ELSEVIER

Diabetes Research and Clinical Practice 55 (2002) 99–103

DIABETES RESEARCH AND CLINICAL PRACTICE

www.elsevier.com/locate/diabres

Efficacy and safety of voglibose in comparison with acarbose in type 2 diabetic patients

Apichati Vichayanrat *, Sirirat Ploybutr, Monchaya Tunlakit, Praneet Watanakejorn

Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine & Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Accepted 18 June 2001

Abstract

We performed a randomized crossover open comparative study to evaluate the efficacy and safety of voglibose and acarbose in 30 patients with type 2 diabetes who were not well controlled with diet therapy. There was no significant reduction of FBG with either voglibose or acarbose at 4 and 8 weeks after treatment. The 1 h postprandial blood glucose (PPBG) level was significantly decreased from 224.9 ± 42.8 to 204.1 ± 37.6 ($P = 0.005$) and 206.1 ± 38.9 mg/dl ($P = 0.038$) after voglibose therapy at 4 and 8 weeks, respectively. Significant decrease was also obtained after acarbose treatment from 228.3 ± 37.4 to 182.7 ± 35.5 ($P < 0.001$) and 186.6 ± 36.1 mg/dl ($P < 0.001$). The decrease of 1 h PPBG was associated with a significant fall of serum insulin concentration. HbA_{1c} levels were also significantly decreased from 7.07 ± 1.21 to 6.83 ± 1.11 ($P = 0.017$) and $6.79 \pm 1.33\%$ ($P = 0.036$) after voglibose and 6.98 ± 0.98 to 6.70 ± 1.04 ($P < 0.001$) and $6.59 \pm 1.04\%$ ($P < 0.001$) after acarbose at 4 and 8 weeks. In contrast to voglibose, treatment with acarbose significantly decreased the 2 h PPBG at 4 and 8 weeks and the 2 h postprandial serum insulin concentration at 8 weeks. Adverse drug events were more commonly reported in acarbose-treated patients ($P < 0.05$). Increased flatulency was observed in 56.7 and 90% of the patients taking voglibose and acarbose, respectively, while abdominal distention was noted in 10 and 16.7%. Significantly decreased body weights of 0.9 and 0.8 kg were recorded at 8 weeks after voglibose and acarbose therapy, respectively. We conclude that both voglibose (0.2 mg) and acarbose (100 mg) thrice daily significantly decreased HbA_{1c}, PPBG and postprandial insulin levels. At these dose levels, voglibose was associated with less gastrointestinal side effects and slightly less efficacy for postprandial glucose reduction.

Keywords: α-Glucosidase inhibitor; Voglibose; Acarbose; Postprandial hyperglycemia; Treatment of type 2 diabetes

1. Introduction

The importance of good blood glucose control in preventing chronic vascular complications in type 2 diabetic patients has evidence-based support [1]. It is generally accepted that the ability to

* Corresponding author. Tel.: +66-2-419-7797; fax: +66-2-419-7792.

E-mail address: apichativ@hotmail.com (A. Vichayanrat).

0168-8227/02/$ - see front matter
PII: S0168-8227(01)00286-8

achieve the best possible glycemic control both in the fasting and postprandial states is the primary goal in the treatment of diabetic patients. Until recently, the significance and consequences of postprandial metabolic regulation have been ignored. Ceriello reviewed the role of postprandial hyperglycemic spikes in the pathogenesis of diabetic complications [2]. Temelkova-Kurktschiev et al. reported that postchallenge plasma glucose and glycemic spikes were more strongly associated with atherosclerosis than fasting glucose or HbA_{1c} [3]. Several new pharmacological agents have been developed to focus on postprandial glucose control. These include rapid-acting insulin analogues [4], nonsulphonylurea rapid-acting insulin secretagogues [5,6] and digestive enzyme inhibitors [7,8]. α-Glucosidase inhibitors which act as competitive inhibitors of intestinal α-glucosidases can delay the digestion and subsequent absorption of carbohydrate leading to attenuation of postprandial blood glucose rises. Acarbose is the first α-glucosidase inhibitor available for treatment.

There has been no previous direct comparative study with voglibose, a newer α-glucosidase inhibitor. In this study, we evaluated the efficacy and safety of voglibose in comparison with acarbose in type 2 diabetic patients whose blood glucose levels were not well controlled by medical and nutritional therapy.

2. Materials and methods

2.1. Patient population

The study population consisted of male and female patients aged 26–76 years with an established diagnosis of type 2 diabetes. They were not taking insulin or other oral hypoglycemic agents and had no other major medical problems. Their blood glucose levels were not well controlled by diet therapy, showing a 1 or 2 h postprandial blood glucose (PPBG) level of 200 mg/dl or more at the end of a 4 week observation period. The stability of blood glucose was documented by a difference of 30 mg/dl or less in the fasting blood glucose (FBG) levels at the beginning and end of the observation period. The study was carried out in an outpatient setting.

