Effects of BAYm 1099, New α-Glucosidase Inhibitor, on Acute Metabolic Responses and Metabolic Control in NIDDM Over 1 Mo

Abu H.B. Samad, MB
Thomas S. Ty Willing, MD
K. George M.M. Alberti, DPhil
Roy Taylor, MD

To examine the clinical role of BAYm 1099, 15 diet-treated non-insulin-dependent diabetic (NIDDM) subjects were randomized to start drug (50 mg 3 times/day) or placebo after a 4-wk run-in period in a double-blind crossover study. Treatment periods (4 wk) were separated by a 2-wk washout period. During the last week of each treatment period, three test meals (TMs) were administered: 60 g starch (TM1), 25 g sucrose (TM2), and combined 60 g starch and 25 g sucrose (TM3). Twelve subjects completed the study. The peak postprandial blood glucose, lactate, and pyruvate levels (means ± SE) were significantly lower with active drug after all test meals, particularly TM2 (11.3 ± 1.0 vs. 14.3 ± 1.4 mM, $P < .001$; 1.53 ± 0.20 vs. 2.48 ± 0.17 mM, $P < .001$; and 105.1 ± 17.6 vs. 147.6 ± 11.1 μM, $P < .05$, respectively. Peak blood glucose levels were significantly delayed. However, fasting blood glucose, HbA_1, fructosamine, and cholesterol did not change during active treatment (10.0 ± 1.0 vs. 9.9 ± 1.0 mM, 10.0 ± 0.7 vs. 9.4 ± 0.7%, 2.44 ± 0.10 vs. 2.37 ± 0.07 mmol/100 g protein, and 6.7 ± 0.3 vs. 6.5 ± 0.3 mM, P NS). Flatulence and diarrhea were severe in 2 subjects, requiring termination of study. Thus, in NIDDM, BAYm 1099 was effective in diminishing and delaying postprandial excursions of blood glucose, lactate, and pyruvate after high- and low-sucrose meals, but overall metabolic control remained unchanged. The results of acute studies on food absorption cannot be extrapolated to predict longer-term effects on glycemic control in diet-treated NIDDM subjects. *Diabetes Care* 11:337–44, 1988

From the Department of Medicine, University of Newcastle upon Tyne, United Kingdom.
Address correspondence and reprint requests to Dr. Roy Taylor, Department of Medicine, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK.

Inhibition of α-glucosidase offers a new therapeutic approach in the management of diabetes mellitus (1). It reduces postprandial glycemia and prevents the late postprandial dip in blood glucose by inhibiting the intestinal disaccharidases, sucrase, glucoamylase, and maltase (1–4). This inhibition is specific and localized to the small intestine, because α-glucosidase inhibitors have no effect on gastric emptying (5). Viscous unabsorbable carbohydrates such as guar and pectin, and to a certain extent nonviscous fibers such as wheat bran, have also been shown to reduce postprandial glycemia (6–12) and insulinemia (7,8) in diabetic subjects. However, addition of fiber preparations to food is often associated with poor compliance (13). The α-glucosidase inhibitors are available in tablet form and are therefore simple to take with easier dosage manipulations and no unpalatable taste.

BAYm 1099 (*N*-hydroxyethyl-1-desoxynojirimycin) is a new semisynthetic α-glucosidase inhibitor. Unlike acarbose (1), it is rapidly and completely absorbed from the intestine (14) and excreted predominantly unchanged by the kidneys (Bayer AG, unpublished data). In normal humans, BAYm 1099 reduces the plasma glucose and insulin peaks and causes a late fall of glycemia after a sucrose meal (16). This study was designed to evaluate the effects of BAYm 1099 on longer-term metabolic control, on acute metabolic responses to three different test meals, and on patient acceptability in diet-treated non-insulin-dependent diabetic (NIDDM) subjects.

MATERIALS AND METHODS

Informed written consent was obtained from each subject, and the protocol was approved by the Newcastle Health Authority Ethical Committee.

TABLE 1
Clinical data of study subjects

	Subjects who entered study	Subjects who completed study
n	15	12
Age (yr)	58 ± 7	58 ± 7
Sex (M/F)	7/8	5/7
Body weight (kg)	72.2 ± 14.5	69.4 ± 14.9
Body mass index (kg/m^2)	26.9 ± 3.7 (16.6–31.8)	26.3 ± 3.7 (16.6–30.3)
Known duration of diabetes (yr)	2.6 ± 1.8 (0.8–4.8)	2.5 ± 1.8 (0.8–4.3)
HbA_1 (%)	9.2 ± 1.9	9.6 ± 1.9

Values are means ± SD with ranges in parentheses. Normal range for HbA_1, 5–7.5%.

