

EFFECTS OF ACARBOSE, AN α -GLUCOSIDASE INHIBITOR (BAY G 5421), ON ORALLY LOADED GLUCOSE, MALTOSE AND SUCROSE AND ON BLOOD GLUCOSE CONTROL IN NON-INSULIN-DEPENDENT DIABETICS

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ABSTRACT

Fifty g glucose, 50g maltose and 50g sucrose were loaded to 12 nonobese healthy male volunteers with and without 100 or 300 mg α -glucosidase inhibitor, acarbose, and the inhibitory effect on digestion and absorption of these saccharides was studied. In another series of investigations, acarbose 100 mg a day were orally administered to 12 non-insulin-dependent diabetics for 3 months together with meals. Blood glucose was determined to investigate the effect of acarbose on blood glucose control in non-insulin-dependent diabetics. In the saccharide loading tests, orally administered 300 mg acarbose did not practically inhibit absorption of 50g glucose or 50g maltose. When 50g sucrose was loaded, however, 100 or 300 mg acarbose markedly decreased absorption of this disaccharide, resulting in inhibition of increases in blood glucose and insulin. Non-insulin-dependent diabetics had significantly lower fasting blood glucose and HbA_{1c} in 3 months of acarbose ingestion as compared with the corresponding levels in the preceding 3 months. Meteorism, increased flatulence and loose stools were complained of as adverse effects of acarbose, but they were not so serious as to require the discontinuation of medication. Acarbose might afford a safe and effective supplementary means for controlling blood glucose in diabetics.

Keywords: α -glucosidase inhibitor, diabetes, saccharides tolerance test, insulin, glucose

INTRODUCTION

Carbohydrates must be digested into monosaccharides before they are absorbed from the intestinal tract. Starch is obviously such a case. Even disaccharides such as sucrose, maltose and lactose are not absorbed until they are degraded by disaccharidase into monosaccharides such as glucose and fructose. Acarbose, an oligosaccharide with a molecular weight of 645, has been reported to inhibit α -glucosidase including α -amylase, sucrase and maltase.¹⁾ Since dietary carbohydrates consist of starch (60%), sucrose (20–30%) and maltose (ca. 10%), not only starch but also sucrose and maltose should concurrently be protected from digestion, if satisfactory inhibition of digestion and absorption of dietary carbohydrates is intended. In patients with diabetes, obesity or hyperlipemia, acarbose, which potently inhibits amylase and sucrase,^{1,2)} is expected to show a beneficial effect on their pathological conditions by inhibiting digestion and absorption of carbohydrates when ingested with meals.²⁾

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In the present study, acarbose was investigated as to the aspects of its inhibitory effect on digestion and absorption of glucose, maltose and sucrose as well as to its effect on blood glucose control in non-insulin-dependent diabetics.

SUBJECTS AND METHODS

1. *Effects of acarbose on orally loaded glucose, maltose and sucrose in healthy volunteers*

Twelve nonobese healthy male volunteers (20- to 25-year-old students) without family history of diabetes were divided into two groups, each consisting of 6 subjects. The first group was subjected to two series of saccharide loading tests with a 10-day interval in between: first, an oral loading of 50g glucose (glucose tolerance test: GTT) and second, of 50g maltose (maltose tolerance test: MTT). Subjects in the second group were orally loaded with 50g sucrose (sucrose tolerance test: STT). Together with each saccharide, 0, 100 or 300 mg acarbose was also administered in a double blind manner by appropriately combining 100 mg acarbose tablets and placebo tablets. The order of administration of these three dose levels was randomized within each saccharide loading series, and one dose was followed by a different dose after a 3-day interval.

Blood samples were collected from cubital veins before and 30, 60, 90 and 120 minutes after the saccharide loadings. Blood glucose was determined according to the glucose oxidase method and plasma immunoreactive insulin (IRI) was assayed by using an insulin RIA kit (Dinabot).³⁾

Informed consent was obtained from all volunteers. Urinalysis, complete blood count and blood biochemical tests were conducted before and after the trial. Data were presented as means \pm a standard error (SE), and differences between two mean values were statistically analyzed by ordinary t-test for equal variance and Cochran-Cox test for unequal variance. Probabilities less than 5% were considered statistically significant.

2. *Effects of acarbose on blood glucose control in diabetic patients*

In 12 patients with non-insulin-dependent diabetes, 100 mg acarbose was orally administered three times a day together with meals for 3 months. Fasting blood glucose levels determined weekly were separately averaged for 3 months before and during the acarbose trial. HbA_{1c} was estimated before and at the end of the acarbose trial.⁴⁾ The meals and drugs were not changed before and during the trial.

