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Effect of an α-Glucosidase Inhibitor (Voglibose), in Combination with Sulphonylureas, on Glycaemic Control in Type 2 Diabetes Patients

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A multicentre study was conducted to evaluate the effect of the α-glucosidase inhibitor, voglibose, on glycaemic control in 113 patients with type 2 diabetes whose blood glucose control was poor on treatment with a sulphonylurea drug. The patients were treated for 24 weeks with 0.6 mg voglibose, given orally three times daily, before a meal, together with their usual sulphonylurea drug treatment. In the 86 patients who completed the study, fasting plasma glucose, 2-h post-prandial plasma glucose and haemoglobin showed statistically significant decreases in FPG, 2h-PPG and HbA_{1c} compared with the baseline ($P < 0.05$) at almost all time-points during treatment. No serious adverse reactions were reported and there were no significant changes in mean body weights. Plasma glucose control was considered to be improved in 65% of patients; there were no adverse events in 92.9% of patients. The results suggest that the combined use

of this α-glucosidase inhibitor and sulphonylurea drugs may be effective in controlling plasma glucose in patients with type 2 diabetes and that this combination might delay the onset of vascular complications in these patients.

KEY WORDS: VOGLIBOSE; α-GLUCOSIDASE INHIBITORS; SULPHONYLUREAS; TYPE 2 DIABETES; FASTING PLASMA GLUCOSE; TWO-HOUR POST-PRANDIAL PLASMA GLUCOSE; GLYCATED HAEMOGLOBIN

INTRODUCTION

Diabetes mellitus is one of the most prevalent diseases in industrialized countries. Poor control of this disease results in the development of vascular disorders such as retinopathy, nephropathy and neuropathy, in addition to the progression of arterial sclerosis, which subsequently leads to an increased risk of myocardial infarction.[1] Sulphonylurea drugs have been most important as oral hypoglycaemic drugs for the control of hyperglycaemia in patients with type 2 diabetes, formerly known as non-insulin dependent diabetes mellitus. Until recently, sulphonylurea drugs had been the main hypoglycaemic agents since Bach and his associates in the USA reported that biguanide increased the risk of lactic acidosis.[2] Sulphonylurea drugs, however, are not effective in some patients with type 2 diabetes. Rifkin pointed out that approximately 20% of patients with type 2 diabetes exhibited primary medication failure.[3] Even if type 2 diabetes patients have good glycaemic control in the early phase of treatment, they may eventually become resistant to sulphonylurea drugs and plasma glucose (PG) levels become poorly controlled.[3]

Recently α-glucosidase inhibitors have been developed, widening the choice of treatments for type 2 diabetes.[4] Voglibose is an α-glucosidase inhibitor which has been available for clinical practice in Japan since 1994. This drug inhibits disaccharide hydrolases, which convert disaccharides to monosaccharides, impeding digestion and adsorption of glucose and resulting in decreased postprandial plasma glucose levels. Combined use of a sulphonylurea drug and an α-glucosidase inhibitor is therefore expected to be effective in controlling plasma glucose in type 2 diabetes patients who are resistant to sulphonylurea drugs. The aim of this study was to evaluate the effect of voglibose on glycaemic control in type 2 diabetes patients whose plasma glucose control with a sulphonylurea drug was poor.

PATIENTS AND METHODS

PATIENTS

This was a multicentre study conducted at 34 institutions in the Tokyo Metropolitan area of Japan. The study period was from April 1995 to March 1996. The institutional review board of each institution approved the protocol and the conduct of the study. Diabetic patients were invited to participate in the study. Written informed consent was obtained prior to entry into the study. The patients included were males or females aged 16 years or older, and had fasting plasma glucose levels of more than 140 mg/dl or 2-h post-prandial plasma

glucose levels (2h-PPG) of more than 200 mg/dl, and fluctuations of less than 1% in the levels of glycated haemoglobin (HbA_{1c}) during the period of 3 months before entry into the study. The patients excluded were those treated with insulin and those who had been treated with a sulphonylurea drug for less than 1 month prior to entry into the study, those with a history of hypoglycaemic episodes due to sulphonylurea therapy, chronic alcoholics, women who were pregnant or planning to become pregnant, those with serious cardiac, renal or hepatic diseases, those with a history of gastrectomy, enterectomy or other gastrointestinal surgery, those with a history of hypothyroidism, and those judged by the attending physician to be unsuitable for this study.

