ORIGINAL ARTICLE

Effects of Acarbose in Metabolic Control of Patients with Type 1 Diabetes Mellitus

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Acarbose is a reversible inhibitor of the intestinal alpha-glucosidases, the oral administration of which delays absorption of carbohydrates. The aim of this study was to investigate the effect of administration of acarbose on parameters of glycaemic control, lipid parameters and tolerability in ambulant type 1 diabetic subjects.

Materials and Methods: Entry criteria included being: diabetic, age below 30 years and a history of at least one episode of diabetic ketoacidosis insufficiently controlled with diet and insulin. The data of 17 patients (6 men and 11 women, mean age 17.2±3.5 (range 14–26) years, median duration of diabetes 8 (range 1–20) years were valid for statistical analysis.

Results: During the run-in period HbA1c levels tended to decrease from 9.5±1.1 to 9±1.7%. After 12 weeks of acarbose treatment, the mean level had decreased further to 7.6±1.6% (P: 0.002). After discontionuing acarbose, HbA1c levels increased to a mean level of 8.8±0.9%. A significant reduction in Fasting Plasma Glucose (FPG) (from 195±62 to 139±73 mg/dL, P<0.01) and 2 hour post prandial glucose (2 hppG) was observed with acarbose (from 231±82 to 159±72 mg/dL, P<0.001). Reduction in total cholesterol (from 159±36 to 146±26 mg/dL, p: 0.09) and triglycerides (from100±22 to 81±23 mg/dL, p: 0.02) was detected after treatment with acarbose. No significant changes were observed in HDL cholesterol. The most frequent reported adverse events were flatulence (7 subjects) and mild abdominal pain (2 subjects).

Conclusion: We conclude that acarbose up to 3×100 mg/day can be a valuable adjunct to insulin in improving metabolic control in persons with type 1 diabetes

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Key Words: Type 1 diabetes; Glycemic control; Acarbose; Alpha glucosidase inhibitors

Received: 31.9.2007 **Accepted**: 27.2.2008

Introduction

The ultimate aim of the treatment of patients with diabetes mellitus is to attain near-normoglycaemia with the purpose of preventing long term complications.[1] The landmark clinical trial in type 1 diabetes is the Diabetes Control and Complications Trial (DCCT), which showed that there is no threshold below which a reduction in glycemia would not provide further benefit against diabetes-related microvascular complications. This study in particular provides the rationale for attempting to achieve as near normoglycemia as possible. Appropriate insulin therapy is central to the management of all individuals with type 1 diabetes mellitus. Unstable blood glucose levels, especially in the post absorptive phase, as seen in many subjects with type 1 diabetes mellitus can be prevented by adequate timing of the insulin injection before the meals, the use of insulin analogues

with a fast absorption rate and/or delaying nutrient absorption. The latter can be achieved by enriching food with naturally occurring dietary fiber[2] or by changing the composition of meals to contain a higher amount of slowly absorbed carbohydrates,[3] dietary manipulations which are quite impractical both from the point of food choice and palatability. Another possibility of decreasing postprandial hyperglycaemia is to delay carbohydrate digestion by competitive inhibition of the α-glucosidase enzymes in the ciliated border of the small intestine. Several compounds with such an action have been developed, one of which is acarbose (Glucobay®), a pseudo-tetrasaccharide, which is not absorbed in the small intestine. Acarbose, a reversible inhibitor of the intestinal alpha-glucosidases, the oral delays or diminishes the postprandial increase of glucose. Usage of this compound has been documented in the treatment of persons with type 2 diabetes.[4] Only a limited number of investigations has been performed in type 1 diabetic subjects.[5-11] Sufficient data about other metabolic effects of alpha glucosidase inhibitors such as lipid profile or weigh changes can not be found in previous studies.

The aim of this study was to investigate the effect of administration of acarbose on parameters of glycaemic control, lipid profile, body weight and tolerability in ambulant type 1 diabetic subjects insufficiently controlled with diet and insulin.

Materials and Methods

Subjects: Subjects eligible for participation were patients with a history of diabetes of at least 1 year, diagnosed as type 1 with an episode of diabetic ketoacidosis and age of onset <30 years. Patients with a BMI ≤ 35 kg/m^2, a HbA1c level of more than 7.5%, using at least two injections of insulin were enrolled. Exctuded were those patients with impaired liver or kidney function, gastrointestinal motility disorders or malabsorption, pregnancy or use of drugs affecting carbohydrate metabolism. All patients were enrolled serially from a diabetes clinic in Vali-e- asr general hospital in Zanjan, a city about 300 km, west of Tehran. All participants had uncontrolled diabetes for the past year, in spite of education on diet and physical activity and regulation of their insulin dosage.

