Effect of Acarbose in Treatment of Type II Diabetes Mellitus: A Double-blind, Crossover, Placebo-controlled Trial

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Abstract

This study evaluated the efficacy of acarbose in improvement of metabolic control in patients with fairly, well controlled non-insulin-dependent diabetes mellitus (NIDDM). Fifteen patients with mean age and duration of diabetes of 57.5±2.6 (SE) and 7.5±1.5 years, respectively were recruited and completed our study protocol. This study was a double-blind, crossover, placebo-controlled design consisting of two twelve-week treatments of acarbose and placebo separated by an eight-week washout period. Acarbose was effective in lowering of 1-hour and 2-hour postprandial plasma glucose from 251.7±10.7 and 205.3±9.1 mg/dl to 197.4±7.0 (p= 0.001) and 181.5±8.5 mg/dl (p=0.03), respectively. Fasting plasma glucose was slightly decreased but without significant change, from 150.8±7.3 to 140.8±6.1 mg/dl (p=0.07). Overall glycemic control tended to improve during the study period as indicated by the falling of HbA1c levels from 7.7±0.4 to 7.0±0.2 per cent (p=0.05). Serum C-peptide both fasting and postprandial as well as serum lipids were not affected by acarbose. Almost half of the patients treated with acarbose had mild and tolerable gastrointestinal adverse effects. In conclusion, acarbose, as combined therapy with other oral hypoglycemic agents, was effective in improvement of glycemic control particularly postprandial hyperglycemia in fairly, well controlled NIDDM patients with mild and acceptable adverse effects.

One of the major therapeutic goals in treatment of patients with diabetes mellitus is to reduce blood glucose to or near normal levels in order to reduce the risk of development of late diabetic complications. The Diabetes Control and Complication Trial (DCCT) conclusively demonstrated that in patients with type I diabetes, the risk of development and progression of retinopathy, nephropathy, and neuropathy is reduced 50-75 per cent by intensive treatment regimens compared

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with conventional treatment[1]. The reduction in risk of developing these complications positively correlated with the reduction in glycosylated hemoglobin (HbA1c). In type II diabetes, the degree of metabolic control also correlated with the development of microvascular and macrovascular complications[2,3]. Intensive therapy in type II diabetes, to levels mimicking those in the DCCT, has been shown to result in comparable reduction in microvascular complications[4].

Characteristically, patients with full-blown type II diabetes have elevation of both fasting and postprandial blood glucose. Treatment of these patients with sulfonylureas or biguanide or both have been shown to effectively reduce fasting plasma glucose (FPG) and HbA1c levels. However, the reduction in HbA1c is inappropriately less than the reduction in FPG levels in some occasions as demonstrated by UK Prospective Diabetes Study[5]. This might be due to the ineffectiveness of sulfonylureas or biguanide in decreasing postprandial blood glucose levels.

Acarbose, an α-glucosidase inhibitor, reversibly inhibits α-glucosidase enzyme in the brush border of the small intestine. It delays the cleavage of oligo-and disaccharides to monosaccharides, resulting in delay in carbohydrate absorption, and thus leads to a delayed and reduced blood glucose rising after a meal[6]. Results from clinical trials in patients with type II diabetes have shown that treatment with acarbose resulted in significant reduction in postprandial hyperglycemia and HbA1c levels[7-14]. However, the efficacy of acarbose in Thai patients may possibly be different from others considering a larger amount of carbohydrate-containing meal in Thai patients[15]. To our knowledge, there has been no double-blind, placebo-controlled study of acarbose conducted in Thailand.

The present study was designed to evaluate the efficacy of acarbose in treatment of fairly, well controlled type II diabetes. The primary analysis of drug efficacy was the change from baseline of HbA1c. The secondary analysis of efficacy included the change from baseline of fasting and postprandial plasma glucose and serum C-peptide as well as serum lipids levels.

PATIENTS AND METHOD

This study was a randomized, crossover, double-blind, and placebo-controlled design, consisting of two twelve-week treatment periods separated by an eight-week washout period. Type II diabetic patients from diabetic clinic of Songklanagarind Hospital who had fair glycemic control (defined by FPG < 200 mg/dl), were treated with oral hypoglycemic drugs and had achieved stable glycemic control indicated by having fluctuation of FPG levels ≤ 50 mg/dl or changing in HbA1c levels ≤ 1.5 per cent in the last two consecutive visits, were enrolled for the study. Patients were excluded from the study if they had one or more of the following reasons: presence of significant diseases or conditions which were likely to alter the course of diabetes or unable to complete the study; presence of documented gastrointestinal diseases and taking medications likely to alter gut motility or absorption; concomitant therapy with drugs that might interfere with the action of acarbose[16]; elevated serum creatinine > 2.0 mg/dl.