Fifteen NIDDM subjects, suboptimally controlled (HbA_1 above normal range) on diet alone, participated in the study and were randomly allocated to either the study drug or equivalent placebo. Clinical details of the subjects are given in Table 1. None had micro- or macrovascular complications of diabetes, and all had normal serum creatinine concentration. Subjects maintained their regular diet, activity pattern, and other drug therapy throughout the study period. Daily intake of carbohydrate, fat, and protein averaged 182 ± 12, 62.3 ± 4.3, and 50.6 ± 3.0 g, respectively. This was taken as three meals and two snacks (range 10–15 g each) per day. Snacks were taken at 2200 h and either 1100 or 1600 h. Preparation of the randomization schedule, drug, and placebo tablets was undertaken by Bayer UK (Wuppertal, FRG).

The study consisted of a 4-wk run-in and two treatment periods of 4 wk duration separated by a washout period of 2 wk. Each subject received placebo tablets for the run-in and washout periods. In the first treatment period, each subject received either the study drug (50 mg 3 times/day) or corresponding placebo, and vice versa for the second treatment period. Subjects were instructed to take one tablet with the first mouthful of each main meal throughout the study period. The regimen of 50 mg 3 times/day was chosen based on findings of previous human studies (Bayer AG, unpublished data; 17).

Before inclusion into the study, at the beginning and at the end of each 28-day treatment period, body weights were recorded and the following tests performed: fasting blood glucose, HbA_1, serum fructosamine, total cholesterol, high-density lipoprotein (HDL) cholesterol, fasting triglycerides, blood urea, serum electrolytes, creatinine, uric acid, calcium, phosphate, liver function tests, and full blood counts. Gastrointestinal side effects (abdominal pain, abdominal distension, flatulence, diarrhea, indigestion, nausea, vomiting) and other side effects (apathy, fatigue, headache, anxiety, sweating, vertigo, taste disturbance, skin reactions) were assessed by a single observer (A.H.B.S.) with a standard questionnaire. Drug compliance was evaluated by counting the returned tablets.

At the end of each treatment period, three test meals (TMs), consisting of a 60-g starch meal (TM1: 250 ml semiskimmed milk, 60 g whole-meal bread, 7 g butter, and 35 g bran flakes), a 25-g sucrose drink (TM2), and combined 60-g starch meal and 25-g sucrose drink (TM3), were administered, with a 2-day interval between tests. The sucrose drink was prepared by dissolving 25 g sucrose in 100 ml of orange-flavored water. The test meals were consumed within 10 min for TM1 and TM3 and 2 min for TM2 at 0900 h after an overnight fast. Fifty milligrams of BAYm 1099 or a placebo tablet was taken with the first mouthful of the meal or with the drink. At −30, 0, 15, 30, 45, 60, 75, 90, 120, 150, and 180 min after ingestion, venous blood was sampled from an indwelling cannula inserted into a forearm vein for estimation of glucose, immunoreactive insulin (IRI), glucagon, gastric inhibitory polypeptide, intermediary metabolites (lactate, pyruvate, glycerol, 3-hydroxybutyrate, alanine), and nonesterified fatty acids (NEFA).

Blood glucose measurements were made immediately by a glucose oxidase method (YSI glucose analyzer, Yellow Springs, OH). Sera and plasma obtained for hormonal assays were kept cool at −20°C and later analyzed for IRI (18) and glucagon (19). Blood samples for intermediary metabolites were immediately deproteinized in perchloric acid (5% vol/vol), separated, and later analyzed by a modified automated enzymatic fluorometric technique (20) with the Cobas Bio Centrifugal Analyser (Roche, Welwyn Garden City, UK). Plasma NEFA measurements were made by an enzymatic colorimetric method (Wako, Neuss, FRG) adapted for automated analysis on the Cobas Bio Centrifugal Analyser. Serum fructosamine was assayed at pH 10.4 with the Cobas Bio Centrifugal Analyser (21). HbA_1 concentrations were determined by the agar gel electrophoretic technique (Glytrac, Corning, Palo Alto, CA) (22).

