Optimum effectiveness of intestinal α-glucosidase inhibitors: Importance of uniform distribution through a meal[1]

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ABSTRACT A major barrier to the widespread clinical use of an α-glucosidase inhibitor such as Acarbose, is the unpleasant gastrointestinal symptoms of carbohydrate malabsorption associated with its use. Acarbose is usually administered as a tablet and eaten with the first mouthful of the meal, making its uniform distribution through the meal unlikely. In the present study, Acarbose was crushed to a powder and mixed through a test meal before it was consumed. Six healthy young men consumed test meals containing 75 g carbohydrate either as whole brown rice or as ground brown rice. When Acarbose was uniformly mixed through a ground rice meal prior to digestion it produced dose-dependent reductions in the postprandial glucose, insulin and GIP responses which were evident at doses as low as 12.5 mg. The responses to whole brown rice were intermediate between those to 12.5 and 25 mg Acarbose in ground brown rice. In tablet form Acarbose was only one quarter as effective in flattening the post prandial glucose and insulin responses as it was in powder form. These results highlight the importance of uniform distribution of Acarbose through a carbohydrate meal in order to achieve maximum effectiveness in delaying digestion and absorption and yet not promoting carbohydrate malabsorption. *Am J Clin Nutr* 1985;41:511–516.

KEY WORDS α-glucosidase inhibitors, glucose tolerance, insulin response, gastric inhibitory polypeptide

Introduction

The α-glucosidase inhibitor Acarbose (BAY g 5421) has been shown to competitively inhibit the intestinal digestion of starch as well as sucrose. Addition of Acarbose to a starch or sucrose load reduces the postprandial glucose and insulin responses in a dose-dependent manner (1–3). The lower postprandial insulin levels are considered to form the basis for its potential use in the treatment of carbohydrate-dependent lipid disorders, diabetes and obesity. Numerous studies in animals have demonstrated the efficacy of Acarbose in such conditions (1, 4–6). However, a major barrier to its acceptance by human subjects is the unpleasant side effects associated with carbohydrate malabsorption (flatulence, meteorism, diarrhea) which occur in an unpredictable fashion when Acarbose is administered (3, 7–10). Acarbose is usually administered as a tablet and eaten with the first mouthful of the meal. It is unlikely that a uniform distribution of the drug through the food is obtained under these circumstances and this may result in malabsorption of part of the carbohydrate load and the associated highly unpleasant gastrointestinal

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symptoms. In the present study the drug was crushed into a powder and mixed through the test meal uniformly before being consumed. A short time after this study was completed Acarbose was withdrawn from clinical use after an increased incidence of renal tumours was reported in rats treated with the drug for two years. However the findings in the present study have general implications for any similar drugs acting to retard the rate of carbohydrate digestion in the small intestine.

We have previously shown that the metabolic responses to rice are a function of its physical form and can be predicted by the in vitro rate of starch digestion (11). Ground rice, which has a much larger surface area/starch ratio than whole rice, is hydrolysed much more rapidly in vitro and gives rise to proportionately greater postprandial glucose and insulin responses in vivo. This was considered to be an ideal model in which to study the action of the α-glucosidase inhibitor on the metabolic responses to a starch which is usually rapidly digested and absorbed. Increasing doses of Acarbose were added to ground rice and the postprandial glucose, insulin and gastric inhibitory polypeptide (GIP) responses were compared with those to whole rice in normal volunteers.

Materials and methods

Metabolic tests

Six males aged between 20 and 26 years (mean age 22.7 ± 1.0 years) participated in the study. Their weight was 72.6 ± 4.0 kg and body mass index 23.0 ± 1.0 kg/m^2. The subjects were admitted to the Clinical Research Unit of the Alfred Hospital and the studies were performed over a period of two weeks. During this period they consumed a weight maintaining diet which contained at least 250 g carbohydrate each day. Their mean daily energy intake was 3000 kcal comprising 40% fat, 15% protein and 45% carbohydrate. No subject ingested any drug known to affect glucose metabolism or insulin secretion. No alcohol was consumed for the duration of the study and those who smoked were asked to refrain from doing so on the mornings of the tests. The tests were performed on alternate days in random order. The test carbohydrate meals contained 75 g carbohydrate as either glucose or 97 g brown rice (either whole or ground). Short-grain brown rice was used in this study and the available carbohydrate content was determined after incubation of finely ground cooked rice overnight with excess α-amylase and amyloglucosidase and measuring the released monosaccharide colorimetically as previously described (11). When Acarbose was administered with the ground rice it was crushed into a powder and dispersed uniformly through the meal. This study was approved by the Ethics Committee of the Alfred Hospital, Prahran, Victoria, Australia.

