasma glucose levels suggests

Table 2—*Mean change from baseline in selected study variables (ITT population)*

Parameters	Placebo	MIG	MET	MIG + MET	MET versus MIG + MET (*P*)
n	82	80	81	75	
HbA_{1c} (%)	0.38 ± 0.12	0.02 ± 0.10	−0.85 ± 0.12	−1.39 ± 0.11	0.002
Fasting plasma glucose (mg/dl)	−0.9 ± 5.7	−1.0 ± 5.6	−20.4 ± 5.1	−44.8 ± 5.1	0.0025
Postprandial plasma glucose (mg/dl)					
60 min	6.2 ± 7.8	−16.3 ± 7.6	−28.7 ± 7.0	−81.9 ± 8.1	<0.0001
90 min	6.9 ± 8.3	−24.1 ± 8.5	−33.7 ± 7.7	−95.4 ± 9.1	<0.0001
120 min	4.0 ± 8.5	−23.2 ± 8.5	−37.9 ± 7.9	−86.4 ± 9.3	<0.0001
Incremental plasma glucose AUC (mg · h/dl)	7.9 ± 7.0	−34.7 ± 7.2	−18.0 ± 7.3	−59.0 ± 7.2	
Fasting plasma insulin (pmol/l)	−0.3 ± 14.0	−18.5 ± 14.0	−17.4 ± 4.7	−12.4 ± 3.8	NS
Postprandial plasma insulin (pmol/l)					
60 min	−48.8 ± 18.0	−68.2 ± 18.1	−19.9 ± 15.0	−33.5 ± 14.4	NS
90 min	−40.3 ± 17.4	−88.4 ± 18.6	−18.9 ± 14.8	−81.6 ± 18.1	0.0143
120 min	−48.4 ± 19.0	−63.6 ± 19.8	3.9 ± 14.8	−59.1 ± 19.3	0.0177
Incremental plasma insulin AUC (pmol · h/l)	−45.0 ± 23.1	−72.8 ± 21.9	0.5 ± 17.7	−60.1± 19.4	0.0592
Body weight (kg)	−0.69 ± 0.27	−0.42 ± 0.29	−0.79 ± 0.33	−1.87 ± 0.33	NS

Data are mean ± SE. NS, not significant, MIG, miglitol, MET, metformin.

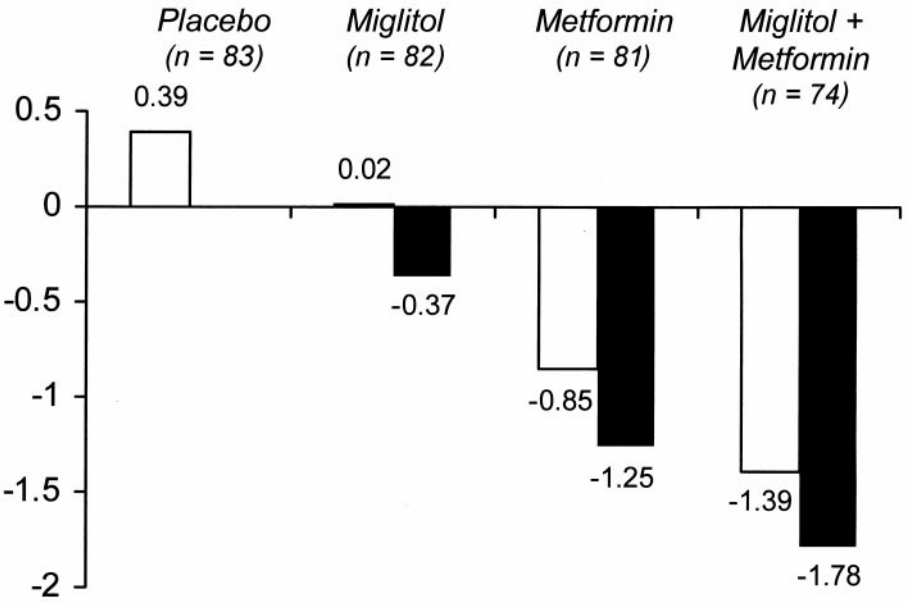

Figure 1—*The mean absolute change (open bar) and the placebo-subtracted change (closed bar) in HbA_{1c} from baseline to end of treatment for miglitol monotherapy, metformin monotherapy, and miglitol plus metformin combination therapy.*