The patients were informed about the present study and only those who gave their consent were comprised in the trial. Urinalysis, complete blood count and blood biochemical tests were also conducted before and after the initiation of the trial.

RESULTS

1. *Effects of acarbose on digestion and absorption of glucose, maltose and sucrose in healthy volunteers*

There was no difference among the 0 mg, 100 mg and 300 mg acarbose doses in their effects on the time course of blood glucose or plasma IRI in 50 g GTT (Fig. 1).

In 50 g MTT, the three dose levels of acarbose did not differ from one another in their effects on blood glucose. Plasma IRI, however, was significantly decreased from its control level (0 mg acarbose) at 60 minutes after 100 mg acarbose, and at 60 and 90 minutes after 300 mg acarbose (Fig. 2).

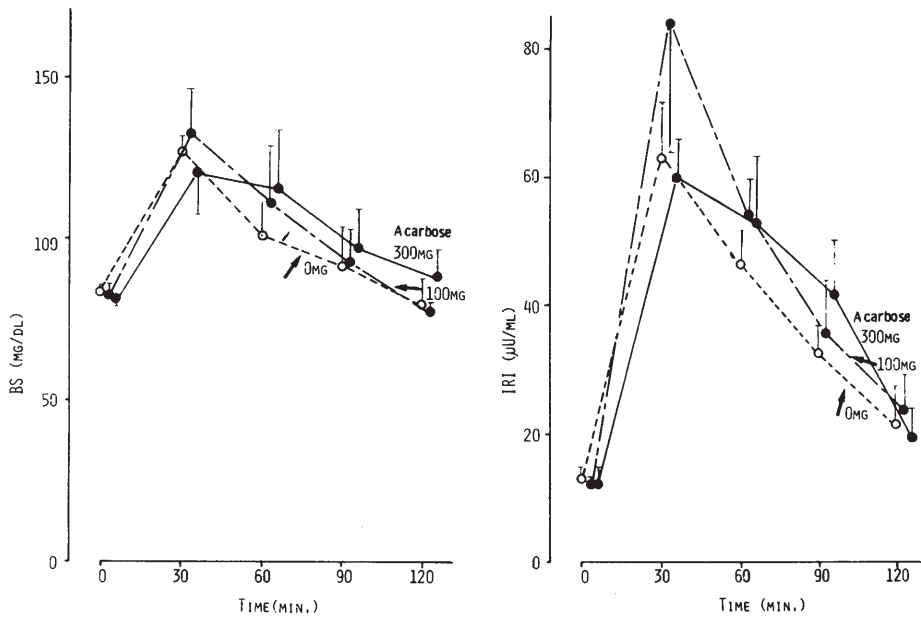


Fig. 1 Effects of acarbose on blood sugar and IRI in oral load of 50g glucose. (n = 6 healthy volunteers; points and bars represent mean and standard error, respectively.)

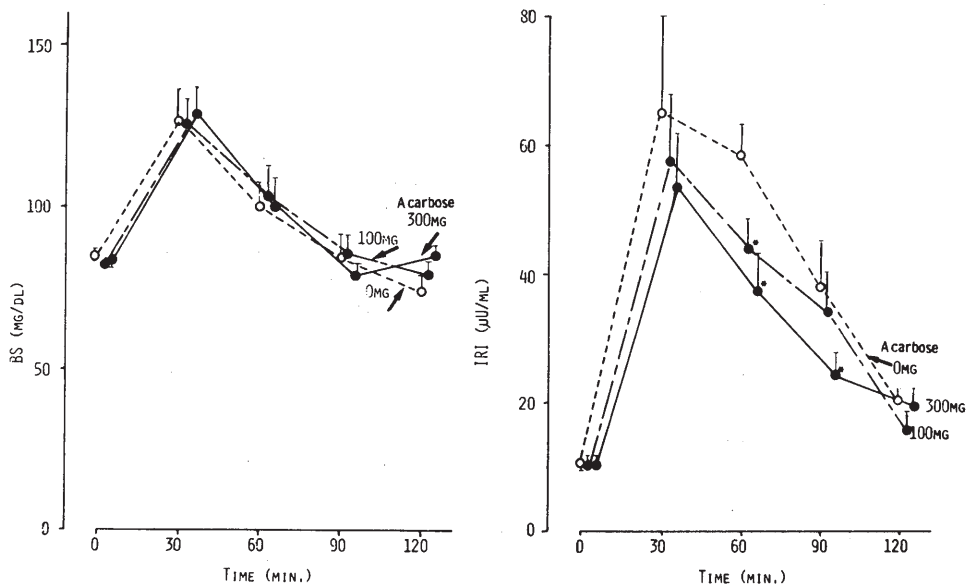


Fig. 2 Effects of acarbose on blood sugar and IRI in oral load of 50g maltose. (n = 6 healthy volunteers; points and bars represent mean and standard error, respectively.) Asterisks indicate statistical difference against control (0 mg).