TREATMENT

The patients enrolled, all of whom had previously either been untreated or had been treated with a sulphonylurea drug for more than 1 month were observed for more than 8 weeks before they were prescribed voglibose (Basen™, Takeda Chemical Industries Ltd, Osaka, Japan) 0.6 mg orally three times daily for 24 weeks.Those who had been on treatment with an antilipaemic agent such as 3-hydroxy-3-methylglutanyl coenzyme A reductase inhibitor, a β-blocker or a calcium antagonist were allowed to continue the medication throughout the study period but were not allowed to use any additional medications. Patients were encouraged to comply with the daily diet programme and were asked to attend the hospital once every week throughout the study. Patients who visited the hospital irregularly, had poor compliance or changed to another hospital were excluded from the analysis.

ASSESSMENT

Peripheral blood was sampled at the cubital vein. FPG (fasting plasma glucose), 2h-PPG and HbA_{1c} (glycated haemoglobin) were used to monitor the degree of the glycaemic control. FPG and 2h-PPG were measured by the glucose oxidase electrode method, and HbA_{1c} by high performance liquid chromatography (HPLC, Kyoto Daiichi Kagaku, Kyoto, Japan). Patients were weighed at each hospital visit and body mass index (BMI) was calculated using the formula[5]: patient's weight (kg)/[patient's height (m)]^2.

The patients were classified into two groups: one with BMIs of 25 or more and the other with BMIs of less than 25, based on the study of Kobayashi and his associates.[6] The patients were also divided into two groups according to their HbA_{1c} levels: 8.5% or higher and less than 8.5%.

During the treatment with voglibose, the patients were carefully observed for any adverse events, particularly hypoglycaemia, abdominal distension and increases in flatulence and defaecation. The latter two are often associated with this drug.[4] The severity of these adverse events was classified as: severe (+3), moderate (+2), mild (+1) or none (0). Other subjective symptoms monitored were xerostomia and polyuria.

After completion of the study treatment, plasma glucose control was assessed as markedly improved, moderately improved, slightly improved, showing no change or worse.

STATISTICAL ANALYSIS

Statistical analysis was performed using the paired *t*-test (SAS, SAS Institute Japan, Tokyo, Japan) for evaluation of changes in FPG, 2h-PPG, HbA_{1c} and BMI. A difference of $P < 0.05$ was considered statistically significant. Data are expressed as means ± SDs.

RESULTS

STUDY POPULATION

A total of 113 patients were enrolled and, due

to an unusually high dropout rate, 86 (76.1%) completed the study treatment. The characteristics of the patients are summarized in Table 1. The mean age was 59.9 ± 9.8 years, ranging from 37 to 79 years. Approximately two-thirds of them had had type 2 diabetes for more than 4 years. More than three-quarters were on treatment with glibenclamide. A total of 24 patients (27.9%) had complications of type 2 diabetes including retinopathy, nephropathy, neuropathy, hyperlipidaemia and hypertension. Less than one-third of the patients (27.9%) were on a strictly controlled diet, but approximately half of all the patients took regular physical exercise. Rice was the most common source of daily carbohydrate intake. FPG, 2h-PPG, HbA_{1c} and BMI at the beginning of the study in the 86 patients who completed the study are shown in Table 2. The mean baseline FPG, 2h-PPG and HbA_{1c} were 175.6 ± 30.9 mg/dl, 261.4 ± 46.0 mg/dl and 9.0 ± 1.7%, respectively (Tables 3, 4 and 5).

FASTING PLASMA GLUCOSE

The concentrations of FPG decreased after treatment with voglibose with statistically significant differences at week 4 ($P < 0.01$), as shown in Table 3. A statistically significant decrease in FPG was also observed at weeks 4, 8 and 16 in patients with BMIs of less than 25 ($P < 0.05$) but not in those with BMIs of 25 or more. FPG was also generally decreased in the patients with HbA_{1c} levels of less than 8.5%, showing a statistically significant reduction at weeks 4 and 20 ($P < 0.01$); in patients with HbA_{1c} levels of 8.5% or higher there were no statistically significant changes in FPG.

2-HOUR POST-PRANDIAL PLASMA GLUCOSE

2h-PPG decreased significantly ($P < 0.05$) at all time-points after treatment with voglibose when all of the patients were included (Table 4). Statistically significant decreases were also observed at all time-points in patients with BMIs of less than 25 ($P < 0.05$) or HbA_{1c} levels of less than 8.5% ($P < 0.05$). There was a significant decrease in 2h-PPG in patients with HbA_{1c} levels of 8.5% or more at weeks 4 and 8 ($P < 0.01$) and weeks 12 and 24 ($P < 0.05$) of the study.