Approval from the ethics committee of Zanjan University of Medical Sciences was obtained. All participants were informed about the goals of the study and all gove informed consent.

Protocol: This was an uncontrolled follow-up study, i.e. a study to monitor the natural course of type 1 diabetic persons in an outpatient setting under standard acarbose treatment with HbA1c as primary outcome parameter.

The study started with a run-in period (12 weeks) of intensive education for diet and exercise without any changes in insulin dosage, followed by an acarbose treatment period of 12 weeks. Acarbose was started at a dose of 50 mg tid for 2 weeks, followed by 100 mg tid for 10 weeks. This period was followed by a run-out period of 12 weeks, in which the same amounts of placebo tablets were taken as during the latter phase of the active drug period. Tablets were taken with first morsel of breakfast, lunch and evening meals. Patients were instructed to maintain their dietary habits consisting of three main meals and, if desired, three snacks. The composition of the diet remained unchanged throughout the entire study period. Patients were instructed to ingest glucose when hypoglycaemic. All patients were on conventional methods of insulin therapy with twice daily injections of NPH and regular insulin. No change in insulin dosage was considered along the study period. Only in the case of recurrent hypoglycemia the was dosage reduced by 10 to 20 %.

Blood glucose profiles (FPG and 2 hppG) were measured every 12 weeks with an extra measurement taken 6 weeks after acarbose adminstration. HbA1c was to be measured during the out-patient clinic visits, scheduled every 12 weeks. Lipid parameters (total

cholesterol, HDL-cholesterol, triglycerides) were measured at the start of the study and at the start and end of the acarbose treatment period.

Measurements: Weight was measured by a physician using a balanced-beam scale with light clothing during the clinical examination, and height was measured using the clinic stadiometer.

Laboratory measurements were done at the laboratory of Zanjan University of medical sciences, Vali-e-asr Hospital. Plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method with a sensitivity of 5 mg/dL and intra –assay coefficients of variation (CV) of 1.7% in lower limit and 1.4 % in the upper limit concentrations. Inter-assay CV for the assay was 1.1% in the lower limit and 0.6% in the upper limit concentrations. Serum cholesterol and triglycerides of all the participants were measured with colorimetric method with a sensitivity of 5 mg/dL. Intra-and inter-assay CV for the assay were 1.6% & 1.1% in lower limit and 0.6% & 0.9% for upper limit concentrations respectively. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. HbA1c (normal value: 4.8–6.2%) was measured by Ion exchange chromatography with DS5 the same centre.

Statistical analysis: HbA1c was evaluated as the primary outcome measurement. Fasting plasma glucose and 2hpp glucose and lipid profile changes were secondary outcome measurements. The results were analyzed by SPSS version 11.5 software. Data are expressed as the means±SD. Paired t test was used to compare quantitative variables such as FPG, TG, cholesterol, HDL and body weight before and after acarbose administration in the subjects. Pearson correlation coefficient was used to determine the correlation between the parameters such as HbA1c before and after the intervention. Significance was considered at a level of 0.05.

Results

Overall, 17 patients (6 men, 11 women) with a mean age of 17.2±3.5 (range 14–26) years and a median duration of diabetes of 8 (range 1–20) years were enrolled in this study; mean body weight of the participants was 58.8±12 kg .

Primary outcome parameter: At the start of the run-in period, HbA1c levels varied between 7.6 and 12.3% with a mean of 9.5%. During the run-in period HbA1c levels tended to have a non significant decrease; at the end of this period they varied between 6.9 and 12% with a mean of 9%. After 12 weeks of acarbose treatment, the mean level had decreased further to 7.6% (range: 5.5–10.5) (Fig. 1).

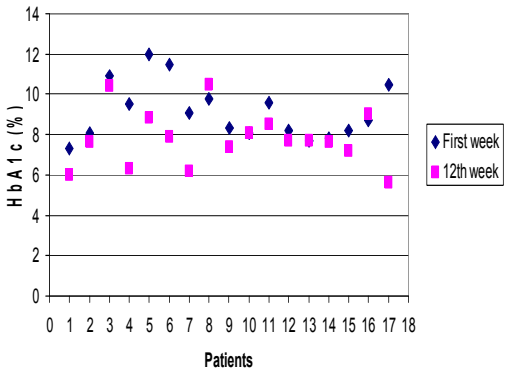

Fig. 1. HbA1c before and after treatment with acarbose in 17 patients with type 1 diabetes mellitus

