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Effect of two α-glucosidase inhibitors, voglibose and acarbose, on postprandial hyperglycemia correlates with subjective abdominal symptoms

Tomomi Fujisawa, Hiroshi Ikegami*, Kaori Inoue, Yumiko Kawabata, Toshio Ogihara

Department of Geriatric Medicine, Osaka University Graduate School of Medicine, Osaka 565-0871 Japan

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Abstract

To assess the possible difference in effectiveness of 2 α-glucosidase inhibitors, voglibose and acarbose, the relationship between postprandial hyperglycemia and subjective abdominal symptoms was investigated.

A total of 21 inpatients with type 2 diabetes were recruited to a single-center, 2-period, crossover trial. The subjects were given acarbose (150 mg/d) or voglibose (0.9 mg/d) under an isocaloric diet, and the postprandial (2 hours) increment in blood glucose level, M value which is a marker for fluctuation of blood glucose levels, and subjective abdominal symptom score were monitored.

There was no significant difference between the 2 agents in postprandial increment in blood glucose level, M value, and subjective symptom score. When patients were divided according to subjective symptoms, however, the sum postprandial glucose increments were significantly different according to the agent ($P = .03$), with favorable efficacy in patients in whom the α-glucosidase inhibitor caused abdominal symptoms, demonstrating a significant interaction ($P = .04$) between treatment and symptomatic grouping.

The results demonstrated that 50 mg acarbose and 0.3 mg voglibose had similar overall effects on postprandial hyperglycemia as well as subjective symptoms, but marked interindividual variation existed. Subjective symptoms may be a predictor of the divergent clinical response to each agent.

1. Introduction

While the prevalence of type 2 diabetes mellitus is still increasing in many countries, postprandial hyperglycemia has been shown to be particularly important in the development of macrovascular disease [1-3]. Therefore, effective control of postprandial hyperglycemia is more strongly warranted than previously thought. To control postprandial hyperglycemia, α-glucosidase inhibitors are widely used, as monotherapy as well as combination therapy with other antidiabetic agents [4-7]. This class of agent retards gastrointestinal absorption of dietary carbohydrates by inhibiting digestion of polysaccharides and disaccharides and thus lessens the postprandial increase in blood glucose level. Considerable diversity in their clinical effectiveness, however, has been noted among individuals with diabetes [8,9]. The physiological explanation for this interindividual diverse response to the agents remains unclear.

In this study, 2 α-glucosidase inhibitors, acarbose and voglibose, which have different biologic properties in inhibiting gastrointestinal enzymes [10,11], were administered to inpatients with type 2 diabetes mellitus in a crossover manner, and the relationship between postprandial hyperglycemia and subjective abdominal symptoms was investigated. The results indicated a divergent response to these 2 agents among individuals and the usefulness of subjective symptoms as a predictive marker for clinical efficacy.

2. Materials and methods

2.1. Subjects

Inpatients (n = 21) with diabetes mellitus at Osaka University Hospital were investigated. Diabetes mellitus was diagnosed according to the guidelines of the American Diabetes Association [12]. Patients whose level of post-

* Corresponding author. Tel.: +81 6 6879 3852; fax: +81 6 6879 3859.
E-mail address: ikegami@geriat.med.osaka-u.ac.jp (H. Ikegami).

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Table 1
Baseline characteristics of study patients with diabetes mellitus

Sex (M/F)	12/9
Age (y)	59 ± 10
Body mass index (kg/m^2)	22.9 ± 3.4
Duration of diabetes (y)	14.5 ± 8.5
Retinopathy (NDR/BDR/PDR)	14/5/2
Nephropathy (normoalbuminuria/ microalbuminuria/macroalbuminuria)	18/2/1
HbA1c (%)	7.8 ± 1.4
Concurrent antidiabetic medication (none/OHA/insulin)	3/9/9

Data are mean ± SD. NDR indicates nondiabetic retinopathy; BDR, background diabetic retinopathy; PDR, proliferative diabetic retinopathy; OHA, oral hypoglycemic agent.

prandial hyperglycemia was not optimal were enrolled in the present study after informed consent was obtained. Subjects who had undergone gastrointestinal surgery, as well as those with severe hepatic disease, malignant disease, or inflammatory bowel disease were excluded. Duration of diabetes was estimated from the time of the first symptoms attributable to the disease or, if symptoms were absent, from the time of the first detection of glycosuria.

Subjects received either acarbose (150 mg/d) or voglibose (0.9 mg/d) for 2 or 3 consecutive days under an isocaloric diet whose nutritional composition was 50% to 55% carbohydrate, 27% to 30% fat, and 18% to 20% protein, in a crossover manner; that is, 1 set of patients received voglibose for a period and then were switched to acarbose, and the other set received acarbose first and then voglibose. Blood glucose was monitored before and 2 hours after each meal as well as at bed time (7 points per day) by a glucose-oxidative method with a Glutest Ace (Sanwa Kagaku Kenkyusho Co, Nagoya, Japan). Subjective symptoms were monitored just after administration of drug by ranking the degree of gas/flatulence, abdominal distension, and abdominal rumbling on visual analog scales. Subjects were asked to mark on the analog scale from 1 to 5, where 1 meant “not at all” and 5 meant “very much.”