GLYCATED HAEMOGLOBIN (HbA_{1c})

There were statistically significant decreases in the levels of HbA_{1c} for all patients at all time-points ($P < 0.001$; Table 5). In all of the patient subgroups there were statistically significant decreases compared with the baseline value at all time-points ($P < 0.05$) except for week 12 in patients with BMIs of 25 or more, and week 16 in those with HbA_{1c} levels of less than 8.5%.

BODY WEIGHT

There were no statistically significant changes in body weight before, during or after completion of this study.

ADVERSE EVENTS

There were no serious adverse events during the study period or during the subsequent follow-up. As shown in Table 6, minor events such as abdominal distension and slight hypoglycaemia were reported in seven patients. Moderate skin eruption was observed in one patient. The hypoglycaemic patient was hospitalized as a precaution. The patient recovered after stopping the sulphonylurea drug (gliclazide). There were no adverse events in 92.9% (105/113) of the patients in the study. There were no significant differences in the incidence of gastrointestinal symptoms or polyuria either before or during the study treatment.

OVERALL EVALUATIONS

Plasma glucose control (as indicated by FPG, 2h-PPG and HbA_{1c}) was improved in 65.1% of the patients who completed the study treatment (Table 7).

TABLE 1

Characteristics of type 2 diabetic patients (n = 86) treated with sulphonylureas and voglibose for 24 weeks

Characteristic variables		No. (%) of patients
Sex	Men	44 (51.2)
	Women	42 (48.8)
Age distribution (years)	≤39	1 (1.2)
	40 – 49	17 (19.8)
	50 – 59	18 (20.9)
	60 – 69	34 (39.5)
	≥70	16 (18.6)
Mean age (± SD)		59.9 ± 9.8
Marital status	Yes	50 (58.1)
	No	36 (41.9)
Duration of disease	>3	17 (19.8)
from onset (years)	4 – 10	30 (34.9)
	≥10	27 (31.4)
	Uncertain	12 (13.9)
Sulphonylurea drug taken	Glibenclamide	65 (75.6)
	Gliclazide	18 (20.9)
	Tolbutamide	3 (3.5)
Complications	Yes	24 (27.9)
	No	62 (72.1)
Type of complication	Retinopathy	23
	Nephropathy	13
	Neuropathy	22
	Hyperlipidaemia	30
	Hypertension	26
	Ischaemic heart disease	9
	Cerebrovascular disorder	6
	Lower limb gangrene	1
	Others[a]	10
Diet programme	Yes	24 (27.9)
	No	62 (72.1)
Main type of carbohydrate	Rice	55 (64.0)
	Bread	4 (4.7)
	No record	27 (31.3)
Regular exercise	Yes	42 (48.8)
	No	32 (37.2)
	No record	12 (14.0)

[a] Others (number of episodes): gout (3), fatty liver (1), hobnail liver (1), hyperuricaemia (1), cholelithiasis (1), atrial fibrillation (1), tuberculosis (1) and iron-deficiency anaemia (1).

TABLE 2

Fasting plasma glucose (FPG) 2-hour post-prandial plasma glucose (2h-PPG) glycated haemoglobin (HbA_{1c}) and body mass index (BMI) in type 2 diabetic patients treated with 0.6 mg voglibose orally three times daily, together with their usual sulphonylurea drug, for 24 weeks

