Scope and Specificity of Acarbose in Slowing Carbohydrate Absorption in Man

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SUMMARY

Fifty-gram carbohydrate tolerance tests were performed on healthy volunteers to test the activity and specificity of an α-glucoside hydrolase inhibitor, acarbose (BAY g 5421). Two hundred milligrams acarbose reduced the area under the blood glucose response curve by 89% ($P < 0.001$) after sucrose, by 80% ($P < 0.002$) after starch, by 19% (N.S.) after maltose, with no effect on glucose. Breath hydrogen measurements indicated an almost complete malabsorption of the sucrose. At 50 mg acarbose, some reduction in blood glucose and insulin response to sucrose was still seen, but no significant hydrogen production. It is suggested that at lower doses, acarbose may prolong the time course over which carbohydrate is absorbed as does dietary fiber; as with fiber, it may be a useful adjunct to diabetic therapy. DIABETES *30*:951–954, November 1981.

The possibility that various aspects of carbohydrate and lipid metabolism may be regulated by events taking place within the gastrointestinal tract has recently attracted much attention.[1]

Dietary fiber supplements have been shown to reduce urinary glucose loss[2] by slowing carbohydrate absorption[3], and to lower fasting serum cholesterol levels[4–7] in association with an increased bile acid output.[6,7] In addition to this physical approach, a chemical/enzymatic approach to these problems has also been developed involving the use of specific enzyme inhibitors of carbohydrate[8] and fat absorption.[9] Similar inhibitors are also found in unprocessed foods. The first inhibitor with a potential therapeutic use was an α-amylase inhibitor from wheat (BAY g 7791), which inhibited the rise in blood glucose in man, dogs, and rats after starch-loading tests.[8]

More recently, a bacterial α-glucoside hydrolase inhibitor has been used to reduce the rise in blood glucose in both normal[10] and diabetic subjects[11] after meals containing starch and sucrose. The present study was done to compare the effect of this inhibitor on the digestion and absorption of individual sugars and starch taken separately and to quantitate the carbohydrate malabsorption it may induce. Such knowledge is important for the clinical use of the drug.

SUBJECTS AND METHODS

From a pool of 13 healthy male volunteers (mean age 38 ± 3 yr, 114 ± 2% desirable weight), groups of 6–7 volunteers took paired tolerance tests, one with and the other without 200 mg acarbose, in random order in the morning after overnight fasts. The carbohydrates tested were 50 g of sucrose, maltose, lactose, glucose, or starch (as 62 g instant mashed potato, Winfield brand). In addition, four subjects took 50 g sucrose with both 200 mg and 50 mg acarbose to allow comparison of doses. Active or placebo tablets were chewed in the mouth 30 s before the start of the test. Sugars were taken in 400 ml water and drunk over 10 min. The instant mashed potato was mixed with 200 ml boiling water, served hot, and eaten over a 10-min period. Two hundred milliliters cold water was drunk with this.

Blood samples were obtained for glucose analysis (glucose-oxidase method, 23AM Glucose Analyzer, Yellow Springs Instruments, Ohio)[12] from an indwelling "butterfly" cannula kept patent with heparinized saline and positioned in a forearm vein. Samples were taken at 0, 15, 30, 45, 60, 90, and 120 min after the start of the meal.

In all the sucrose experiments, blood was also taken for insulin assay by a double antibody method.[13] In addition, in the dose-response studies, 5 ml of blood was collected into tubes containing heparinized trasylol, for analysis of gastric inhibitory peptide (GIP).[14]

Forced end-expiratory samples of alveolar air were obtained at 15-min intervals during the 2½-h test using a modi-

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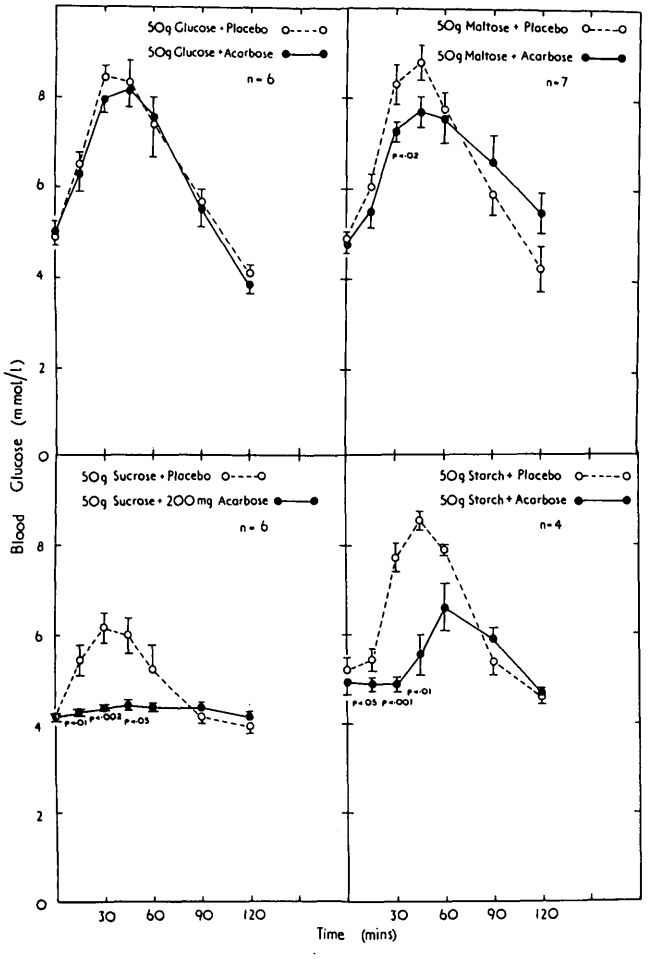