Twelve subjects completed the entire study. One subject withdrew at wk 7 after an acute viral infection, and 2 subjects withdrew because of unacceptable side effects. Data obtained from the 12 subjects completing the whole study were analyzed by Student's *t* test for paired data apart from serum insulin and glucagon data, which were analyzed by Wilcoxon's signed-rank matched-pairs test. Results are presented as means ± SE.

RESULTS

Acute metabolic responses. Blood glucose, serum IRI, blood lactate, pyruvate, and alanine responses to each test meal after BAYm 1099 or placebo are shown in Figs. 1 and 2. BAYm 1099 produced an overall decrease in blood glucose, lactate, and pyruvate concentrations and flattening of curves after all three test meals. Blood glucose increased to significantly lower peak values after BAYm 1099 than after placebo for each test meal

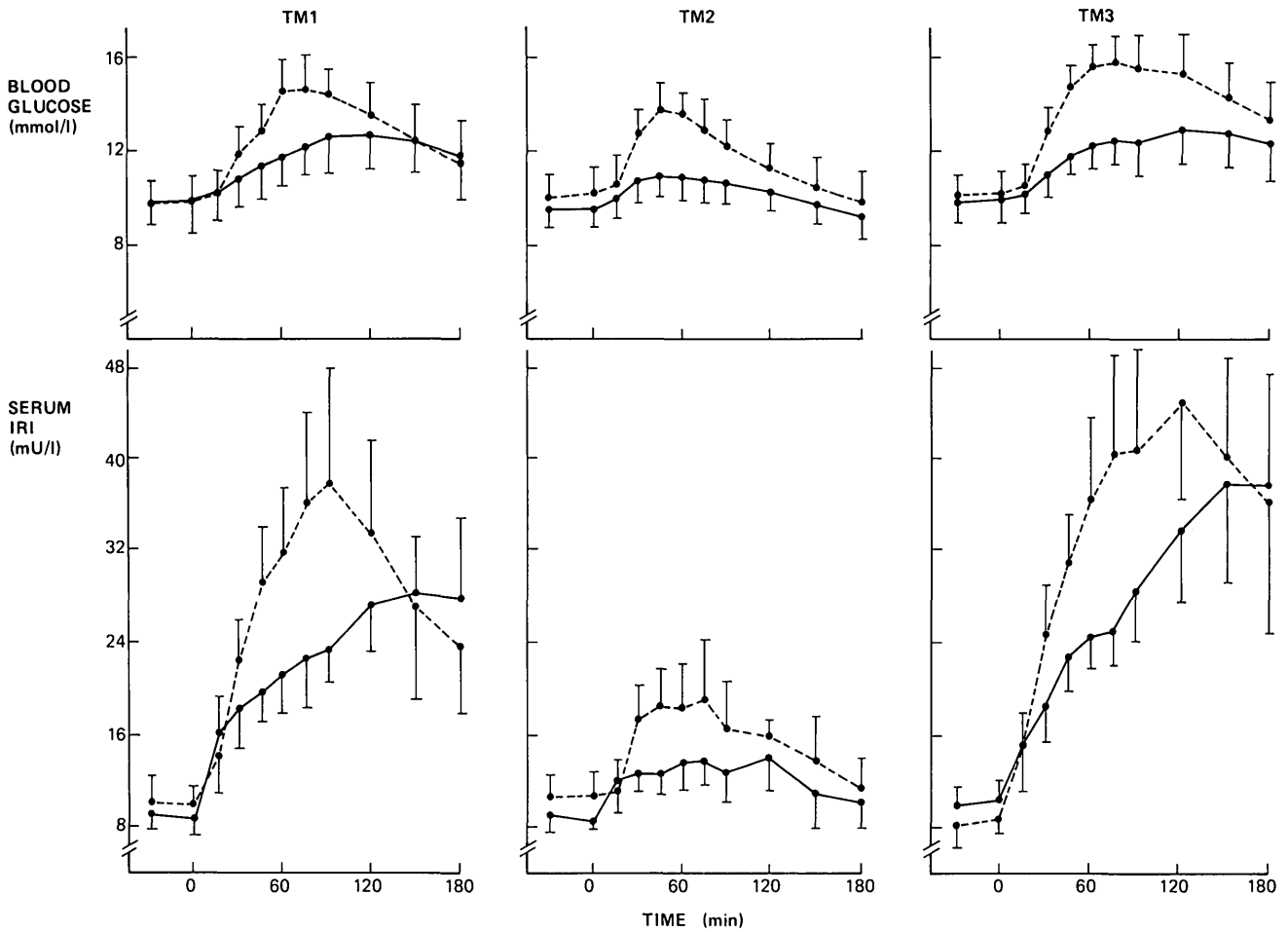

FIG. 1. Changes in blood glucose and serum insulin concentrations after each test meal during BAYm 1099 (*solid line*) or placebo (*dashed line*) therapy.