After a 4-week run-in period, acarbose or match placebo was started at the dose of 50 mg three times daily taken with the first bite of each meal for 4 weeks and then increased to 100 mg for 8 weeks. After a washout period of 8 weeks, the treatment was crossed-over for another 12 weeks. The dosage of study medication could be decreased at any time if intolerable adverse events occurred. Throughout the study period, the dosage of oral hypoglycemic agents were maintained unchanged unless hypoglycemia occurred.

Patients were seen every 4 weeks and were instructed to continue with the same diet and exercise habits throughout the study period. At each visit, body weight, blood pressure and FPG were recorded. Mixed-meal tolerance test, fasting serum lipids and HbA1c were measured at, before and after the end of each treatment period. Mixed-meal tolerance test was performed after overnight fast using Sustacal as a test meal. This liquid meal contains 55 per cent carbohydrate (64% sucrose, and 36% corn syrup), 21 per cent lipids, and 24 per cent proteins. Eight fl oz (240 Kcal) of Sustacal was given at 8.00 am and ingested over 15 min. Acarbose or placebo was recommended to be taken with the first sip of the liquid meal. Patients were told to continue taking the test pill even at the day of meal tolerance test. Blood samples were drawn at times 0, 60, and 120 min for measurement of plasma glucose and serum C-peptide.

Adverse drug reactions and drug compliance assessed by tablet counts were recorded at each clinic visit. The study was approved by the

ethics committee of Faculty of Medicine, Prince of Songkla University and all patients gave written informed consent before entering the study.

Laboratory analysis

FPG, serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, and serum triglyceride were determined by enzymatic method using automated machine Hitachi model 704. The low-density lipoprotein (LDL)-cholesterol fraction was calculated by the Friedewald formula[17]. HbA1c was determined by immunoturbidity method using commercial kit (Boehringer Mannheim, Germany), with normal value of 3.9-5.7 per cent. Serum C-peptide was determined by double antibody radioimmunoassay using commercial kit (Diagnostic Product Cooperation, U.S.A.). At serum C-peptide concentrations of 1.65-1.92 ng/ml and 0.24-0.28 ng/ml, the intraassay CV of the test were 4.21 per cent and 5.79 per cent, respectively.

Statistical analysis

All pairwise comparison of the change in outcome parameters from baseline to the end of treatment was done using a paired Student's *t*-test. The change of body weight was analyzed using an analysis of variance model. All results were expressed as means ± SE. A p value < 0.05 was considered to be statistically significant.

RESULTS

Of the 21 patients initially entered into the study, 15 (5 men and 10 women) completed the study protocol. Their mean age was 57.5±2.6 years (range 40-75) with body mass index (BMI) of 25.9±1.0 kg/m^2 (range 16.5-32.6). Duration of diabetes was 7.5±1.5 years (range 1.5-16). Diabetes treatments for 15 patients were as follows: sulfonylurea alone for 5 patients, and combined sulfonylurea and metformin for 10 patients. The doses of oral hypoglycemic agents were unchanged throughout the study period with the exception of one acarbose-treated patient whose dose of oral hypoglycemic drug was reduced due to the development of hypoglycemia. Six patients (5 on placebo, 1 on acarbose) were dropped from the study. 3 patients treated with placebo withdrew from the study prematurely because of intolerable adverse events (2 diarrhea, 1 abdominal discomfort), 2 patients treated with placebo had poor compliance and 1 patient treated with acarbose developed congestive heart failure after 1 month of treatment.

The body weight did not significantly change during the study period both in placebo (from 64.2±2.2 kg to 63.9±2.2 kg) and acarbose group (from 64.4±2.1 kg to 63.5±2.1 kg). As shown in Table 1, HbA1c and postprandial plasma glucose were significantly reduced at the end of the treatment period in the acarbose group, whereas,

Table 1. Metabolic parameters before and after treatment.