FIGURE 1. Blood glucose response to glucose, maltose, sucrose, and starch with acarbose 200 mg and placebo.

fied Haldane-Priestley tube, analyzed for hydrogen using a Gow-Mac gas chromatograph,[15] and expressed in parts per million (ppm). Hydrogen is produced in the body from bacterial fermentation of unabsorbed carbohydrate in the caecum, and thus can be used to give an index of the amount of carbohydrate that has not been absorbed in the small bowel.

The subjects who took sucrose underwent further tests with 30 or 50 g 50% (w/w) lactulose solution (25 g lactulose) to calibrate their hydrogen-producing capacity for malabsorbed carbohydrate. Lactulose is a nonabsorbable sugar and, depending on the individual, a set proportion is fermented to hydrogen by colonic bacteria. Approximately 18% of this is exhaled in the breath.[16] A figure can thus be obtained relating the hydrogen evolved over a given period of time with the amount of carbohydrate malabsorbed.

The results are expressed as means ± SEM, and the significances of the differences were calculated using Student's *t* test for paired and unpaired data.

RESULTS

The blood glucose response to glucose was unaffected by acarbose (Figure 1). However, with the other carbohydrates, acarbose reduced the blood glucose value significantly below the control on at least one occasion during the first hour of the test (Figure 1). The greatest decrease was with sucrose (−85 ± 2%; $P < 0.001$), and there were lesser changes with starch (−39 ± 15%) and maltose (−14 ± 9%). The percentage glucose areas over the first hour were significantly decreased after acarbose for both sucrose (−89 ± 2%; $P < 0.001$) and starch (−80 ± 7%; $P < 0.002$), but not significantly changed for maltose and glucose. After sucrose, acarbose almost abolished the rise in serum insulin (Table 1), the peak rise being reduced by 90 ± 2% ($P < 0.001$) and the area by 88 ± 3% ($P < 0.001$) of the control.

An increase in breath hydrogen concentration was seen only with sucrose over the 2½-h experimental period; all mean breath hydrogen results after acarbose were significantly above the control from 105 min onwards, the mean hydrogen area being 141 ± 49 ppm · h from 0 to 150 min.

Calibration of these individuals with 30 g lactulose solution (15 g lactulose) resulted in significant hydrogen production from 75 min onwards, the mean hydrogen area being 68 ± 17 ppm · h. Assuming a linear relationship, these results suggest that of approximately 30 g of the 50 g of sucrose ingested was malabsorbed in response to acarbose treatment.

In all subjects, after lactulose and after acarbose taken with sucrose, increased flatulence was experienced from the first hour onwards. In most instances after acarbose with sucrose the subjects passed a loose or watery motion on conclusion of the test.

In the four individuals in whom the dose response to acarbose was studied with 50 g sucrose, the 200-mg dose again produced an almost complete absence of blood glucose response (Figure 2). However, 50 mg acarbose still produced a response that was less than that seen when sucrose was taken alone.

Breath hydrogen results indicated that when 200 mg acarbose was taken with 50 g sucrose, almost all the sucrose was malabsorbed. However, when 50 mg acarbose was taken at most only 10 g sucrose would have been lost, with two

TABLE 1
Serum insulin levels in a group of six (series I) or four (series II) healthy volunteers who took 50 g sucrose with or without acarbose

	Serum insulin (mU/L)						
	0 min	15 min	30 min	45 min	60 min	90 min	120 min
Control I	7 ± 1	31 ± 10	44 ± 12	39 ± 4	31 ± 4	19 ± 6	14 ± 5
Acarbose I (200 mg)	8 ± 1	9 ± 1	11 ± 1†	12 ± 1§	12 ± 1‡	10 ± 1	9 ± 1
Control* II	8 ± 1	44 ± 17	63 ± 14	37 ± 7	25 ± 10	9 ± 2	7 ± 2
Acarbose II (50 mg)	6 ± 2	21 ± 10	38 ± 15†	30 ± 8	23 ± 4	12 ± 1	10 ± 1
Acarbose II (200 mg)	6 ± 2	9 ± 2	11 ± 2†	12 ± 3‡	11 ± 2	9 ± 2	8 ± 2

* Only 40 g sucrose taken. Significance from control † $P < 0.05$, ‡ $P < 0.02$, § $P < 0.01$.