decreased β-cell function. This could be caused by glucotoxicity resulting from increased plasma glucose in the placebo group (21). Changes in fasting serum insulin and triglyceride levels observed from baseline to the end of treatment did not differ significantly between metformin plus miglitol combination therapy and metformin monotherapy and showed no consistent trend.

A total of 324 patients were valid for the safety analysis. After randomization, 302 (93.2%) patients reported adverse events. The proportion of patients experiencing adverse events in the metformin group was 78 of 83 (94.0%), compared with 74 of 76 (97.4%) on metformin plus miglitol combination therapy (Table 3), which is an increased incidence of 3.4%. For comparison, the incidence was 85.5% in the placebo group and 96.3% in the miglitol group. Most adverse events were gastrointestinal; flatulence and diarrhea were reported more frequently by patients receiving miglitol or metformin plus miglitol combination therapy than those receiving the other treatments.

A total of 37 (11.4%) randomized patients discontinued the study prematurely because of adverse events: 2 (2.4%) in the placebo group, 11 (13.4%) in the miglitol group, 5 (6.0%) in the metformin group, and 19 (25.0%) in the metformin plus miglitol combination therapy group. Flatulence and diarrhea were the most common adverse events associated with premature discontinuation from the study.

A total of 16 patients reported 18 serious adverse events postrandomization: 3 of these events occurred in the placebo group, 2 in the miglitol group, 4 in the metformin group, and 9 in the metformin plus miglitol combination group. None of these serious adverse events were deemed by the investigators to be either probably or possibly related to the study drug. No deaths occurred during this study. No severe hypoglycemic episodes were reported. The rate of hypoglycemia was slightly higher in patients receiving metformin plus miglitol combination therapy (13.2 vs. 9.6% receiving metformin), but this difference was not clinically significant.

Treatment groups did not show any clinically or statistically significant differences in hematological and biochemical parameters or urinalysis. One patient in the metformin group showed an elevation >1.8 times the upper limit of normal in alanine aminotransferase, but this was not considered clinically relevant. Glycosuria was observed considerably less frequently for the metformin plus miglitol combination group, with an incidence of 7% compared with 26% for metformin monotherapy. There was no significant laboratory abnormality or change in vital signs during the study. Although all treatment groups showed a mean decrease in body weight, intergroup comparison suggested that patients who received metformin plus miglitol combination therapy lost more weight (Table 2) than those in the other treatment groups: −1.87 kg for metformin plus miglitol combination compared with −0.79 kg for metformin alone, −0.42 kg for miglitol alone, and −0.69 kg for placebo (P = NS).

Table 3—*Incidence of most common adverse events*

	Placebo	MIG	MET	MIG + MET
n	83	82	83	76
Any adverse events	71 (85.5)	79 (96.3)	78 (94.0)	74 (97.4)
Digestive system				
Any event	29 (34.9)	58 (70.7)	50 (60.2)	66 (86.8)
Flatulence	12 (14.5)	46 (56.1)	24 (28.9)	48 (63.2)
Diarrhea	9 (10.8)	35 (42.7)	23 (27.7)	42 (53.3)
Constipation	5 (6.0)	5 (6.1)	7 (8.4)	7 (9.2)
Nausea	2 (2.4)	7 (8.5)	14 (16.9)	13 (17.1)
Dyspepsia	2 (2.4)	6 (7.3)	7 (8.4)	11 (14.5)
Abdominal cramps	2 (2.4)	4 (4.9)	5 (6.0)	6 (7.9)
Hypoglycemia	7 (8.4)	7 (8.5)	8 (9.6)	10 (13.2)

Data are *n* (%). Common adverse events are considered those with incidence >7% in at least one treatment group. MIG, miglitol, MET, metformin.