Parameters	Placebo		p	Acarbose		p
	Before	After	value	Before	After	value
HbA1c (%)	7.7±0.4	7.6±0.4	0.38	7.7±0.4	7.0±0.2	0.05
Fasting plasma glucose (mg/dl)	160.3±9.7	161.8±8.5	0.86	150.8±7.3	140.8±6.1	0.07
Postprandial plasma glucose (mg/dl)						
1 hour	243.9±12.6	248.7±10.1	0.68	251.7±10.7	197.4±7.0	0.001
2 hour	217.1±13.1	229.7±10.8	0.35	205.3±9.1	181.5±8.5	0.03
Fasting serum C-peptide (ng/ml)	2.02±0.27	1.8±0.22	0.25	1.74±0.01	2.02±0.23	0.27
Postprandial serum C-peptide (ng/dl)						
1 hour	3.43±0.46	3.31±0.43	0.74	3.46±0.27	3.30±0.27	0.48
2 hour	3.30±0.40	3.58±0.43	0.49	3.57±0.27	3.96±0.35	0.13
Triglyceride (mg/dl)	156.7±18.4	145.4±11.3	0.33	149.6±17.0	154.4±3.9	0.73
Total cholesterol (mg/dl)	220.6±11.5	222.8±8.5	0.76	223.1±11.9	221.1±10.8	0.80
HDL-cholesterol (mg/dl)	46.1±2.4	44.8±2.7	0.51	47.0±3.1	42.8±2.6	0.07
LDL-cholesterol (mg/dl)	143.4±11.9	148.9±8.4	0.48	146.2±11.1	147.4±10.6	0.87

HDL = high-density lipoprotein; LDL = low-density lipoprotein

no significant effect was observed in the placebo group. The degree of reduction in postprandial plasma glucose was greatest at 1 hour after the test meal. FPG in acarbose group was also reduced from 150.8±7.3 mg/dl to 140.8±6.1 mg/dl but it did not reach statistically significance. There were no significant changes from baseline in both fasting and postprandial serum C-peptide and serum lipids levels in both placebo and acarbose groups.

During 12 weeks of treatment, 7 patients from the acarbose and 2 patients from the placebo group complained of gastrointestinal adverse events. Flatulence was noted in 6 patients (2 in the placebo group, 4 in the acarbose group) and flatus was noted in 3 patients treated with acarbose. All of these symptoms were mild and tolerable. None developed hypoglycemia during treatment with acarbose except one patient who had hypoglycemic episodes after the first month of therapy, which was solved by reducing the dose of glibenclamide.

DISCUSSION

The previous studies in Thailand by Vannasaeng et al[18] and Deerochanawong et al[19] have shown that acarbose, whether as a monotherapy or combined with other oral hypoglycemic agents, can improve glycemic control in Thai NIDDM patients. Our study, with a placebo-controlled, did confirm the previous studies. Degree of reduction in HbA1c levels varied from 0.9-2.2 per cent in most studies[10,13,14,18]. The modest degree (0.7%) of improvement in HbA1c levels in our study might be explained by the lower HbA1c levels at baseline and shorter duration of treatment compared with others where the maximum effect of acarbose in lowering HbA1c level has been shown after 6 months of therapy[10]. The improvement of glycemic control results mainly from a reduction in postprandial glycemic excursion which have been reported to be varied from 20-40 per cent[10,13,14,18]. Since acarbose selectively delays carbohydrate absorption, therefore, the amount of ingested carbohydrate might possibly be an important factor to determine its effects. Hara et al[15] reported that the percentage of carbohydrate amount in all calories sources was an important factor for the expression of acarbose effects. In cases where the percentage of carbohydrate was low even when total calories were kept constant, blood glucose control was not shown to be improved by acarbose. Acarbose improved blood glucose control only when the percentage of carbohydrate in an ingested meal was high.

As in other studies, FPG of our NIDDM patients was slightly decreased after treatment with acarbose. This is not surprising considering the mechanism of action of acarbose[6]. The unchange of fasting and postprandial C-peptide levels in the acarbose group compared with the placebo agrees with others and confirms its non-insulin secreting effect. Since hyperglycemia can aggravate insulin resistance,[20] the lowering effect of acarbose on FPG levels might be explained by the improvement in insulin sensitivity due to the reduction in postprandial hyperglycemia. Our study also agrees with other studies that acarbose had little or no effect on serum cholesterol levels[7-14]. The effect of acarbose on serum triglyceride was conflicting. Some studies did not demonstrate the significant degree of reduction in triglyceride levels whereas some studies did. Those latter studies usually had high baseline levels of serum triglyceride. The mechanism of acarbose in lowering serum triglyceride levels is probably *via* the reduction in triglyceride production from carbohydrate[21]. Given the normal baseline levels of serum triglyceride in the majority of our patients, the unchange in serum triglyceride after acarbose treatment is not unexpected.