	Range	No. of patients (%)
FPG (mg/dl)		
	140 – 159	13 (15.1)
	160 – 179	12 (14.0)
	180 – 199	7 (8.1)
	200 – 219	4 (4.7)
	≥220	3 (3.5)
	No record	47 (54.6)
2h-PPG (mg/dl)		
	200 – 219	9 (10.5)
	220 – 239	9 (10.5)
	240 – 259	9 (10.5)
	260 – 279	6 (7.0)
	280 – 299	5 (5.8)
	300 – 319	1 (1.2)
	320 – 339	7 (8.1)
	340 – 359	3 (3.5)
	≥360	2 (2.3)
HbA_{1c} (%)		
	5.0 – 5.9	1 (1.2)
	6.0 – 6.9	5 (5.8)
	7.0 – 7.9	17 (19.8)
	8.0 – 8.9	19 (22.1)
	9.0 – 9.9	19 (22.1)
	10.0 – 10.9	15 (17.4)
	11.0 – 11.9	4 (4.7)
	12.0 – 12.9	2 (2.3)
	≥13.0	2 (2.3)
	No record	2 (2.3)
	<8.5	34 (39.5)
	≥8.5%	50 (58.1)
BMI (patient's weight (kg)/ [patient's height (m)]^2)		
	17.0 – 19.0	6 (7.0)
	20.0 – 21.9	19 (22.1)
	22.0 – 23.9	19 (22.1)
	24.0 – 26.4	16 (18.6)
	26.5 – 27.9	6 (7.0)
	28.0 – 29.9	4 (4.7)
	≥30.0	2 (2.3)
	No record	12 (14.0)
	<25	51 (59.3)
	≥25	23 (26.7)

TABLE 3

Changes in fasting plasma glucose levels when type 2 diabetic patients treated with sulphonylurea drugs were also treated with voglibose orally three times daily for 24 weeks

	Fasting plasma glucose concentration (mg/dl)[a]				
Week	**All patients**	**Patients with BMI ≥ 25**	**Patients with BMI < 25**	**Patients with HbA_{1c} ≥ 8.5%**	**Patients with HbA_{1c} < 8.5%**
0	176.1 ± 32.0 (33)	175.2 ± 27.2 (11)	174.9 ± 34.7 (22)	193.1 ± 33.8 (16)	160.0 ± 20.2 (17)
4	156.7 ± 37.1 (32)**	162.6 ± 54.4 (9)	153.1 ± 39.4 (23)*	173.9 ± 43.5 (16)	141.3 ± 16.9 (15)**
8	161.9 ± 43.7 (29)	183.8 ± 36.3 (9)	143.4 ± 38.9 (19)*	172.8 ± 53.9 (13)	148.7 ± 28.6 (15)
12	171.7 ± 49.6 (29)	188.0 ± 51.4 (8)	161.1 ± 50.4 (20)	174.8 ± 52.9 (13)	162.1 ± 40.8 (15)
16	166.7 ± 41.1 (23)	172.2 ± 33.0 (5)	155.3 ± 36.5 (16)*	189.5 ± 46.1 (10)	150.3 ± 28.2 (12)
20	165.0 ± 49.7 (25)	163.0 ± 18.5 (6)	158.3 ± 54.2 (17)	206.2 ± 37.7 (11)	132.6 ± 31.2 (13)**
24	158.6 ± 38.8 (33)	161.3 ± 27.0 (8)	154.8 ± 46.5 (21)	171.8 ± 41.1 (16)	146.3 ± 34.1 (16)

BMI, body mass index, patient's weight (kg)/[patient's height (m)]^2; HbA_{1c}, glycated haemoglobin.

[a] Numbers of patients are given in parentheses.

* $P < 0.05$; ** $P < 0.01$ compared with baseline.

TABLE 4

Changes in 2 h post-prandial glucose levels when type 2 diabetic patients treated with sulphonylurea drugs were also treated with voglibose orally three times daily for 24 weeks

	2h post-prandial glucose level[a]				
Week	**All patients**	**Patients with BMI ≥ 25**	**Patients with BMI < 25**	**Patients with HbA_{1c} ≥ 8.5%**	**Patients with HbA_{1c} < 8.5%**
0	262.3 ± 48.0 (25)	253.2 ± 72.3 (6)	261.0 ± 37.9 (14)	265.6 ± 56.8 (17)	255.1 ± 21.3 (8)
4	215.3 ± 52.6 (22)***	220.8 ± 41.6 (5)	201.1 ± 44.4 (12)***	228.2 ± 50.0 (13)**	196.8 ± 53.5 (9)*
8	221.3 ± 51.3 (21)***	212.8 ± 50.7 (5)	225.8 ± 49.1 (12)**	243.0 ± 47.8 (14)**	178.0 ± 23.4 (7)**
12	223.5 ± 54.5 (22)**	188.8 ± 34.6 (6)	226.5 ± 56.5 (12)*	242.8 ± 45.5 (15)*	182.3 ± 51.5 (7)**
16	225.8 ± 72.0 (24)**	205.2 ± 64.2 (6)	222.6 ± 72.9 (14)**	244.9 ± 52.9 (16)	187.5 ± 92.3 (8)**
20	225.5 ± 65.4 (22)*	208.6 ± 81.2 (5)	223.8 ± 69.6 (13)**	231.9 ± 62.5 (15)	211.7 ± 74.3 (7)*
24	202.3 ± 69.3 (20)***	186.6 ± 83.9 (5)	185.2 ± 60.5 (11)**	225.9 ± 66.2 (13)*	158.4 ± 54.9 (7)*

BMI, body mass index, patient's weight (kg)/[patient's height (m)]^2; HbA_{1c}, glycated haemoglobin.
[a] Numbers of patients are given in parentheses.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with baseline.