CONCLUSIONS— Previous studies have shown the efficacy and safety of miglitol as monotherapy and in combination with sulfonylureas in type 2 diabetes (11,13,18,20,22,23). The present study demonstrates that miglitol in combination with metformin provides a synergistic effect on glycemic control, as indicated by the marked reductions in HbA_{1c} and plasma glucose levels in middle-aged patients in whom type 2 diabetes is insufficiently controlled by dietary manage-

ment. Combination therapy produced significantly greater reductions in HbA_{1c}, fasting plasma glucose, and particularly postprandial plasma glucose than metformin monotherapy. The mean HbA_{1c} at the end of treatment of patients receiving metformin was 7.3%, which is slightly higher than the goal HbA_{1c} level of <7% given by current clinical practice recommendations (20), whereas patients on metformin plus miglitol combination therapy achieved the treatment goal with a mean end-of-treatment HbA_{1c} level of 6.9%. The greater reduction in HbA_{1c} in patients on the metformin plus miglitol combination therapy is therefore clinically significant in achieving the treatment goal. The clinical importance of this is supported by the U.K. Prospective Diabetes Study data, which indicates that for every 1% reduction in HbA_{1c}, there is a 35% reduction in risk of microvascular complications (24). The superiority of the combination treatment was also demonstrated by the higher response rate of patients on the metformin plus miglitol combination therapy than on monotherapy. These observations support those of Mooradian in elderly type 2 diabetic subjects (18).

Postprandial hyperglycemia is recognized as an independent risk factor for macrovascular complications (25,26). However, the normalization of postprandial plasma glucose peaks in clinical practice is recognized as more problematic than the overall management of fasting plasma glucose levels. Because α-glucosidase inhibitors have been reported previously to smooth and lower postprandial plasma glucose peaks (8–10), miglitol in combination with metformin does offer an advantage in achieving the important goal of postprandial glucose management as well as overall glycemic control, especially for patients with postprandial hyperglycemia refractory to other treatments.

The reductions in fasting and postprandial plasma glucose as well as in HbA_{1c} in response to metformin plus miglitol combination therapy were greater than the added effects of both miglitol and metformin alone. It is suggested that the administration of the two drugs together has a synergistic effect on glycemic control; this is plausible because miglitol and metformin reduce plasma glucose levels through completely different mechanisms of action. Metformin acts on the liver directly by decreasing hepatic glucose production and release and indirectly by increasing peripheral tissue sensitivity to insulin (27); miglitol acts at the small intestine by delaying the digestion of complex carbohydrates (28). Interestingly, patients receiving metformin plus miglitol combination therapy tended to lose more weight than those on the other treatment regimens (4). Weight loss may indirectly improve glycemic control by decreasing insulin resistance (29), which might have been another positive contributory factor to the superiority of the metformin plus miglitol combination therapy. Although combination therapy did not have any significant effect on fasting plasma insulin compared with metformin alone (-12.4 ± 3.8 vs. -17.4 ± 4.7 pmol/l; P = NS), it did have a tendency to decrease the postprandial incremental plasma insulin area under the curve (AUC) (-60.1 ± 19.4 vs. $+0.5 \pm 17.7$ pmol · h/l; $P = 0.059$). This is probably caused by the effect of miglitol because miglitol alone resulted in a decrease in postprandial plasma insulin AUC of -72.8 ± 21.9 pmol · h/l. The reduction in postprandial plasma glucose and insulin could result in improved insulin sensitivity, as we have shown in elderly type 2 diabetic subjects with acarbose treatment (30).