Patients with the following conditions were excluded: alcohol abuse, pregnant women or patients with a desire of child bearing, patients with severe cardiac, hepatic, renal or pancreatic diseases, patients with chronic gastrointestinal diseases, patients with severe infections or severe injuries, and all patients judged by the investigators to be unsuitable for the study.

Informed consent from all subjects and approval from the ethnic committee of the Faculty of Medicine Siriraj Hospital, Mahidol University were obtained prior to the study.

2.2. Study design

This was a randomized crossover open comparative study to evaluate the efficacy and safety of voglibose and acarbose in type 2 diabetic patients whose blood glucose levels were not well controlled with dietary treatment. The study consisted of a 4 week observation period followed by an 8 week treatment period. After the observation period, patients were randomized alternately to receive either voglibose (0.2 mg) or acarbose (100 mg) thrice daily with meals for 8 weeks. This was followed by a 4 week washout, a 4 week observation and an 8 week treatment with the alternate drug.

Patients on oral hypoglycemic agents stopped their medications at least 4 weeks before the observation period. During observation, washout, and treatment periods, patients were instructed to follow medical and nutritional therapy for diabetes mellitus. Patients who were on pharmacological treatment for concomitant chronic illnesses, e.g. hypertension, dyslipidemia, etc. continued to use the drugs without changing the dosage. Commencement of any new drugs or changing the dosage of drugs that may interfere with the result of the study was avoided.

After an overnight fast, FBG levels were determined at the beginning and the end of the observation period. If the difference was 30 mg/dl or less, patients were given a breakfast which consisted of 350–400 cal (carbohydrate 50–55%, fat 25–30% and protein 20%). PPBG levels at 1 and 2 h and the corresponding serum insulin levels (IRI) were measured. If the results met inclusion

criteria, patients were given the study drugs and were scheduled to be seen by the investigators every 4 weeks. At 4 and 8 weeks after treatment, FBG, 1 and 2 h PPBG (after breakfast with a tablet of study drug), and corresponding IRI levels were determined. HbA_{1c} and lipid profiles were determined at the end of the observation period and at the end of 8 weeks of treatment. Additional HbA_{1c} levels were also measured at 4 weeks after treatment and 4 weeks after stopping treatment. Complete blood count, urine analysis and blood chemistry including serum total protein, albumin, SGOT, SGPT, alkaline phosphatase, LDH, bilirubin, amylase, BUN, creatinine, calcium, phosphate and electrolytes were determined prior to and at 8 weeks after drugs treatment.

Clinical data including body weight, vital signs, symptoms and signs particularly those related to the abdominal system were obtained at each study visit. All adverse drug events during the study were also recorded.

HbA_{1c} concentration was assayed using DCA 2000 analyser, based on latex immunoagglutination inhibition method (Bayer corporation, normal mean $\pm$ SD, $5.0 \pm 0.35\%$). Serum insulin concentration was determined by radioimmunoassay using commercial kits (Diagnostics Products Corporation, USA). Lipid profiles was performed by an enzymatic method. Blood glucose concentration was measured by a glucose oxidase method. Blood chemistry and urine analysis were performed by the central laboratory.

Compliance to drug treatment was ascertained by tablet counting at each visit. Data are expressed as mean $\pm$ SD. Statistical analyses was by Student's *t*-test and chi-square test where appropriate. Differences were considered statistically significant at $P \leq 0.05$.

3. Results

3.1. Efficacy

Study participants included three men and 27 women, with a mean age of 55.0 ± 11.6 years ($\pm$ SD; range 28–76 years) and a mean body mass index (BMI) of 21.1 ± 3.6 kg/m^2 ($\pm$ SD; range 17.8–33.3 kg/m^2). They had been diagnosed type 2 diabetes for 1.7 ± 2.6 years (mean $\pm$ SD, range 0.3–13.0 years). Fourteen patients had a history of taking either sulphonylurea or metformin or both before enrollment. The mean FBG, HbA_{1c} and IRI levels at study baseline prior to voglibose and acarbose treatment were not significantly different. The effects of drugs on FBG and PPBG at 4 and 8 weeks after treatment are shown in Table 1. There was no significant reduction of FBG with voglibose and acarbose at 4 and 8 weeks after treatment. The 1 h PPBG was significantly decreased after 4 and 8 weeks of treatment for both drugs. However, 2 h PPBG was significantly decreased only after acarbose therapy at 4 and 8 weeks.