(13.4 ± 1.4 vs. 15.2 ± 1.4 mM, $P < .01$; 11.3 ± 1.0 vs. 14.3 ± 1.4 mM, $P < .001$; and 13.8 ± 1.4 vs. 16.7 ± 1.4 mM, $P < .001$ for TM1, TM2, and TM3, respectively. Lower postprandial peak values were also obtained for blood lactate and pyruvate after each test meal (Table 2). The area under the curve above the fasting levels (incremental area under the curve) over the course of 180 min for blood glucose was significantly less after BAYm 1099 than after placebo in all test meals (353 ± 21 vs. 548 ± 20 mM/min, $P < .05$; 123 ± 12 vs. 269 ± 11 mM/min, $P < .01$; and 391 ± 15 vs. 736 ± 26 mM/min, $P < .001$, respectively, which are 36, 54, and 47% reductions, respectively).

Peak values for serum IRI after BAYm 1099 were significantly lower in TM3 only (43.7 ± 9.7 vs. 50.1 ± 11.1 mU/L, $P < .05$); they were not significantly different in either TM1 or TM2 (34.5 ± 8.0 vs. 40.8 ± 10.0 mU/L and 17.7 ± 3.1 vs. 22.6 ± 6.2 mU/L, respectively). The incremental areas under the serum IRI curves for TM1, TM2, and TM3 were 1764 ± 364 vs. 2990 ± 624 (*P* NS), 552 ± 155 vs. 784 ± 286 (*P* NS), and 2182 ± 337 vs. 3244 ± 735 ($P < .02$) $mU \cdot L^{-1} \cdot min^{-1}$, respectively. Thus BAYm 1099 significantly decreased the total insulin secretion over the test period only after the combined sucrose and starch meal.

The time taken to reach the peak postprandial blood glucose concentrations (peak time) was significantly longer after BAYm 1099 than after placebo for TM1 and TM3 (109 ± 9 vs. 79 ± 10 min, $P < .025$; and 111 ± 9 vs. 74 ± 7 min, $P < .005$, respectively). These delays were equally matched by the serum IRI peak times (126 ± 10 vs. 85 ± 6 min, $P < .01$; and 126 ± 14 vs. 106 ± 9 min, $P < .05$, respectively). Peak times for both blood glucose and serum IRI after BAYm 1099 and placebo were not different after the sucrose drink (TM2). Similar significantly delayed peak times were also observed in TM2 and TM3 for blood lactate and in all test meals for blood pyruvate (Table 2). The sharp rises in plasma lactate and pyruvate levels seen after all placebo-preceded test meals, especially sucrose-containing test meals, were markedly diminished after BAYm 1099 administration (Fig. 2). The postprandial profiles for plasma glucagon, blood alanine, glycerol, 3-hydroxy-