The change in mean HbA1c levels during acarbose treatment was statistically significant (p: 0.002). There was a significant negative correlation between the HbA1c concentration before and the percent of reduction in HbA1c after treatment with acarbose (r:-0.52, p:0.03). We found more response to acarbose in patients with higher HbA1c at the beginning of the treatment. After stopping acarbose, HbA1c levels increased again to a mean level of 8.8 (range: 5.7–11.5)%. Differences between female and male participants in the primary outcome parameter have been shown

in Table 1. Although a significant reduction in 2 hpp Glucose was observed in both genders, FPG and cholesterol concentrations decreased significantly only in females.

Other results: After treatment with acarbose, fasting plasma glucose and 2hpp glucose levels decreased by about 28.8% (p:0.012) and 31% (p<0.001) respectively; following cessation of acarbose treatment values returned to pre-study levels. Total cholesterol, HDL-cholesterol and triglycerides changes are shown in Table 2. Daily insulin dose reduced about 15% in three patients during treatment with acarbose.

Table 1: Comparison between two sexes for the changes in parameters of metabolic control after treatment with acarbose in patients with type 1 diabetes mellitus (n. 17)

SEX	Parameter	Mean±SD		Mean difference	P value
		Pre acarbose	Post acarbose		
Male	FPG(mg/dL)	186±69	115±53	-70.8	0.1
(n:6)	2hpp G (mg/dL)	212±72	149±47	-63	0.007
	HbA1c (%)	9.3±1.6	7.3±1.6	-2	0.014
	Chol(mg/dL)	154±28	142±24	-12	0.1
	HDL(mg/dL)	43.7±3.9	43.3±5	-0.4	0.8
	TG(mg/d/L)	103±27	72±20	-31	0.048
Female	FPG(mg/dL)	200±61	152±82	-48	0.038
(n:11)	2hppG (mg/dL)	243±97	165±87	-78	0.008
	HbA1c (%)	9±1.3	8±1.2	-1	0.07
	Chol(mg/dL)	161±42	147±32	-14	0.09
	HDL(mg/dL)	39.6±2.1	39.5±4.2	-0.1	0.9
	TG(mg/dL)	98.6±21	89±24	-9.6	0.2

FPG: Fasting plasma glucose, 2hppG: 2 –Hour post prandial glucose; TG: triglyceride, Chol: Cholesterol.

Table 2. Changes in different parameters of metabolic control in type 1 diabetic patients at the end of run-in period and acarbose administration (n: 17)

Parameter	Treatment Phase			P* value
	(1)End of the first period	(2)End of Acarbose	(3)End of the third period (Placebo)	
Weight (Kg)	58.8±12	59.5±12.2	59.1±12.3	0.1
HbA1c (%)	8.98±1.7	7.6±1.6	8.8±0.9	0.002
FPG (mg/dL)	195±62	139±73	180±60	0.012
2hpp G (mg/dL)	231±82	159±72	206±69	0.001
Cholesterol (mg/dL)	159±36	146±26	152±26	0.09
TG (mg/dL)	100±22	81±23	95±20	0.02
HDL cholesterol (mg/dL)	40±3	41.2±5	41±4	0.1

For continues variables data shown are mean± SD; FPG: Fasting plasma glucose, 2hppG: 2 –hour post prandial glucose; TG: triglycerides; *Comparison between phase 1 and 2.

Adverse events: Adverse events were reported for 8 (47%) patients, of which 3 (17.6%) occurred during the placebo run-out phase and 5 (29.4%) during the acarbose phase. The most frequent reported adverse events were flatulence (7 subjects), abdominal pain (2 subjects) and mild diarrhea (1 subject); adverse events were mild and temporary. All

the patients continued their treatment period. Severe hypoglycemic events needing assistance of other persons or admission to hospital were considered as very severe events that were not noted during the study.

Discussion

In this study, a significant decrease of about 1.4% mean HbA1c level was observed after 12 weeks of active treatment with acarbose in patients with uncontrolled type 1 diabetes mellitus. We found more response rate in patients with higher HbA1c levels at the initiation of the active treatment phase. Although we did not have a control group in this study, but consideration of run-in and run-out period in the study design validate the study findings regarding the effect of acarbose in metabolic control of the patients.

The landmark clinical trial in type 1 diabetes is the Diabetes Control and Complications Trial (DCCT), a study which, in particular, provides the rationale for attempting to achieve as near normoglycemia as possible. However, near-normal blood glucose and HbA1c values are difficult to achieve in most subjects, especially in the postprandial phase. Additional treatment with inhibitors of intestinal glucosidases is a possibility to limit the postprandial blood glucose rise.