Monotherapy with miglitol alone resulted in a treatment effect of −0.37% in HbA_{1c} compared with placebo (Fig. 1). This is a much smaller effect than that observed in previously reported studies (11,13,22,23,31), in which a reduction in HbA_{1c} between 0.74 and 1.19% was shown. It is interesting that Johnston et al. (11) could not show any better efficacy of miglitol 100 mg three times a day compared with 50 mg three times a day. However, postprandial plasma glucose was lower after 100 mg three times a day on the test meal. It is possible that the discordance between HbA_{1c} and postprandial plasma glucose was caused by the lower compliance at 100 mg three times a day because of increased gastrointestinal side effects. Similarly, in the present study, the effect of miglitol on incremental postprandial plasma glucose AUC during the test meal was significantly greater than with metformin alone (-34.7 ± 7.2 vs. -18.0 ± 7.3 mg · h/dl; $P < 0.001$), confirming the efficacy of the drug. Again, the discordance between HbA_{1c} and postprandial plasma glucose could be caused by poor compliance with the study medication. It is possible that slower titration of miglitol would reduce the gastrointestinal side effects and improve compliance, resulting in better improvement in HbA_{1c}.

Miglitol in combination with metformin was found to be safe and well tolerated in the study cohort. The incidence of gastrointestinal adverse events was higher in the treatment groups receiving miglitol; this is in line with the known mechanism of action of an α-glucosidase inhibitor. It is possible that slower titration of the drug, as with acarbose, could diminish the incidence of gastrointestinal side effects (32). Overall, the incidence of side effects with metformin plus miglitol combination therapy was not significantly different from that observed for either miglitol or metformin monotherapy, although the rate of discontinuations was higher with combination therapy. Only a trend toward an increase in the number of gastrointestinal side effects in the metformin plus miglitol combination therapy group was observed. There was no evidence of any serious adverse events associated with this combination regimen. No severe hypoglycemic episodes were observed in this study, and the incidence of mild-to-moderate hypoglycemia was low and comparable across all study treatments. The lack of deleterious effects on liver enzymes indicates that regular monitoring of liver function during combination therapy with miglitol and metformin is not required.

From the present study, it can be concluded that miglitol, the first pseudomonosaccharide α-glucosidase inhibitor, can be combined effectively with metformin therapy to give significantly greater reductions in HbA_{1c} and postprandial plasma glucose levels than metformin alone, with a good safety profile, in patients in whom type 2 diabetes is insufficiently controlled by diet alone. Miglitol and metformin may act synergistically to confer this additional glycemic control, especially on postprandial plasma glucose peaks, and may thereby help to reduce the risk of microvascular and macrovascular diabetic complications.