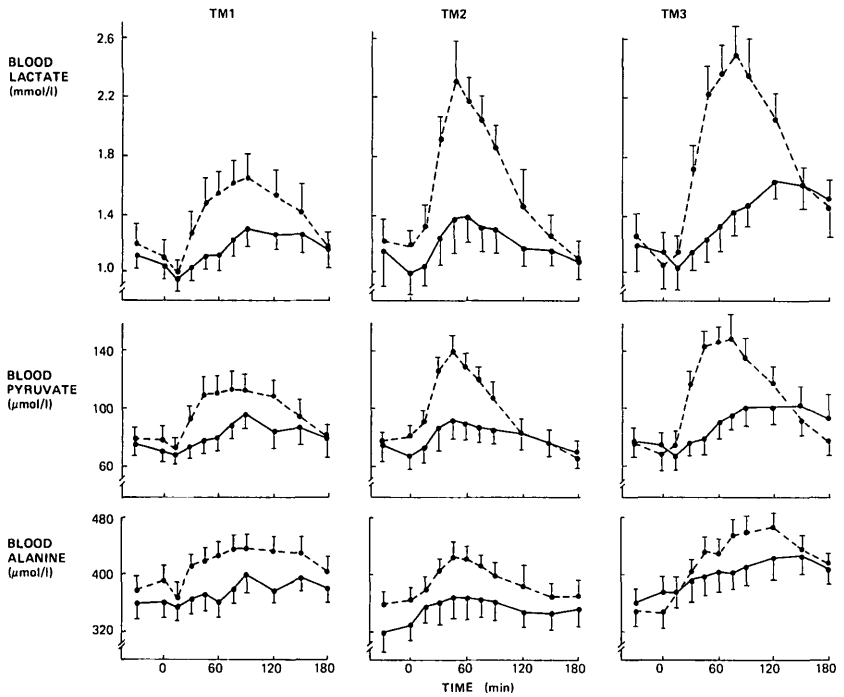

FIG. 2. Changes in blood lactate, pyruvate, and alanine concentrations after each test meal during BAYm 1099 (*solid line*) or placebo (*dashed line*) therapy.

butyrate, and plasma NEFA were not significantly different after all the three test meals for both BAYm 1099 and placebo (Figs. 2–4).

Metabolic control during 4 wk of treatment. After 4 wk of treatment with BAYm 1099, the overall glycemic control remained unchanged as assessed by serum fructosamine, HbA_1, and fasting blood glucose (Table 3). The serum total cholesterol, HDL cholesterol, and fasting triglycerides were similar throughout. Body weights were also unchanged during the study period.

TABLE 2
Peak concentrations and peak times for blood glucose, serum IRI, blood lactate, pyruvate, and alanine after ingestion of three different test meals with 50 mg BAYm 1099 or placebo

	Peak concentrations			Peak time (min)		
	Placebo	BAYm 1099	*P*	Placebo	BAYm 1099	*P*
Blood glucose (mM)						
TM1	15.2 ± 1.4	13.4 ± 1.4	<.01	79 ± 10	109 ± 9	<.025
TM2	14.3 ± 1.4	11.3 ± 1.0	<.001	47 ± 7	63 ± 10	NS
TM3	16.7 ± 1.4	13.8 ± 1.4	<.001	74 ± 7	111 ± 9	<.005
Serum IRI (mU/L)						
TM1	40.8 ± 10.0	34.5 ± 18.0	NS	85 ± 6	126 ± 10	<.01
TM2	22.6 ± 6.2	17.7 ± 3.1	NS	66 ± 14	74 ± 11	NS
TM3	50.1 ± 11.1	43.7 ± 9.7	<.05	106 ± 9	126 ± 14	<.05
Blood lactate (mM)						
TM1	1.92 ± 0.3	1.48 ± 0.2	<.05	93 ± 14	105 ± 18	NS
TM2	2.48 ± 0.2	1.53 ± 0.2	<.001	49 ± 3	91 ± 15	<.02
TM3	2.65 ± 0.3	1.89 ± 0.2	<.005	68 ± 3	124	<.005
Blood pyruvate (μM)						
TM1	138 ± 14	107 ± 14	<.01	78 ± 10	109 ± 10	<.05
TM2	148 ± 10	105 ± 20	<.05	48 ± 7	70 ± 10	<.02
TM3	164 ± 17	129 ± 21	<.05	69 ± 10	114 ± 14	<.01
Blood alanine (μM)						
TM1	478 ± 31	425 ± 31	NS	83 ± 17	112 ± 17	NS
TM2	443 ± 24	403 ± 31	NS	54 ± 15	75 ± 14	NS
TM3	491 ± 24	460 ± 28	NS	83 ± 7	115 ± 10	<.05

Values are means ± SE. TM, test meal. TM1, 60 g starch; TM2, 25 g sucrose; TM3, 60 g starch and 25 g sucrose.