The decrease in HbA1c detected in our study is comparable with results reported by Hollander et al[12] and Spengler.[13] Since in the DCCT a 35% decrease of the incidence of new or of worsening retinopathy was reported with each percent drop of HbA1c, this would imply that the improvement with acarbose, although modest, would be meaningful to achieve. Jefferies et al[14] reviewed the use of recognized pharmacologic agents as potential insulin adjunctives in children and adolescents with type 1 diabetes. Many of these agents have been found to be effective in short-term studies with decreases in glycosylated hemoglobin of 0.5-1.0%, lowered postprandial blood glucose levels, and decreased daily insulin doses.

For FPG and blood glucose levels, measured 120 min after breakfast, a statistically significant decrease was observed during acarbose treatment in our study. Although the FPG finding may seem somewhat surprising, a decrease in HbA1c can only be explained by a real decrease in blood glucose levels. In agreement with our results, Escobar-Jiménez et al. in a multicenter study[15] found significant statistical differences in HbA1c ($p=0.0005$) and in postprandial glycemia ($p=0.007$) with acarbose in patients with type 1 diabetes; there were differences, though not statistically significant, in the amounts of fasting glycemia between placebo and acarbose in this study. The lack of any significant reduction in FPG of males in our study can be due to the small sample size.

It has optimistically been perceived that acarbose has an insulin-sparing effect in subjects with type 1 diabetes.[16] Indeed, in 1981, Gérard and colleagues reported, in a group of 28 type 1 diabetics, that mean daily insulin dose was 46 U while on acarbose and 48 U on placebo;[7] Therefore, we have systematically recorded possible changes of insulin requirements by interviewing the patients during their clinic visits, but did not find any significant change in daily insulin dose during the acarbose treatment period in most of the patients. This finding may also be in slight contrast with the report of Marena et al;[17] in a 6-week placebo-controlled cross-over study comprising 14 subjects with type 1 diabetes on a multiple injection regimen, they found that acarbose treatment resulted in a 35% decrease of insulin requirement assessed over a 14 hour period by means of an artificial β-cell. However, these authors report no change of insulin dose, which amounted to 47±13 (range 20–78) U/day, during everyday life. This is identical to the results of Hollander et al,[12] who also reported no change of mean insulin dose during placebo and a small drop of insulin dose from 46 to 43 U in 114 subjects during acarbose

use; there was no significant difference between the two treatment groups.

An interesting finding of our study is the mild reduction of the mean HbA1c level, as observed during the first 12 weeks of the study. During this period, patients were under increased supervision of their physician; The insignificant decrease thus suggests a positive effect of increased supervision of patients. Hollander et al.[12] did not find this in their study.

During this study a significant reduction in triglycerides as observed, results perhaps comparable with the findings of Marena et al.[17] who reported lower plasma triglycerides after acarbose compared with placebo (1.2±0.2 vs. 1.4±0.2 mmol/L). In our patients we also found no changes in total cholesterol levels, which may indicate the different mechanism of action of acarbose in comparison to dietary fiber, which reduces serum cholesterol levels.[18] Again, the absence of effects of acarbose on cholesterol in comparison with placebo as reported by Hollander et al[12] is in complete agreement with our findings.

The results of Sels et al[19] who reported no changes in lipid profile in type 1 diabetic patients with acarbose is in contrast to our data. It may be possible that beneficial effects on serum lipids, especially triglycerides, be found only in subjects who exhibit poorer metabolic control.

We found that patients with higher HbA1c may benefit more from treatment with acarbose. In agreement with this result Spengler and Catagay in a large postmarketing surveillance[20] noted that the improvement of metabolic control due to acarbose treatment was greater when previous metabolic control was poorer, as assessed by HbA1c measurement.

In our patients, adverse events were mainly of gastrointestinal origin but do not cause premature termination of the study. In the Sels et al study[19] although about 20% of subjects prematurely withdrew from the study due to adverse events considered to be related to acarbose treatment, on an average, the side effects were of mild nature. Spengler reported 13.7% flatulence, 2.2% diarrhea and hypoglycaemia in 0.07% of patients.[13] Neuser et al.[21] also concluded that acarbose is safe for treatment of type 1 diabetes mellitus.

In conclusion, acarbose titrated up to a maximum dose of 3×100 mg/day can be a valuable adjunct to insulin in improving metabolic control in persons with type 1 diabetes.