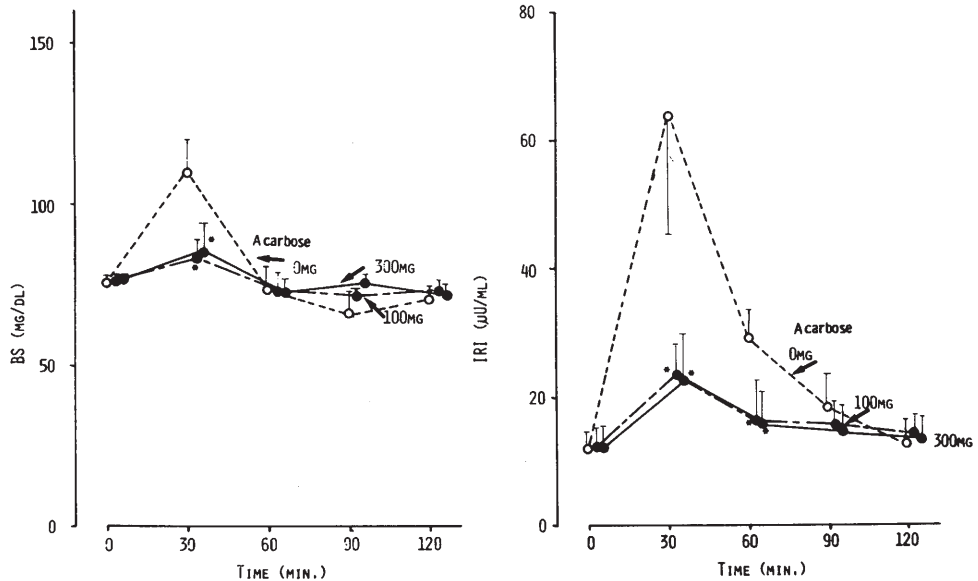


Fig. 3 Effects of acarbose on blood sugar and IRI in oral load of 50g sucrose. (n = 6 healthy volunteers; points and bars represent mean and standard error, respectively.) Asterisks indicate statistical difference against control (0 mg).

Fifty g sucrose loading did not increase blood glucose as greatly as that seen in GTT or MTT. There was a significant increase in blood glucose 30 minutes after administration of a placebo (control), while increase in blood glucose was insignificant in the subjects ingesting 100 or 300 mg of acarbose. Elevation of plasma IRI following sucrose loading was also significantly inhibited by acarbose; compared with the control, the inhibition was significant at 30 and 60 minutes after administration of 100 or 300 mg acarbose. (Fig. 3).

2. Effects of acarbose on blood glucose control in non-insulin-dependent diabetics

To 12 patients with non-insulin-dependent diabetes, 100 mg acarbose was orally administered three times a day, at the beginning of each meal, for 3 months. Table shows mean fasting blood glucose levels for 3 months before and during the trial as well as HbA_{1c} percentages before and at the end of the trial. Acarbose significantly decreased fasting blood glucose and HbA_{1c}.

3. Adverse effects of acarbose

Blood biochemical test, complete blood count and urinalysis conducted before and after the initiation of the trial revealed no abnormal reactions either in healthy volunteers or diabetics. During STT four of six healthy volunteers passed loose stool. Four out of the 12 diabetic patients complained of meteorism, increased flatus and loose stool during the trial. These symptoms were not so severe as to require discontinuation of the acarbose trial.

Table Effects of acarbose on blood glucose control in non-insulin-dependent diabetics

No.	Case	Age	Sex	Treatment	Fasting blood glucose (mg/dl)			Hemoglobin A _{1c} (%)		
					Before ^{##}	After ^{##}	Δ	Before	After	Δ
1	F	46	M	Diet	246	189	57	13.4	12.5	0.9
2	W	40	M	Diet	242	211	31	11.6	11.0	0.6
3	A	40	M	SU [#]	256	153	103	11.6	7.8	3.8
4	Y	64	M	Diet	235	164	71	12.0	9.2	2.8
5	H	66	M	Diet	130	140	-10	-	-	-
6	S	36	M	Diet	142	114	28	10.6	10.3	0.3
7	Tu	61	F	SU	188	219	-31	13.4	12.5	0.9
8	Ta	63	F	Diet	154	134	20	-	-	-
9	U	60	F	Diet	160	124	36	8.6	8.1	0.5
10	Hg	27	F	Diet	133	120	13	7.3	6.9	0.4
11	Ha	58	F	Diet	227	210	17	-	-	-
12	K	59	F	Diet	202	145	57	12.5	10.9	1.6
Mean±S.E.					192.9±13.8	160.3±10.9	32.7±10.4* (n=12)	11.22±0.69	9.91±0.68	1.31±0.41* (n=9)