Almost 50 per cent of our patients treated with acarbose developed gastrointestinal adverse effects. This did not differ from other studies in which flatulence or abdominal discomfort was found to be the most common adverse effect occurring in over half of the patients[7,9-13,19]. However, these gastrointestinal adverse effects were often mild and tolerable in the majority of patients. These adverse effects resulted from the accumulation of gas which is produced from the decomposition of incompletely digested carbohydrate content by bowel flora. The other adverse effects of acarbose are rare. It does not aggravate hypoglycemia unless it is combined with insulin or sulfonylurea[13]. Only one of our patients developed hypoglycemia while taking acarbose and glibenclamide. FPG at baseline before starting treatment of this patient was < 100 mg/dl. It is important to recognise that hypoglycemia in patients who are taking acarbose must be corrected with oral glucose only. Starch and sucrose are not recommended since acarbose can inhibit their

breakdown to glucose resulting in delay in glucose absorption. Body weight of our acarbose-treated NIDDM patients also did not change which is consistent with several studies(7-12,19,21).

In conclusion, we have demonstrated that acarbose, in combination with sulfonylurea with or without metformin, can improve glycemic control particularly postprandial hyperglycemia in fairly, well controlled NIDDM patients with mild and acceptable adverse effects.

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ผลการรักษาเบาหวานชนิดไม่พึ่งอินสุลินด้วยยาอะคาร์โบส: การศึกษาแบบ double-blind, crossover, placebo-controlled

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คณะผู้วิจัยได้ทำการศึกษาถึงประสิทธิภาพของยาอะคาร์โบสในการรักษาผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลินที่มีการควบคุมเบาหวานดีพอสมควร ผู้ป่วยจำนวน 15 รายที่รับประทานยาครบตลอดการศึกษา มีค่าเฉลี่ย±ความคลาดเคลื่อนมาตรฐานของอายุและระยะเวลาที่เป็นเบาหวาน 57.5±2.6 และ 7.5±1.5 ปี ตามลำดับ การศึกษานี้เป็นการศึกษาแบบ double-blind crossover placebo-controlled ประกอบด้วยระยะเวลาในการรับประทานยาอะคาร์โบสและยาหลอกอย่างละ 12 สัปดาห์ โดยมีระยะเวลาที่ไม่ได้รับประทานยาคั่นกลาง 8 สัปดาห์ ภายหลังการรักษาด้วยยาอะคาร์โบส ระดับกลูโคสในเลือดหลังอาหารที่ 1 และ 2 ชั่วโมง ลดลงจาก 251.7±10.7 และ 205.3±9.1 มก./ดล. เป็น 197.4±7.0 (p=0.001) และ 181.5±8.5 มก./ดล. (p=0.03) ตามลำดับ ระดับกลูโคสในเลือดก่อนอาหารลดลงเล็กน้อยแต่ไม่มีนัยสำคัญทางสถิติจาก 150.8±7.3 เป็น 140.8±6.1 มก./ดล. (p=0.07) ผลโดยรวมพบว่าการควบคุมเบาหวานดีขึ้นโดยดูจากระดับ HbA1c ลดลงจาก 7.7±0.4 เป็น 7.0±0.2% (p=0.05) ยาอะคาร์โบสไม่มีผลต่อระดับ serum C-peptide ทั้งก่อนและหลังอาหารและระดับไขมันในเลือด ประมาณครึ่งหนึ่งของผู้ป่วยที่ได้รับยาอะคาร์โบส จะมีอาการแน่นท้องไม่รุนแรงและทนได้ โดยสรุปยาอะคาร์โบสเมื่อให้ร่วมกับยารับประทานลดระดับน้ำตาลในเลือดกลุ่มอื่น สามารถทำให้การควบคุมเบาหวานในผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลินที่มีการควบคุมเบาหวานดีพอสมควรดีขึ้นโดยมีผลข้างเคียงที่ไม่รุนแรงและทนได้

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