Acknowledgment

This study was supported by Zanjan University of Medical Sciences. We thank Dr. Kalantari, Head of Boali laboratory centre, and Ms. Bolaneghbal, nurse of the diabetes clinic in Vali-e- asr hospital for their indispensable help.

References

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-86.
2. Jenkins DJ, Leeds AR, Gassull MA, Cochet B, Alberti GM. Decrease in postprandial insulin and glucose concentrations by guar and pectin. Ann Intern Med 1977; 86: 20-3.
3. Jenkins DJ. Lente carbohydrate: a newer approach to the dietary management of diabetes. Diabetes Care 1982; 5: 634-41.
4. van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005; 28: 154-63.
5. Dimitriadis G, Karaiskos C, Raptis S. Effects of prolonged (6 months) alpha-glucosidase inhibition on blood glucose control and insulin requirements in patients with insulin-

dependent diabetes mellitus. Horm Metab Res 1986; 18: 253-5.
6. Schumann F, Janssen K, Aubell R, Christi H L. Acarbose in diabetic outpatient treatment: results of a 3 months study. In: Creutzfeldt W, editor. Acarbose: Effects on Carbohydrate and Fat Metabolism, Exerpta Medica, Amsterdam 1982. p. 367-72.
7. Gérard J, Luyckx AS, Lefebvre PJ. Improvement of metabolic control in insulin dependent diabetics treated with the alpha-glucosidase inhibitor acarbose for two months. Diabetologia 1981; 21: 446-51.
8. Riccardi G, Giacco R, Parillo M, Turco S, Rivellese AA, Ventura MR, et al. Efficacy and safety of acarbose in the treatment of Type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study. Diabet Med 1999; 16: 228-32.
9. Riccardi G, Giacco R, Parillo M, Turco S, Rivellese AA, Ventura MR, et al. Efficacy and safety of acarbose in the treatment of Type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study. Diabet Med 1999; 16: 228-32.
10. Koch HH, Wudy A, Eberlein G, Quast C. Use of acarbose for eliminating the interval between meal consumption and insulin injection in patients with Type 1 diabetes. Diabetes Nutr Metab 1999; 12: 195-201.
11. Dimitriadis GD, Tessari P, Go VL, Gerich JE. alpha-Glucosidase inhibition improves postprandial hyperglycemia and decreases insulin requirements in insulin-dependent diabetes mellitus. Metabolism 1985; 34: 261-5.
12. Hollander P, Pi-Sunyer X, Coniff RF. Acarbose in the treatment of type I diabetes. Diabetes Care 1997; 20: 248-53.
13. Spengler M, Schmitz H, Landen H. Evaluation of the efficacy and tolerability of acarbose in patients with diabetes mellitus : a postmarketing surveillance study. Clin Drug Investig 2005; 25: 651-9.
14. Jefferies CA, Hamilton J, Daneman D. Potential adjunctive therapies in adolescents with type 1 diabetes mellitus. Treat Endocrinol 2004; 3: 337-43.
15. Escobar-Jiménez F, de Leiva A, Piñón F, Soler J, Tebar J, Sancho MA, et al. Clinical effectiveness and tolerance of acarbose in the treatment of insulin-dependent diabetic patients (type I). Med Clin (Barc) 1993; 100: 488-91.
16. Balfour JA, McTavish D. Acarbose: An update of its pharmacology and therapeutic use in diabetes mellitus. Drugs 1993; 46: 1025-54.
17. Marena S, Tagliaferro V, Cavallero G, Pagani A, Montegrosso G, Bianchi W, et al. Double-blind crossover study of acarbose in type 1 diabetic patients. Diabet Med 1991; 8: 674-8.
18. Sels JPJE, Postmes TJL , Niemann F, Ebert R, Wolffenbuttel BHR. and Nieuwenhuijzen Kruseman AC. Effects of guar bread on type 1 and type 2 diabetes mellitus. Eur J Int Med 1993; 4: 193-200.
19. Sels JP, Verdonk HE, Wolffenbuttel BH. Effects of acarbose (Glucobay) in persons with type 1 diabetes: a multicentre study. Diabetes Res Clin Pract 1998; 41: 139-45.
20. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by post-marketing surveillance study. Clin Invest Med 1995; 18: 325-31.
21. Neuser D, Benson A, Brückner A, Goldberg RB, Hoogwerf BJ, Petzinna D. Safety and tolerability of acarbose in the treatment of type 1 and type 2 diabetes mellitus. Clin Drug Investig 2005; 25: 579-87.