Body mass index was calculated as body weight (kg) divided by height squared (m^2). Diabetic retinopathy was classified as nonretinopathy, background retinopathy, or proliferative retinopathy through fundoscopy, retinal photography, and/or fluorescein angiography after pupillary dilatation. Diabetic nephropathy was classified as normoalbuminuria, microalbuminuria, or clinical albuminuria using 24-hour collection of urine [13]. Glycated hemoglobin was determined using radioimmunoassay.

2.2. Statistical analysis

Data are given as mean ± SD. In each individual, the postprandial (2 hours) increment in blood glucose level was calculated by subtracting blood glucose level before the meal from that 2 hours after the meal on 2 or 3 consecutive days, and the mean postprandial increase for each meal (breakfast, lunch, or dinner) was calculated. These mean increments during administration of each agent were summed and defined as the sum postprandial glucose increment. The sum postprandial glucose increment was compared between the 2 agents using paired t test. To assess the fluctuation of blood glucose levels per se, M value [14] was calculated each day using the 7 measurements of blood glucose level, and the mean M value for each α-glucosidase inhibitor was calculated in each individual. Paired t test was adopted to compare the mean M value between the 2 agents. For subjective symptoms, the 3 scores for symptoms were summed and defined as the sum symptom score, which was subjected to paired t test for comparison between the 2 agents.

To further investigate the difference in efficacy between the 2 agents in relation to subjective symptoms, the patients were divided into 2 groups: patients who had a higher sum symptom score during voglibose than during acarbose treatment and the other patients. Sum glucose increment and M value were analyzed using repeated measurement of analysis of variance, with the symptomatic grouping as dependent factor. The interaction between treatment and symptomatic grouping was also analyzed statistically. A P value of less than .05 was regarded as statistically significant.

3. Results

A total of 21 inpatients with type 2 diabetes mellitus were enrolled in the present crossover study. Among them, 9 were on insulin, none of whom was treated with a rapid-acting insulin analog, 9 were being treated with other antidiabetic agents, and the remaining 3 were not receiving any antidiabetic agent (Table 1).

The sum postprandial (2 hours) glucose increment was not significantly different between the 2 agents (P = .12, paired t test) (Table 2). Similarly, M value, a marker for fluctuation of blood glucose levels [14], was not significantly different between the 2 agents (P = .53, paired t test) (Table 2).

As for subjective symptoms, the symptom score was not significantly different between the 2 agents (P = .57, paired t test). To further assess any difference between the 2 agents in their efficacy in relation to subjective symptoms, these metabolic parameters were assessed according to subjective symptoms. Among the study subjects, 7 had a higher symptom score during voglibose treatment than during acarbose treatment, and the patients were divided into 2 groups: these 7 patients and the remaining 14 patients. As shown in Table 3, the 2 groups showed opposite responses of postprandial glucose increment to the 2 α-glucosidase

Table 2
Metabolic parameters during treatment with voglibose (0.9 mg/d) and acarbose (150 mg/d)

	Voglibose	Acarbose	P
2-h Blood glucose increment (mg/dL)	120 ± 98	148 ± 82	NS
M value [14]	12.0 ± 5.5	15.5 ± 5.3	NS
Subjective symptom score	4.7 ± 1.8	5.0 ± 2.2	NS

Data are mean ± SD. NS indicates not significant (P > .05).

Table 3
Metabolic parameters during treatment with voglibose (0.9 mg/d) and acarbose (150 mg/d) according to subjective symptoms

	Subjects with more symptoms during voglibose (n = 7)	Others (n = 14)	*P*	
			Treatment	Interaction
Sum 2-h blood glucose increment (mg/dL)				
On 0.9 mg voglibose	101 ± 136	130 ± 76		
On 150 mg acarbose	176 ± 113	133 ± 60	.03	0.04
M value [14]				
On 0.9 mg voglibose	11.0 ± 5.9	12.5 ± 5.4		
On 150 mg acarbose	15.0 ± 7.4	11.3 ± 3.7	NS	0.004

Data are mean ± SD. Subjects were divided into 2 groups according to subjective abdominal score; subjects (n = 7) with a higher symptom score during acarbose treatment than during voglibose and others (n = 14). The *P* value was calculated by analysis of variance. NS indicates not significant ($P > .05$).

inhibitors. The 7 patients with a higher subjective score during voglibose than during acarbose treatment showed a smaller, albeit not significant, postprandial glucose increment (101 ± 136 mg/dL) during voglibose treatment than that (130 ± 76 mg/dL) in the other 14 patients. Conversely, during acarbose treatment, the sum increment in the 7 patients (176 ± 113 mg/dL) was higher than, but not significantly different from, that in the remaining 14 patients (133 ± 60 mg/dL). When this symptomatic grouping was taken into account, the sum postprandial glucose increment was significantly different according to treatment ($P = .03$), with a significant interaction ($P = .04$) between treatment and symptomatic grouping. As for M value, although no significant difference was observed according to the treatment itself, a significant interaction ($P = .004$) was detected between treatment and symptomatic grouping.