TABLE 5

Changes in glycated haemoglobin levels when type 2 diabetic patients treated with sulphonylurea drugs were also treated with voglibose orally three times daily for 24 weeks

	Glycated haemoglobin concentration (%)[a]				
Week	**All patients**	**Patients with BMI ≥ 25**	**Patients with BMI < 25**	**Patients with HbA_{1c} ≥ 8.5%**	**Patients with HbA_{1c} < 8.5%**
0	9.1 ± 1.7 (75)	9.2 ± 1.6 (20)	9.0 ± 1.8 (45)	10.0 ± 1.3 (47)	7.4 ± 0.8 (28)
4	8.5 ± 1.4 (68)***	8.5 ± 1.0 (17)*	8.4 ± 1.5 (42)**	9.3 ± 1.1 (40)***	7.3 ± 0.7 (27)*
8	8.4 ± 1.5 (70)***	8.4 ± 1.5 (19)**	8.3 ± 1.6 (41)***	9.1 ± 1.3 (43)***	7.1 ± 0.9 (26)*
12	8.4 ± 1.7 (70)***	8.6 ± 1.7 (19)	8.2 ± 1.7 (42)***	9.2 ± 1.4 (44)***	6.9 ± 0.9 (25)*
16	8.2 ± 1.6 (63)***	8.2 ± 1.5 (16)*	8.0 ± 1.7 (38)**	8.9 ± 1.6 (38)**	7.0 ± 1.0 (24)
20	8.3 ± 1.7 (64)***	8.2 ± 1.5 (16)*	8.0 ± 1.7 (40)**	9.0 ± 1.6 (39)**	7.0 ± 1.1 (24)*
24	8.3 ± 1.8 (69)***	8.3 ± 1.7 (19)*	8.2 ± 1.8 (40)**	9.1 ± 1.7 (43)**	6.9 ± 0.9 (25)*

BMI, body mass index, patient's weight (kg)/[patient's height (m)]^2; HbA_{1c}, glycated haemoglobin.
[a] Numbers of patients are given in parentheses.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with baseline.

TABLE 6

Adverse events in type 2 diabetic patients treated with 0.6 mg voglibose orally three times daily, together with their usual sulphonylurea drug for 24 weeks

Patient no.	Adverse event	Sulphonylurea drug (dose/day)	Time of occurrence and remarks
4-1	Abdominal distension	Gliclazide (80 mg)	At week 24 of treatment. Voglibose was continued
4-2	Abdominal distension	Glibenclamide (7.5 mg)	At week 24 of treatment. Voglibose was continued
9-1	Abdominal distension	Glibenclamide (15 mg)	At week 4 of treatment. Voglibose was continued
11-2	Abdominal distension	Gliclazide (40 mg)	At week 2 of treatment. Voglibose dose was decreased (1.8 mg to 1.2 mg daily). Voglibose was continued
21-3	Abdominal distension	Glibenclamide (15 mg)	At week 8 of treatment. Voglibose was discontinued. Patient recovered from distension
24-2	Abdominal distension	Glibenclamide (2.5 mg)	At week 0 of treatment. Voglibose was continued. ADR disappeared at week 24
16-2	Hypoglycaemia	Gliclazide (40 mg)	At week 7 of treatment (PG: 48 mg/dl). Gliclazide was discontinued. Voglibose was continued. Plasma glucose returned to normal range. Patient was in good condition
21-2	Eczema	Glibenclamide (7.5 mg)	Itching occurred 3 days after starting treatment and eczema 4 days after starting treatment. Voglibose was discontinued at week 4. ADR disappeared 80 days after starting the treatment

DISCUSSION

It is widely accepted that strict control of plasma glucose prevents various microvascular complications in diabetic patients.[5] Unger and his associates defined 'glucose toxicity' as the condition where the presence of hyperglycaemia inhibits insulin secretion from the pancreatic β-cells, as well as reducing sensitivity to insulin in peripheral tissues.[6] These findings suggest that day-to-day suppression of hyperglycaemia, especially post-prandial hyperglycaemia, is essential to prevent microvascular complications in diabetic patients.