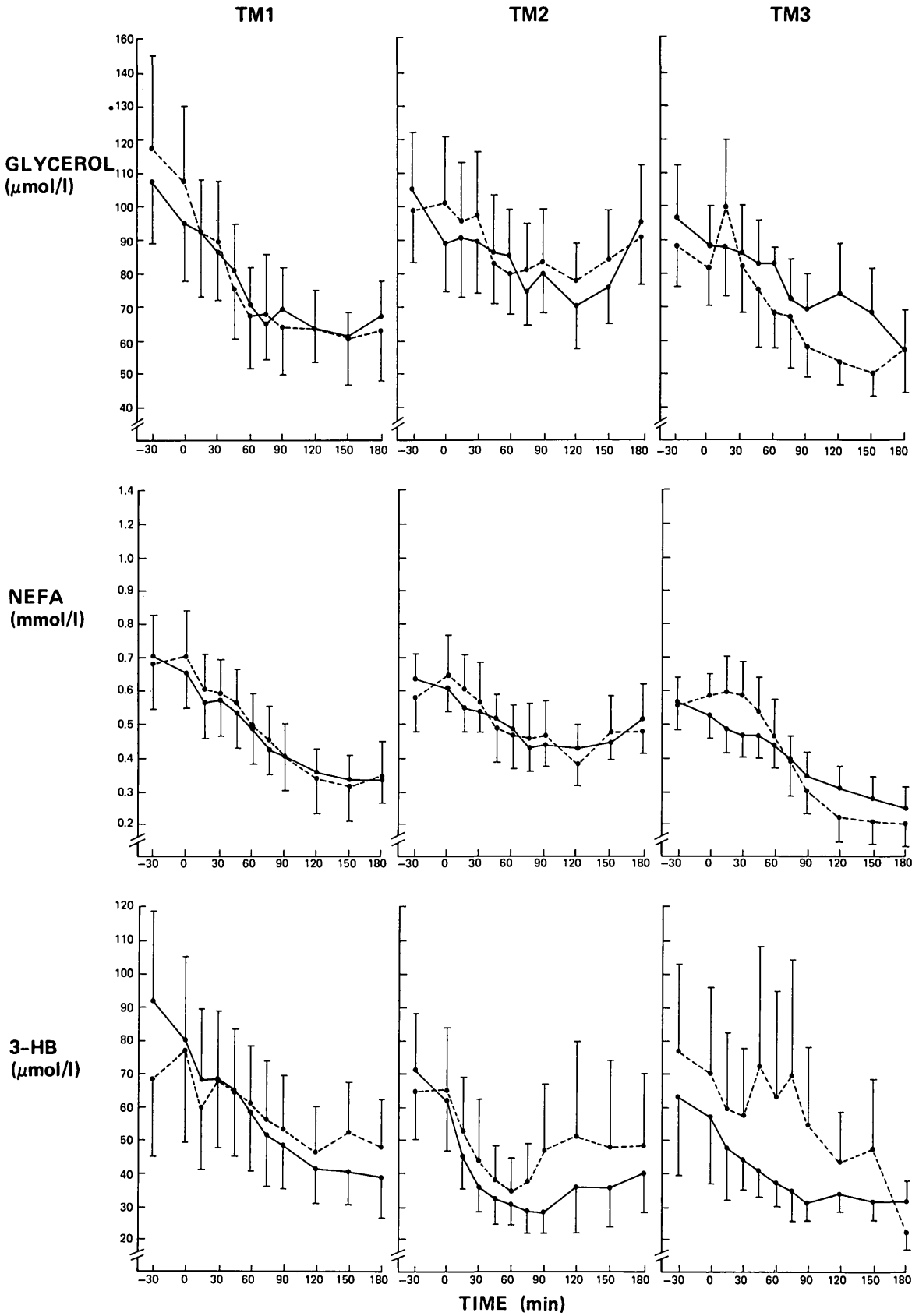

FIG. 3. Changes in glycerol, plasma nonesterified fatty acids (NEFA), and 3-hydroxybutyrate (3-HB) after each test meal during BAYm 1099 (*solid line*) or placebo (*dashed line*) therapy.