SU[#]: Acetohexamide 750 mg,

##: Mean for 3 months before and during the trial

*: significantly different

DISCUSSION

Ingested carbohydrates are not absorbed from the intestinal tract until they are digested into monosaccharides. Acarbose decreases intestinal absorption of poly- and di-saccharides by inhibiting α -amylase and disaccharidase activity. Absorption of glucose, a mono-saccharide, proceeds independently of disaccharidase activity. However, Plus, W. *et al.*⁵⁾ reported that a large dose of acarbose inhibited intestinal absorption of glucose in rats. In the present human study absorption of glucose was not inhibited in GTT even when 300 mg acarbose was administered.

Increase in blood glucose or IRI was markedly inhibited by 100 mg acarbose in STT, while in MTT, even 300 mg of acarbose did not practically inhibit elevation of blood glucose. This suggests a difference in the inhibitory effect on sucrase and maltase. In MTT, acarbose did not effectively inhibit elevation of blood glucose but inhibited increase in IRI. This may be partly due to decreased release of GIP.^{6,7)}

Acarbose does not so potently decrease digestion and absorption of maltose as compared with its marked inhibitory effect on starch or sucrose degradation.^{1,2,8)} In spite of its low potency in inhibiting absorption of maltose, acarbose would still be useful as an inhibitor of carbohydrate absorption, because it sufficiently decreases absorption of starch and sucrose which bear the major portion of dietary carbohydrates.

Acarbose inhibited increase of blood glucose and IRI in STT of healthy volunteers. In insulin-dependent diabetics, however, only hyperglycemia may be inhibited because these patients have already lost their pancreatic β -cell function. Absorption of subcutaneously injected insulin proceeds slower than intestinal absorption of dietary carbohydrates. Slowdown of the postprandial hyperglycemic process, if possible, would offer an advantage to insulin-dependent diabetics. Inhibition or delay of intestinal nutrient absorption is now being considered, at least in part,

to be responsible for the hypoglycemic effect of biguanides.⁹⁾ When insulin or sulfonylureas are not satisfactorily effective as a single treatment, combined use of biguanides improves the therapeutic results.¹⁰⁾ A similar effect is expected for acarbose because it also inhibits postprandial hyperglycemia, although the mechanism is different from that of biguanides.¹¹⁻¹³⁾

The present study demonstrated that acarbose significantly lowered fasting blood glucose levels in non-insulin-dependent diabetics. The above proposed mode of action of acarbose explains the inhibition of postprandial hyperglycemia but cannot explain the decreased fasting level of blood glucose. Sachse *et al.*¹¹⁾ reported that acarbose significantly lowered daily maximal and mean levels of blood glucose and that fasting blood glucose levels were only insignificantly decreased. We observed a significant decrease in the fasting level of blood glucose after a 3-month administration of acarbose, while Sachse *et al.* administered it only for 1 week. Such short treatment might be a cause of the insignificant decrease in the fasting level. Vierhapper *et al.*¹³⁾ followed up the change in postprandial hyperglycemia in patients with non-insulin-dependent diabetes for 4 weeks of treatment with daily administration of 300 mg acarbose. This preparation significantly lowered blood glucose in the 1st, 2nd and 3rd weeks as compared with the placebo, but there was no significant difference in the 4th week. This attenuation of the effect did not appear in our present trial.

Since the levels of HbA₁ are in proportion to the average blood glucose levels determined in the preceding 1 to 2 months, they are considered to indicate a long-term control of the blood glucose.⁴⁾ Acarbose significantly decreased HbA₁ in the present study, suggesting that this compound is also beneficial for postprandial hyperglycemia.

No serious adverse effects were observed after administration of acarbose. No risk of lactic acidosis or other serious symptoms makes acarbose safer than biguanides. Unlike insulin and sulfonylureas, acarbose does not directly decrease glucose in the blood stream, but only inhibits intestinal absorption. Accordingly, the use of acarbose involves no risk of accidental hypoglycemia.

CONCLUSION

Acarbose of 100 or 300 mg markedly decreased digestion and absorption of sucrose by its inhibitory action on sucrase and subsequently reduced increases in blood glucose and insulin. Absorption of glucose and digestion of maltose were not influenced even with 300 mg acarbose. Ingestion of 100 mg acarbose together with meals three times a day for three months lowered fasting blood glucose and HbA₁ in non-insulin-dependent diabetics when compared with levels in the preceding periods, without serious adverse effects. Therefore, acarbose might afford a safe and effective supplementary means for controlling blood glucose in diabetics.

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