Pharmacological intervention is needed in patients whose plasma glucose levels are not well controlled by diet and exercise. When sulphonylurea drugs are not sufficient to control plasma glucose levels, persistent hyperglycaemia leads to decreased secretion of insulin from the β-cells and increased resistance to insulin.[7] Further, sulphonylurea drugs may

TABLE 7

Overall effects of treating type 2 diabetic patient with 0.6 mg voglibose orally three times daily together with their usual sulphonylurea drug, for 24 weeks

		No. of patients (%)	
Plasma glucose control			
	Markedly improved	17	(19.8)
	Moderately improved	19	(22.1)
	Slightly improved	20	(23.3)
	No change	20	(23.3)
	Worse	10	(11.6)
	Total	86	(100.0)
Efficacy			
	Highly effective	15	(18.1)
	Moderately effective	17	(20.5)
	Somewhat effective	23	(27.7)
	Less effective	27	(32.5)
	Not effective	1	(1.6)
	Total	83*	(100.0)

* Three patients could not be evaluated because of mistakes in recording of information.

cause hypoglycaemic episodes and weight loss when used on a long-term basis.[8,9] α-Glucosidase inhibitor was originally developed as a potential therapy for obesity,[10] and was soon recognized as a drug for the treatment of elevated post-prandial plasma glucose.[11] Voglibose was discovered in Japan in 1981 after its isolation from the culture medium of *Streptomyces hygroscopicus limoneus*.[12,13] Voglibose was initially found to inhibit disaccharidase activity in the intestines, resulting in delayed post-prandial plasma glucose levels.[14,15] Subsequent reports supported the effectiveness of voglibose in reducing the levels of FPG, 2h-PPG and HbA_{1c}.[16 – 23]

The present results are consistent with those of earlier studies and reveal several new findings. Voglibose appeared to be most effective in patients whose BMI was less than 25 and whose plasma HbA_{1c} concentration was less than 8.5%. 2h-PPG was also significantly decreased at weeks 4 and 24 in patients with $HbA_{1c} \geq 8.5\%$, although it was not significantly decreased in the group with a BMI of 25 or above. The results suggest that patients with a low BMI respond better to voglibose than those with a high BMI. The reason for this is unknown but the hypoglycaemic activity of voglibose in obese patients might be affected by a secondary effect on endogenous insulin secretion as suggested by Kohno and his associates.[24] The HbA_{1c} cut-off point of 8.5% was selected because patients with plasma HbA_{1c} levels of 8.5% or above are usually given insulin therapy. Although patients with HbA_{1c} levels of less than 8.5% responded better to voglibose than those with higher HbA_{1c} levels, the results from this study could not be compared with the previous reports which used different cut-off points.[25,26] Further studies are needed to confirm the effectiveness of voglibose, in combination with sulphonylurea drugs[27,28] or rapid-acting insulin[29] for improving glycaemic control in type 2 diabetes.

Adverse events occurred in eight patients in this study. Four patients were forced to discontinue the voglibose treatment because of

abdominal distension. They experienced no symptoms after withdrawal of the drug. One patient taking gliclazide (40 mg orally once daily) had hypoglycaemia (plasma glucose 48 mg/dl) at week 7 of the study. Gliclazide was discontinued without withdrawal of voglibose and the patient recovered. One patient experienced a moderate skin eruption within 1 week of starting voglibose treatment. Voglibose was continued for 4 weeks because the patient had no other subjective symptoms but was finally discontinued from the fifth week. The eruption disappeared 45 days after withdrawal of the drug. The frequency of these adverse events was similar to the frequency of adverse events observed in previous studies, i.e. 4.8 – 12.7%.[16 – 19, 21 – 23] Giving voglibose in low doses may avoid these adverse events.[30]

The fact that the patients did not show any weight gain during the study is consistent with the view that voglibose may have value for the treatment of obesity.[31,32] Animal studies have demonstrated significant effects of voglibose on reduction of both body weight and plasma glucose in genetically obese diabetic mice.[31 – 33] Improvement of fatty liver was also observed in obese rats after treatment with voglibose, probably due to decreased supply of free fatty acid from the portal vein.[34,35]

New criteria for the diagnosis of diabetes mellitus were recommended by the Expert Committee at the 57th Annual Meeting of the American Diabetes Association on 23 June 1997, and subsequently adopted by the World Health Organization (WHO) as the world standard.[36] In this recommendation, an FPG level of more than 126 mg/dl or a casual plasma glucose level of more than 200 mg/dl was defined as diabetes mellitus. There was no recommendation for the level of plasma HbA_{1c}. Since the present study was completed before announcement of the new criteria, it has not been revised to accommodate the new standard.