Table 1
The effects of voglibose and acarbose treatment for 8 weeks on FBG and PPBG levels in 30 patients with type 2 diabetes

	Voglibose		Acarbose	
	mean $\pm$ SD	*P* vs. 0 week	mean $\pm$ SD	*P* vs. 0 week
−4 weeks FBG (mg/dl)	151.9 ± 28.5		157.2 ± 33.5	
0 weeks FBG (mg/dl)	145.1 ± 30.0		147.9 ± 35.0	
1 h PPBG	224.9 ± 42.8		228.3 ± 37.4	
2 h PPBG	197.5 ± 42.4		199.9 ± 45.6	
4 weeks FBG (mg/dl)	142.7 ± 37.0	ns	143.0 ± 26.8	ns
1 h PPBG	204.1 ± 37.6	0.005	182.7 ± 35.5	<0.001
2 h PPBG	189.9 ± 50.4	ns	166.5 ± 32.4	<0.001
8 weeks FBG (mg/dl)	141.1 ± 37.5	ns	140.6 ± 35.6	ns
1 h PPBG	206.1 ± 38.9	0.038	186.6 ± 36.1	<0.001
2 h PPBG	192.4 ± 51.4	ns	173.9 ± 44.8	<0.001

Table 2
The effects of voglibose and acarbose treatment for 8 weeks on HbA_{1c} and serum insulin (IRI) levels in 30 patients with type 2 diabetes

	Voglibose		*P* vs. 0 week	Acarbose	*P* vs. 0 week
HbA_{1c} (mean ± SD, %)					
0 week	7.07 ± 1.21		6.98 ± 0.98		
4 weeks	6.83 ± 1.11	0.017	6.70 ± 1.04	<0.001	
8 weeks	6.79 ± 1.33	0.036	6.59 ± 1.04	<0.001	
4 weeks off treatment	6.72 ± 1.32	0.035	6.68 ± 1.16	<0.005	
IRI (mean ± SD, μU/ml)					
0 week fasting	13.51 ± 7.52		14.97 ± 11.29		
1 h	48.38 ± 26.56		47.54 ± 31.39		
2 h	45.40 ± 26.41		46.46 ± 29.10		
8 week fasting	12.88 ± 8.66	ns	14.46 ± 11.27	ns	
1 h	33.14 ± 19.02	<0.001	31.07 ± 19.70	0.002	
2 h	38.61 ± 23.29	0.06	31.53 ± 19.85	<0.001	

Table 2 shows the effects of drugs therapy on HbA_{1c} and serum IRI levels. There was a significant decrease of HbA_{1c} concentration at 4 and 8 weeks after both voglibose and acarbose treatment. A mean reduction of 0.24 and 0.28% was observed at 4 and 8 weeks, respectively, after voglibose therapy. The corresponding figures for acarbose treatment were 0.28 and 0.39%. After stopping drug therapy for 4 weeks, HbA_{1c} levels were still significantly decreased compared with baseline, an absolute reduction of 0.35 and 0.30% after voglibose and acarbose, respectively.

At 8 weeks after drugs therapy, there was no significant change of fasting serum IRI levels ($P > 0.05$). However, 1 and 2 h postprandial serum IRI levels were significantly decreased after both voglibose and acarbose treatment except for the effects of voglibose at 2 h ($P = 0.06$).

3.2. Safety and adverse drug reactions

Adverse drug events were significantly more common in acarbose-treated patients ($P < 0.05$). One or more adverse drug reactions were reported in 56.7% (17/30) and 90% (27/30) of patients who took voglibose and acarbose, respectively. However, problematic symptoms were observed in 3.3 versus 43.4% of the patients who took the respective drugs. Increased flatulence was reported in 56.7 and 90% of patients who took voglibose and acarbose, respectively, while abdominal distention was noted in 10 and 16.7%.

The body weight was significantly decreased from 60.0 ± 8.4 to 59.1 ± 8.4 kg and from 59.9 ± 8.4 to 59.1 ± 8.4 kg at 8 weeks in patients who were given voglibose and acarbose, respectively ($P < 0.05$). However, there was no significant change of body weight at 4 weeks.

There were no significant changes of complete blood count, urine analysis, lipid profiles and blood chemistry values over time.

4. Discussion

This study demonstrated that voglibose, an α-glucosidase inhibitor, at a dose of 0.2 mg 3 times daily, can significantly lower 1 h PPBG levels in type 2 diabetic patients who were not adequately controlled with diet alone. The effects were seen both at 4 and 8 weeks after treatment. More importantly, HbA_{1c} levels decreased. In animal models, voglibose or AO-128 suppressed elevation of the blood glucose concentration after oral sucrose, maltose and starch, but not after oral glucose, fructose and lactose [9]. In contrast to acarbose, voglibose leaves the α-amylase activity nearly unaffected. It is 190–3900-fold and 23–33-fold more potent than acarbose in inhibiting rat and porcine intestinal disaccharases, respectively.