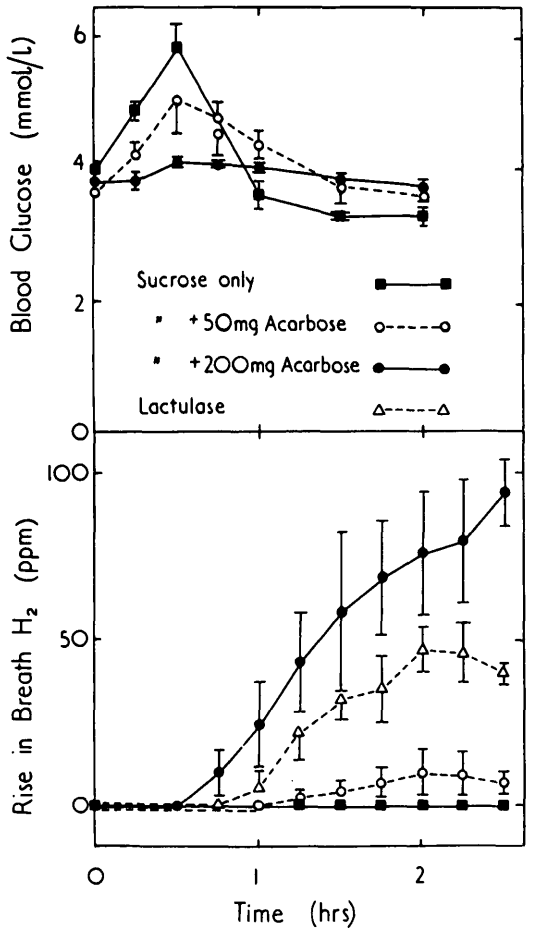

FIGURE 2. Blood glucose response to sucrose with acarbose 50 mg, acarbose 200 mg, and placebo. Breath hydrogen responses to sucrose and lactulose.

individuals producing no hydrogen at all (Figure 2). The areas under the hydrogen response curves were 50 g sucrose 200 mg acarbose, 101 ± 28 ppm · h; 50 g sucrose 50 mg acarbose, 9 ± 5 ppm · h; 40 g sucrose (see below), 0 ppm · h; 50 g lactulose solution (25 g lactulose), 52 ± 9 ppm · h.

No symptoms of carbohydrate malabsorption were reported after the 50-mg dose though the symptoms after 200 mg acarbose or lactulose were the same as those experienced with sucrose and lactulose in the first series.

Since 10 g was the maximum amount of carbohydrate likely to have been malabsorbed after the 50-mg acarbose dose, 40 g rather than 50 g sucrose was therefore fed as the control to simulate the actual amount of carbohydrate absorbed in this situation. Nevertheless, the blood glucose curve still lay above the 50 g sucrose 50 mg acarbose curve, the 1-h blood glucose area being 51% more and the mean blood glucose value at 60 min being significantly below the control ($P < 0.02$, Figure 2). The mean insulin level was reduced significantly at 30 min ($P < 0.05$, Table 1) and though not significant, the mean GIP response was also diminished (Table 2).

The blood glucose response after 200 mg acarbose in the four individuals was similar to that seen in the previous tests on six individuals. Virtually no rise was seen in blood glucose. Serum insulin levels were markedly reduced (Table 1). In addition, the GIP response was flattened, the peak rise being reduced by 73 ± 19% in comparison with 40 g sucrose (Table 2).

DISCUSSION

The results demonstrated that acarbose has an inhibitory effect on the absorption of sucrose, potato starch, and possibly maltose. The inhibitor flattens rises in blood glucose most effectively after sucrose, to a very appreciable extent after starch, and only to a small extent after maltose.

Increases in breath hydrogen were observed only after sucrose. The massive hydrogen evolution suggested that 200 mg acarbose taken with 50 g sucrose caused almost complete sucrose malabsorption. This is in accordance with the virtual absence of any rise in the blood glucose over the 2-h period.[17] A previous report on using 200 mg acarbose with 100 g sucrose suggested that on the basis of the lactulose studies, only 40% of the sucrose was malabsorbed, but in these experiments, a rise of 1–2 mmol/L was seen in the blood glucose over the first 2 h. Since acarbose is a reversible competitive inhibitor, it might be predicted that if 200 mg leads to 40% malabsorption of the 100-g sucrose load, then it would cause 80% malabsorption after ingestion of 50 g of sucrose. In our first group, we estimated malabsorption of the 50-g sucrose load to be on the order of 60% after 200 mg acarbose, while in the second group, the figure was 100%, giving an overall mean of around 80% as predicted. It may be that larger doses of the inhibitor are required to deal with very large sucrose loads.