In conclusion, the results of this study are consistent with previous observations that combination therapy with voglibose and a sulphonylurea drug is effective in controlling post-prandial plasma glucose in type 2 diabetes patients who were previously being treated with sulphonylurea drugs. Because diabetic complications develop in the longer term, regular observation of these patients in the future is warranted.

REFERENCES

1 Zatz R, Brenner BM: Pathogenesis of diabetic microangiopathy: the hemodynamic view. *Am J Med* 1986; **80:** 443 – 453.

2 Brach BB, Blackard W, Rothschild H: A review of deaths due to suspended lactic acidosis at a large metropolitan hospital. *South Med J* 1975; **68:** 202 – 205.

3 *The Physician's Guide to Type II Diabetes (NIDDM): Management of Type II Diabetes Mellitus* (Rifkin H,ed). New York: American Diabetes Association, 1984; 20 – 52.

4 Toto Y: Glucosidase inhibitor. *Diabetes Frontier* 1992; **3:** 557 – 564.

5 Rossetti I, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 1990; **13:** 610 – 630.

6 Unger RH, Grundy S: Hyperglycemia as an inducer as well a consequence of impaired islet cell function and insulin

resistance: implications for the management of diabetes. *Diabetologia* 1985; **28:** 19 – 121.

7 Grodsky GM: Pancreatic action of the sulfonylureas. *FASEB J* 1977; **36:** 2714 – 2719.

8 Riddle MC, Hart JS, Bouma D, *et al*: Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetics. *Diabetes Care* 1989; **12:** 623 – 629.

9 Clarke BF, Duncan LJP: Comparison of chlorpropamide and metformin treatment on weight and blood glucose response of uncontrolled obese diabetics. *Lancet* 1968; **1:** 123 – 126.

10 Schmidt DD, Plus W: Amylase inhibitor. *Dtsch Offenlegunsschrift* 2003934. 1971;1.

11 Gray GM: Carbohydrate digestion and absorption: role of the small intestine. *N Engl J Med* 1975; **292:** 1225 – 1230.

12 Kameda Y, Asano N, Yoshikawa M, *et al*: Valiolamine, a new α-glucosidase inhibiting aminocyclitol produced by *Streptomyces hygroscipius*. *J Antibiot (Tokyo)* 1984; **37:** 1301 – 1307.

13 Horii S, Fukase H, Matsuo T, *et al*: Synthesis and α-D-glucosidase inhibitory activity of N-substituted valiomine derivatives as potential oral antidiabetic agents. *J Med Chem* 1986; **29:** 1038 – 1046

14 Matsuo T, Okada H, Ideda H: Effect of an intestinal disaccharidase inhibitor (AO)-128), on obesity and diabetes. Am J Clin Nutr 1992; **55**(suppl 1): 314 – 317.

15 Okada H, Miki N, Ikeda H, *et al*: Effect of disaccharidase inhibitor, AO-128, on postprandial hyperglycemia on rats. *J Jpn Soc Nutr Food Sci* 1992; **45:** 27 – 31.

16 Goto Y, Baba S, Nakagawa S, *et al*: Utility of an α-glucosidase inhibitor, AO-128, in NIDDM-Phase III double-blind test. *Jpn Advance in Medicine (Igaku no Ayumi)* 1992; **160:** 943 – 971.

17 Kiura K, Umeda F, Nawada A: Clinical utility of AO-128 long-term medication for non-insulin dependent diabetes mellitus (72 cases); Report 2. *Jpn Clin Exp Med* 1992; **69:** 919 – 932.

18 Koizumi J, Mabuchi H, Takedoshi T, *et al*: Effects of oral hypoglycemic agents in combination controlled non-insulin dependent diabetes mellitus on AO-128. *New Remed Clin* 1992; **29:** 241 – 252.