4. Discussion

In the present crossover study in inpatients with type 2 diabetes mellitus, there was no significant difference between treatment with 150 mg acarbose and with 0.9 mg voglibose in the sum postprandial increment in glucose level, a marker for fluctuation of daily blood glucose profile as assessed by M value [14], or subjective abdominal symptom score, indicating similar overall clinical effects of the 2 agents. When patients were divided into 2 groups according to abdominal symptoms, however, the sum postprandial glucose increment was significantly different according to treatment, with favorable efficacy in patients in whom the α-glucosidase inhibitor caused abdominal symptoms, which showed a significant interaction between treatment and symptomatic grouping. These data demonstrated interindividual diversity in the clinical response to the 2 α-glucosidase inhibitors and a possible correlation of subjective symptoms with clinical effectiveness, suggesting the usefulness of subjective symptoms as a predictive marker for the clinical efficacy of each agent.

Food contains various kinds of polysaccharides, which are enzymatically broken down to monosaccharides within the gastrointestinal tract. Because only monosaccharides are absorbed from the intestinal tract, this digestive process is an important step determining postprandial glucose metabolism. α-Glucosidase inhibitors retard this digestive process through their inhibition of intestinal digestive enzymes. As a result, undigested polysaccharides are forwarded to the distal gut, where undigested and unabsorbed polysaccharides undergo fermentation by bacterial flora. This fermentation is considered to cause abdominal symptoms, such as gas, abdominal distention, and flatulence. It is rational, therefore, that subjects with more abdominal symptoms induced by an α-glucosidase inhibitor which have often been considered "adverse," are expected to have more effective inhibition of gastrointestinal enzymes, leading to better control of postprandial glucose. Although there could be a possible correlation between glycemic control and symptoms of carbohydrate malabsorption, there was no apparent correlation between the sum glucose increment and sum symptom score for each agent (r^2 of 0.03 and 0.002, for voglibose and acarbose, respectively), indicating that the postprandial increment of blood glucose level per se is not merely predicted by abdominal symptoms. This may be caused by several other confounding factors, including antidiabetic comedication and severity of insulin deficiency.

The present data indicated divergent sensitivity to each α-glucosidase inhibitor among individuals. This divergent sensitivity may be plausibly explained by distinct pharmacological properties between the 2 agents in their inhibitory effects on the spectrum of gastrointestinal enzymes. One in vitro study [15] demonstrated that acarbose inhibited pancreatic α-amylase, which catalyzes the first step in the breakdown of polysaccharides such as starch, whereas voglibose has more specific inhibition of disaccharidases, such as maltase and sucrase. Therefore, voglibose might be potentially effective in individuals with low disaccharidase activities, in whom blockade of dissaccharidases by voglibose would greatly affect postprandial digestion and absorption of polysaccharides. In contrast, given the marked interindividual diversity in serum amylase activity [16], acarbose is considered to be effective in patients in whom amylase activity is crucial for carbohydrate metabolism. Thus, the diverse response to these 2 α-glucosidase inhibitors in each individual may be explained by the distinct pharmacological properties of the 2 agents. From another aspect, a combination of the 2 α-glucosidase inhibitors would be expected to be more universally effective than each monotherapy.

Considerable interindividual diversity in the effectiveness of α-glucosidase inhibitors has been noted clinically [8,9]. One clinical study showed an association of the

relative carbohydrate content in total food with the clinical effectiveness of α-glucosidase inhibition [17], and thus, the daily habitual food intake would contribute to such clinical diversity in effectiveness. If patients received more sucrose and less starch, they would have better glycemic control and more carbohydrate malabsorption under voglibose. As mentioned in the Materials and methods, however, the present study adopted a crossover design, and each individual received food with a basically similar content under both agents.

It is also possible that postprandial hyperglycemia under α-glucosidase inhibitors is affected by differences in the glycemic index of carbohydrates in the diet. The mixed meals given to the patients in the study, however, contained various kinds of carbohydrates with different glycemic indices, which were not precisely determined. One previous study in type 2 diabetes mellitus demonstrated that addition of acarbose was more effective when patients received carbohydrates with a low glycemic index (all bran) than with a high glycemic index (cornflakes), although abdominal symptoms were not described [18].

Of the 14 patients without a higher symptom score during voglibose treatment than during acarbose treatment, 8 reported more symptoms during acarbose than during voglibose, and their postprandial glucose increment and M value were comparable to those in the 6 patients with the same symptom scores with the 2 medications. Further studies are required to address this point.

In conclusion, the present crossover study in inpatients with type 2 diabetes mellitus demonstrated that 50 mg acarbose and 0.3 mg voglibose had similar effects overall on postprandial hyperglycemia, as well as similar subjective symptoms. However, the response to each agent in terms of postprandial glucose control was divergent among individuals, and the subjective symptoms, which were often considered “adverse,” produced by each agent were correlated with their clinical efficacy. The present results suggest the usefulness of subjective symptoms as a predictive marker for clinical efficacy of each agent, which is applicable for the proper selection of α-glucosidase inhibitor in each patient for better management of diabetes mellitus.

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