The difference between the estimates of malabsorption in our two groups is likely to be the result of both variation between subjects and variability in the test. Thus, the mean malabsorption for the two individuals who took part in both the 200-mg acarbose-sucrose series was 79% for the first but only 64% for the second. Greater differences may be seen between individuals, where in the first series 15 g lactulose produced 68 ppm · h hydrogen while in the second the larger dose (25 g) produced only 52 ppm · h. The two individuals who took part in both series were below the

TABLE 2
Serum GIP levels in a group of four (series II) healthy volunteers who took 50 g sucrose with or without acarbose

	Serum GIP (pmol/L)						
	0 min	15 min	30 min	45 min	60 min	90 min	120 min
Control* II	26 ± 3	30 ± 5	41 ± 18	32 ± 12	27 ± 10	23 ± 11	23 ± 6
Acarbose II (50 mg)	18 ± 7	24 ± 11	23 ± 10	20 ± 12	21 ± 3	22 ± 3	20 ± 5
Acarbose II (200 mg)	20 ± 4	21 ± 4	21 ± 5	21 ± 6	21 ± 5	20 ± 6	20 ± 6

* Only 40 g sucrose taken.

mean for H_2 production in the first series but not different from the mean in the second.

Nevertheless, even though the quantity of carbohydrate malabsorbed may not be directly predicted from lactulose hydrogen studies, the combined evidence from blood glucose and breath hydrogen responses emphasizes that acarbose is a very potent inhibitor of sucrose uptake in vivo.

The effect on sucrose uptake of 50 and 200 mg of inhibitor demonstrated that 50 mg caused no significant increase in breath hydrogen while it resulted in some reduction in blood glucose and insulin levels. This was of special interest for here the comparison was made with a 40-g sucrose tolerance test representing the minimum carbohydrate that should have been absorbed on the basis of breath hydrogen studies. The lower glucose, insulin, and GIP values cannot be ascribed to malabsorption and it is possible that acarbose inhibited absorption high up in the small intestine allowing slower absorption to take place more distally. In this respect, the effect is similar to that of certain types of dietary fiber that have been shown after a meal or glucose challenge to flatten both the blood glucose rise[3,18] and the rise of insulin, GIP, and other hormones of the enteroinsular axis[19] without causing carbohydrate malabsorption.[3,18] However, with viscous fibers, the rate of urinary excretion of xylose taken by mouth[18] or the appearance of ingested paracetamol in the blood[20] is significantly delayed, and this slower rate of substrate delivery may be the reason for the flatter blood rises.

The relatively flat blood glucose response curve when starch was taken with acarbose in the absence of any increase in breath hydrogen may reflect a slower small intestinal (SI) transit of the insoluble starch as opposed to the soluble sugars. The SI transit time for solid food has been reported to be of the order of 8 h[21] while the head of a column of fluid may reach the caecum within the hour.[15] Any fermentation of starch would therefore take place after the period of observation.

Of particular interest was the small effect of acarbose on maltose. Dextrins of molecular size less than G_{9-10} are hydrolyzed at the brush border by glucoamylase (α-1,4 glucosidase, maltase) and α-dextrinase (α-1,6 glucosidase, isomaltase) without requiring amylase. The effect of acarbose on maltose seen here is in keeping with the report by Caspary that 50% of maltase activity (resulting from glucoamylase and sucrase) was inhibited by acarbose.[22] This may result in a mild overall effect on dextrins, which are becoming commonly used sweeteners in jams and other foods.

Breath hydrogen studies alone were performed during 50-g lactose tests. No hydrogen was produced and though no blood data are available, it is unlikely that an effect would be seen using an α-galactosidase.

The absense of effect on glucose suggests that acarbose does not interfere with the diffusion, uptake, and transport of monosaccharides.

We conclude that acarbose slows the absorption of starch and sucrose with a small, statistically nonsignificant slowing of maltose uptake. With acarbose 200 mg, most of the sucrose is malabsorbed. As judged from breath hydrogen evidence, carbohydrate malabsorption is greatly reduced at the 50-mg dose where the flattening of the blood glucose and endocrine response appears to be related to slow absorption rather than malabsorption. Acarbose appears to have potential use, already demonstrated in other studies, in the treatment of diabetes because it renders the carbohydrate more slowly available in a wide range of foods.

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