19 Umeda F, Mimura K, Nawada A: Effects of sulfonylureas long-term medication in combination controlled non-insulin dependent diabetes mellitus (NIDDM) on AD-128 (α-glucosidase inhibitor). *Jpn J Clin Exp Med* 1992; **69:** 1309 – 1322.

20 Kawamori R, Morishima T, Shiba Y, *et al*: The effectiveness of a new disaccharidase inhibitor AO-128 in glycemic control of insulin-treated diabetic patients. *J Jpn Diab Soc* 1992; **35:** 633 – 640.

21 Mimura K, Umeda F, Hisatomi A, *et al*: Clinical utility of AO-128 long-term medication for non-insulin dependent diabetes mellitus (72 cases); Report 2. *Jpn Clin Exp Med* 1992; **69:** 235 – 244.

22 Matsuoka A, Takeuchi K, Makimura H, *et al*: Efficacy and safety of AO-128 long-term treated in non-insulin dependent diabetes mellitus. *Med Consult New Remed* 1992; **29:** 255 – 265.

23 Kamiya F, Hayashi Y, Takeuchi T: Clinical utility of AO-128 long-term treatment in non-insulin dependent diabetes mellitus. *J Adult Dis* 1992; **22:** 573 – 591.

24 Kohno S, Imamura K, Koji S, *et al*: Effects of α-glucosidase inhibitor on insulin sensitivity and decreased level of postprandial plasma glucose in NIDDM patients: evaluation by glucose clamp method (Part 1). *Jpn J Clin Exp Med* 1997; **74:** 952 – 954.

25 Nao K, Ymazaki Y, Katsura K, *et al*: Glycemic threshold for prevention of diabetic retinopathy: a retrospective

study of diabetic outpatients. *J Jpn Diab Soc* 1989; **32:** 307 – 312.

26 Kawahara R, Nakagami T: Clinical study of treatments on diabetes mellitus: clinical factors for prevention of diabetic retinopathy. The Ministry of Health and Welfare, 1993; 267 – 269.

27 Umeno Y, Limori K, Endo M, *et al*: Combination effects of voglibose and sulfonylureas in non-insulin dependent diabetes mellitus (NIDDM) patients. *Jpn Clin Exp Med* 1997; **74:** 739 – 744.

28 Iijima T, Makino T, Takahashi H, *et al*: Usefulness of combination therapy with sulfonylurea and α-glucosidase inhibitor (voglibose) in non-insulin dependent diabetes mellitus: effect of reducing the dose of sulfonylurea. *Jpn Pharmacol Ther* 1997; **25:** 841 – 849.

29 Kanda T, Imano H, Matsushima H, *et al*: Usefulness of combination therapy with preprandial rapid-acting insulin injection and α-glucosidase inhibitor in non-obese NIDDM patients with secondary failure on oral hypoglycemic agents. *J Jpn Diab Soc* 1996; **39:** 183 – 190.

30 Odaka H, Miki N, Ikeda H, Effect of intestinal disaccharidase inhibitor, AO-128, on carbohydrate, protein, fat, and vitamin absorption in rats. *Jpn Pharmacol Ther* 1991; **19:** 4439 – 4450.

31 Ikeda H, Odaka H, Matsuo T: Antiobesity and antidiabetic action of a disaccharidase inhibitor, AO-128, in genetically obese-diabetic mice, KKA^{y}. *J Nutr Sci Vitaminol (Tokyo)* 1991: **19:** 4105 – 4117.

32 Matsuo T, Odaka H, Ikeda H: Effect of an intestinal disaccharidase inhibitor (AO-128) on obesity and diabetes. *Am J Clin Nutr* 1992; **55**(suppl 1.1): 314 – 317.

33 Shimura Y, Odaka H, Ikeda H, *et al*: Obesity suppression and anti-diabetic activity on AO-128. Proceedings of the 7th Congress of Japan Aged Society Supporting Organization 1986; 210 – 211.

34 Inui Y, Kawata S, Matsuzawa Y, *et al*: Inhibitory effect of a new α-glucosidase inhibitor on fatty liver in zucker fatty rats. *J Hepatol* 1990; **10:** 62 – 68.

35 Inui Y, Kawata S, Kohata R, *et al*: The effects of an α-glucosidase inhibitor on fatty liver in obesity. *Jpn J Gastroenterol* 1987; **84:** 1639 – 1644.

36 Report of the Expert Committee on the diagnosis and the classification of diabetes mellitus. *Diabetes Care* 1997; **20:** 1183 – 1197

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