At a dose of 1 mg three times daily in healthy volunteers, voglibose enhanced release of glucagon-like peptide-1 (GLP-1) which is an insulinotropic hormone [10]. The rate of gastric emptying affects the efficacy of voglibose therapy in type 2 diabetic patients. However, voglibose does not alter the rate of gastric emptying [11]. Similar to our study, this paper also showed that FBG and fasting serum IRI concentrations did not change significantly after voglibose therapy. Voglibose lowered daily glycemic excursion and inhibited the β-cell function, but had little effect on insulin sensitivity in NIDDM patients [12].

Compared with voglibose, acarbose treatment also lowered 1 h PPBG at 4 and 8 weeks, HbA_{1c} at 4 and 8 weeks and 1 h postprandial serum IRI at 8 weeks. Acarbose, at a dosage of 100 mg 3 times daily, seemed to be more potent and have a more prolonged action than voglibose at a dose of 0.2 mg 3 times daily because 2 h PPBG at 4 and 8 weeks and 2 h postprandial serum IRI concentration showed significant decrease only after acarbose treatment. However, both drugs significantly lowered HbA_{1c} at 4 and 8 weeks.

With regard to adverse drug events, our study demonstrated that voglibose had less drug reactions compared with acarbose. This might be due to the relatively lower dosage of voglibose used in this study and the less digestive enzyme inhibition of voglibose.

In conclusion, both voglibose and acarbose significantly decreased PPBG, HbA_{1c}, and postprandial serum IRI levels without affecting FBG and fasting serum IRI concentrations in type 2 diabetic patients who did not achieve adequate control with diet therapy. Voglibose therapy was associated with less adverse drug reactions and slightly less postprandial glucose lowering effects.

Acknowledgements

We thank the staff and fellows of the Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine & Siriraj Hospital for referring patients for the study. The study was supported by a grant from Takeda (Thailand), Ltd.

References

[1] UK prospective diabetes study (UKPDS) group, Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), Lancet 352 (1998) 837–853.
[2] A. Ceriello, The emerging role of postprandial hyperglycemic spikes in the pathogenesis of diabetic complications, Diabetic Med. 15 (1998) 188–193.
[3] T. Temelkova-Kurktschiev, C. Koehler, E. Henkel, W. Leonhardt, K. Fuecker, M. Hanefeld, Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level, Diabetes Care 23 (2000) 1830–1834.
[4] E.J. Bastyr III, C.A. Stuart, R.G. Brodows et al., for the IOEZ study group, Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}, Diabetes Care 23 (2000) 1236–1241.
[5] D.R. Owens, I. Ismail, S.D. Luzio, T. Bayer, Increased prandial insulin secretion after administration of a single preprandial oral dose of repaglinide in patients with type 2 diabetes, Diabetes Care 23 (2000) 518–523.
[6] Y. Hirschberg, A.O. Pietri, A.H. Karara, J.F. McLeod, Improved control of mealtime glucose excursions with coadministration of nateglinide and metformin, Diabetes Care 23 (2000) 349–353.
[7] S. Vannasaeng, W. Nitiyanant, A. Vichayanrat, S. Ploybutr, T. Peerapatdit, Effects of alpha-glucosidase inhibitor (acarbose) combined with sulfonylurea or sulphonylurea and metformin in treatment of noninsulin dependent diabetes mellitus, J. Med. Assoc. Thailand 78 (1995) 578–585.
[8] C. Deerochanawong, S. Serirat, P. Kornthong, Efficacy of acarbose as monotherapy in NIDDM, J. Med. Assoc. Thailand 79 (1996) 69–75.
[9] T. Matsuo, H. Odaka, H. Ikeda, Effect of an intestinal disaccharase inhibitor (AO-128) on obesity and diabetes, Am. J. Clin. Nutr. 55 (1992) 314s–317s.
[10] B. Goke, H. Fuder, G. Wieckhorst, et al., Voglibose (AO-128) is an efficient α-glucosidase inhibitor and mobilizes the endogenous GLP-1 reserve, Digestion 56 (1995) 493–501.
[11] T. Kawagishi, M. Inaba, Y. Nishizawa, et al., Relationship between gastric emptying and an α-glucosidase inhibitor effect on postprandial hyperglycemia in NIDDM patients, Diabetes Care 20 (1997) 1529–1532.
[12] K. Matsumoto, Y. Yamaguchi, M. Yano, et al., Effects of voglibose on glycemic excursions, insulin secretion, and insulin sensitivity in non-insulin-treated NIDDM patients, Diabetes Care 21 (1998) 256–260.