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APPENDIX

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References

1. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
2. U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
3. DeFronzo RA, Goodman AM, and the Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995
4. Johansen K: Efficacy of metformin in the treatment of NIDDM: meta-analysis. *Diabetes Care* 22:33–37, 1999
5. Campbell LK, White JR, Campbell RK: Acarbose: its role in the treatment of diabetes mellitus. *Ann Pharmacother* 30: 1255–1262, 1996
6. Bischoff H: Pharmacology of α-glucosidase inhibition. *Eur J Clin Invest* 24 (Suppl. 3):3–10, 1994
7. Joubert PH, Venter HL, Foukaridis GN: The effect of miglitol and acarbose after an oral glucose load: a novel hypoglycemic mechanism? *Br J Clin Pharmacol* 30:391–396, 1990
8. Lebovitz HE: Oral antidiabetic agents: the emergence of α-glucosidase inhibitors. *Drugs* 44 (Suppl. 3):21–28, 1992
9. Holman RR, Steemson J, Turner RC: Postprandial glycaemic reduction by an α-glucosidase inhibitor in type 2 diabetic patients with therapeutically attained basal normoglycaemia. *Diabetes Res* 18:149–153, 1991
10. Heinz G, Komjati M, Korn A, Waldhausl W: Reduction of postprandial blood glucose by the alpha-glucosidase inhibitor Miglitol (BAY m 1099) in type II diabetes. *Eur J Clin Pharmacol* 37:33–36, 1989
11. Johnston PS, Coniff RF, Hoogwerf BJ, Santiago JV, Pi-Sunyer FX, Krol A: Effects of the carbohydrase inhibitor miglitol in sulfonylurea-treated NIDDM patients. *Diabetes Care* 17:20–29, 1994
12. Spengler M, Hansel G, Boehme K: Efficacy of 6 months monotherapy with glucosidase inhibitor Acarbose versus sulphonylurea glibenclamide on metabolic control of dietary treated type II diabetics (NIDDM). *Horm Metab Res* (Suppl.) 26:50–51, 1992
13. Segal P, Feig PU, Schernthaner G, Ratzmann KP, Rybka J, Petzinna D, Berlin C: The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone. *Diabetes Care* 20:687–691, 1997
14. Escobar-Jimenez F, Barajas C, De Leiva A, Cano FJ, Masoliver R, Herrera-Pombo JL, Hernandez-Mijares A, Pinon F, de la Calle H, Tebar J, Soler J, Cobos A, Guardiola E, and the Miglitol Collaborative Group: Efficacy and tolerability of miglitol in the treatment of patients with non-insulin-dependent diabetes mellitus. *Curr Ther Res* 56:258–268, 1995
15. Saunier B, Kilker RD Jr, Tkacz JS, Quaroni A, Herscovics A: Inhibition of N-linked complex oligosaccharide formation by 1-deoxynojirimycin, an inhibitor of processing glucosidases. *J Biol Chem* 257: 14155–14161, 1982
16. Scott LJ, Spencer CM: Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs* 59:521–549, 2000
17. Pagano G, Marena S, Corgiat-Mansin L, Cravero F, Gioada C, Bozza M, Rossi CM: Comparison of miglitol and glibenclamide in diet-treated type 2 diabetic patients. *Diabete Metab* 21:162–167, 1995
18. Mooradian AD: Drug therapy of non-insulin-dependent diabetes mellitus in the elderly. *Drugs* 51:931–941, 1996
19. Franz MJ, Horton ES, Bantle JP, Beebe CA, Brunzell JD, Coulston AM, Henry RR, Hoogwerf B, Stacpoole PW: Nutritional principles for the management of diabetes and related complications. *Diabetes Care* 17:490–518, 1994
20. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 22 (Suppl. 1):S32–S41, 1999
21. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 13:610–630, 1990
22. Johnston PS, Feig PU, Coniff RF, Krol A, Kelley DE, Mooradian AD: Chronic treatment of African-American type 2 diabetic patients with α-glucosidase inhibition. *Diabetes Care* 21:416–422, 1998
23. Johnston PS, Feig PU, Coniff RF, Krol A, Davidson JA, Haffner SM: Long-term titrated-dose α-glucosidase inhibition in non-insulin-requiring Hispanic NIDDM patients. *Diabetes Care* 21:409–415, 1998
24. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
25. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J, and the DIS Group: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
26. Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999
27. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338:867–872, 1998
28. Taylor RH, Barker HM, Bowey EA, Canfield JE: Regulation of the absorption of dietary carbohydrate in man by two new glucosidase inhibitors. *Gut* 27:1471–1478, 1986
29. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL: Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes* 48:839–847, 1999
30. Meneilly GS, Ryan EA, Radziuk J, Lau DCW, Yale J-F, Morais J, Chiasson J-L, Rabasa-Lhoret R, Maheux P, Tessier D, Wolever T, Josse RG, Elahi D: Effect of acarbose on insulin sensitivity in elderly patients with diabetes. *Diabetes Care* 23: 1162–1167, 2000
31. Lebovitz HE: α-glucosidase inhibitors as agents in the treatment of diabetes. *Diabetes Rev* 6:132–145, 1998
32. May C: Efficacy and tolerability of stepwise increasing dosage of acarbose in patients with non-insulin-dependent diabetes (NIDDM), treated with sulphonylureas. *Diabetes Und Stoffwechsel* 4:3–8, 1995