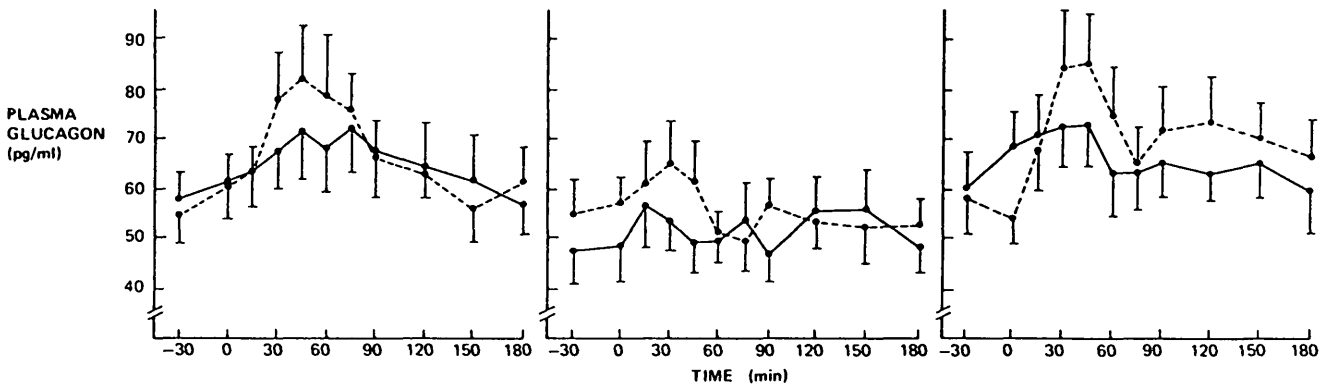

FIG. 4. Changes in plasma glucagon after each test meal during BAYm 1099 (*solid line*) or placebo (*dashed line*) therapy.

Compliance. Compliance to therapy was satisfactory on both BAYm 1099 and placebo. For the first and second treatment periods, respectively, a mean of 1.8 (range 0–14) and 1.9 (range 0–15) tablets were omitted as assessed by tablet counts.

General effects. The hematological parameters, liver profiles, blood urea, serum electrolytes, creatinine, uric acid, calcium, and phosphate levels were unchanged after 4 wk of treatment with BAYm 1099 or placebo.

Side effects. Two subjects left the study prematurely because of untoward side effects. Subject 1 developed severe diarrhea and flatulence associated with mild nausea, abdominal distension, and discomfort after the first few tablets of BAYm 1099. These symptoms persisted on continuation of the drug and disappeared 1 day after cessation of the drug. Symptoms recurred on rechallenge with a single 25-mg dose of BAYm 1099. Subject 15 developed more severe gastrointestinal side effects (nausea, diarrhea, flatulence, abdominal distension, and discomfort) with the first tablet of BAYm 1099, and drug therapy was stopped after three doses. Normal bowel habit returned ~24 h after the last drug dose. Rechallenge was considered unethical. The patient had a previous history of lactose intolerance. Three other subjects on BAYm 1099 and one on placebo developed mild flatulence for the first few days and gradually improved over the next few days on continuation of drug (Table 4). No other side effects were observed during the study.

DISCUSSION

Our results demonstrate that BAYm 1099, like its predecessor acarbose, is effective in reducing and delaying the postprandial rise of blood glucose and to a certain extent the serum IRI response after ingestion of various test meals, particularly those with a high sucrose content. This presumably is because of its predominant effect on intestinal sucrase (16), an effect comparable to that of acarbose (2–4,23). This finding agrees with the previous observations in normal humans (24) and subjects with NIDDM (17,25–27). The more pronounced effect of BAYm 1099 on postprandial glycemia with the mixed food and sucrose test meal (TM3) is probably due to its combined inhibitory effect on various intestinal α-glucosidases. Similar reduced and delayed postprandial rises were obtained for blood lactate and pyruvate, particularly with the high-sucrose meals TM2 and TM3. This profound reduction and flattening of the postprandial

TABLE 3
Effects of 4-wk therapy with BAYm 1099 or placebo on long-term glycemic control, lipid profiles, and body weight

	Placebo		BAYm 1099	
	Before	After	Before	After
Fasting blood glucose (mM)	10.1 ± 1.3	9.9 ± 1.3	10.0 ± 1.0	9.9 ± 1.0
Serum fructosamine (mmol/100 g protein)	2.35 ± 0.10	2.38 ± 0.13	2.44 ± 0.10	2.37 ± 0.07
HbA_1 (%)	9.8 ± 0.7	9.7 ± 0.7	10.0 ± 0.7	9.4 ± 0.7
Total cholesterol (mM)	6.4 ± 0.3	6.4 ± 0.3	6.7 ± 0.3	6.5 ± 0.3
HDL cholesterol (mM)	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
Fasting triglyceride (mM)	2.6 ± 0.7	3.0 ± 0.7	2.9 ± 0.7	3.0 ± 0.7
Body weight (kg)	68.0 ± 4.2	68.0 ± 4.2	68.9 ± 4.3	68.6 ± 4.2

Values are means ± SE. BAYm 1099 dosage, 50 mg 3 times/day.
No statistically significant differences at any time point.

TABLE 4
Gastrointestinal side effects of BAYm 1099 therapy compared to placebo

	BAYm 1099	Placebo
Abdominal pain	1	0
Abdominal discomfort	2	0
Abdominal distension	2	0
Flatulence	5 (3)	1 (1)
Diarrhea	2	0
Indigestion	0	0
Nausea	2	0
Vomiting	0	0

Values in parentheses refer to 12 subjects who completed the whole study; otherwise, data refer to 15 subjects who entered the study.

lactate profiles are probably secondary to the reduced rate of glucose supply to the glycolytic pathway (28) and glycogen synthesis as a result of α-glucosidase inhibition. This effect is again comparable to the effect of acarbose (28).

In diabetic subjects, acarbose was shown to improve overall glycemic control and lipid profiles after long-term administration, but these studies were not placebo controlled (29–31). BAYm 1099 has been shown by serum fructosamine levels to have a minimal effect in improving glycemic control in a mixed group of diabetic subjects treated with diet alone, an oral hypoglycemic agent, or insulin (17). However, we cannot confirm this in a diet-treated group of NIDDM subjects who may be expected to be successfully managed on this drug alone. The fasting blood glucose, serum fructosamine, HbA_1, serum fasting triglycerides, total and HDL cholesterol, and body weight remained unchanged. Lardinois et al. (31) observed considerable individual variation of the response to acarbose in their NIDDM subjects; some were good responders showing marked improvement in HbA_{1c} levels, whereas others did not respond. Because the study was not placebo controlled, any response could have been secondary to intensive study per se rather than drug effect. Analysis of our individual data, however, does not suggest any subgroup of good responders.

In considering reasons for the demonstrated lack of effect of BAYm 1099 therapy on overall glycemic control, the change in shape of the blood glucose curves involving prolongation of hyperglycemia above fasting levels could be important (Fig. 1). Furthermore, the absolute changes in incremental area under the blood glucose curve were small on BAYm 1099 therapy. It is unlikely that the drug, which has a short plasma half-life, could affect measurement of HbA_1 and fructosamine, because these assays depend on very different principles. The snacks taken between meals accounted for only 11–16% of total carbohydrate intake but might explain a small portion of the lack of effect of drug therapy because of the short time of action of the drug. Enthusiasm for the demonstrable acute effects of BAYm 1099 must be tempered by careful consideration of the longer-term metabolic changes. Although it is not impossible that treatment for >4 wk could affect overall metabolic control, it appears unlikely on the basis of our results.

Side effects continue to be a universal problem for α-glucosidase inhibitors. Moderate carbohydrate malabsorption with its attendant gastrointestinal side effects, i.e., flatulence (28) and occasionally diarrhea, is generally expected, although there is individual variation in susceptibility (32,33). Holman et al. (17) reported that several subjects experienced an initial increased flatulence with BAYm 1099. In nine normal men studied by Cauderay et al. (16), three experienced flatulence and abdominal discomfort, and one had diarrhea. In our study, gastrointestinal side effects were severe in two subjects, requiring termination of study, and three others had an initial mild increase of flatulence. In one subject reported herein, the side effects may reflect a particular sensitivity of intestinal α-glucosidases to BAYm 1099, because similar symptoms developed with a smaller dose (25 mg). Previous studies with acarbose suggested that smaller doses (≤50 mg) could still decrease the glycemic response without significantly inducing carbohydrate malabsorption (32–34), but this did not appear to be the case for BAYm 1099 in our subject. In another subject described herein, the severe gastrointestinal side effects could be partly attributable to the presence of lactose intolerance. BAYm 1099 in high concentration has been shown to inhibit the β-galactosidase lactase up to 56.4% (23), which is probably sufficient to trigger the symptoms in this predisposed subject. BAYm 1099 was otherwise well tolerated and showed no other systemic effect or change in biochemical parameters after a 4-wk administration.

With acarbose, the gastrointestinal side effects are less problematic if sucrose intake is low and starch is the main carbohydrate source in the diet (33) because acarbose has a very potent effect on intestinal sucrase. Acarbose was shown to inhibit rat small intestinal sucrase up to 95.6% by competitive inhibition, glucoamylase up to 95.3%, and maltase up to 85.2% (23). It was also shown not to affect the active transport of L-leucine and D-glucoside (23). A similar outcome is expected with BAYm 1099 but requires confirmation in future studies.

In summary, our data suggest that BAYm 1099 does not improve longer-term (4-wk) metabolic control in NIDDM subjects previously managed on diet alone, although it is effective in reducing postprandial blood glucose levels. The drug may be a useful adjunct to therapy for insulin-dependent diabetes mellitus in matching the time course of blood glucose to insulin action. Gastrointestinal side effects are likely to remain a problem for a few individuals.

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