All studies were performed after a 12 hour overnight fast. The rice (ground or whole) was cooked in the morning prior to the study and was consumed in 10–15 minutes. Blood samples were drawn for glucose, insulin and GIP measurements in the fasting state (30 min before and at zero time) and 15, 30, 45, 60, 90, 120, 150 and 180 minutes postprandially.

Breath hydrogen. Forced end-expiratory samples of alveolar air were obtained at half hour intervals during the 3 hour test using a modified Haldane-Priestly tube and analysed for hydrogen using a Gow-Mac gas chromatograph (12).

Analytical methods

Samples for plasma glucose measurements were collected in fluoride oxalate tubes and analysed by the glucose oxidase method using a YSI model 23AM glucose analyser. Plasma immunoreactive insulin concentrations in heparinized plasma were measured using dextran-coated charcoal for precipitation of free hormone with commercially available anti-insulin serum (Burroughs-Wellcome). Human insulin (Novo) was used as a standard. Blood samples for GIP measurements were collected in heparinized tubes containing 3 mg aprotinin (Trasylol) per 10 ml blood. Immunoreactive GIP concentrations in plasma were measured by double antibody radioimmunoassay (13). GIP antiserum was a gift from Professor Vincent Marks (University of Surrey, Guildford, Surrey, England). This antiserum exhibited <1% cross reactivity with cholecystokinin, insulin, pancreatic polypeptide, pancreatic glucagon, porcine gut 'glucagon-like' immunoreactivity, or vasoactive intestinal polypeptide.

Data analysis

Paired t-test and Student's t-test were used for statistical comparisons.

Results

When Acarbose was uniformly mixed through a ground rice meal prior to ingestion it produced dose-dependent reductions in the postprandial glucose and insulin responses which were evident at doses as low as 12.5 mg (**Table 1**). The responses to whole brown rice were intermediate between those to 12.5 mg and 25 mg Acarbose in ground brown rice. At the highest dose employed in this study (50 mg) Acarbose powder almost completely flattened the postprandial glucose and insulin responses to ground brown rice. Breath hydrogen measurements taken over the 3 hour test period did not reveal any significant malabsorption at this high dose level. (**Table 2**). However, three of the six

TABLE 1
Plasma glucose and insulin concentrations following 75 g glucose given as glucose, brown rice or ground brown rice (GBR) in the presence and absence of 12.5, 25 or 50 mg Acarbose. Mean ± SEM (n = 6)

Time	Glucose	Brown rice	Plasma glucose (mmol/L) GBR	GBR + 12.5 mg Acarbose	GBR + 25 mg Acarbose	GBR + 50 mg Acarbose
(mins)						
−30	4.5 ± 0.1	4.7 ± 0.1	4.8 ± 0.2	5.0 ± 0.2	4.7 ± 0.1	4.6 ± 0.1
0	4.6 ± 0.2	4.7 ± 0.1	4.7 ± 0.2	4.9 ± 0.1	4.6 ± 0.1	4.6 ± 0.2
15	6.5 ± 0.4	5.0 ± 0.1‡	6.4 ± 0.5	6.1 ± 0.2	5.4 ± 0.2	5.0 ± 0.1
30	7.2 ± 0.5	6.3 ± 0.2*	7.9 ± 0.2	6.6 ± 0.4‡	5.6 ± 0.2*	5.1 ± 0.2†
45	6.7 ± 0.6	6.4 ± 0.4‡	7.5 ± 0.5	6.6 ± 0.5	5.6 ± 0.3‡	5.1 ± 0.3‡
60	6.6 ± 0.5	5.9 ± 0.4‡	6.8 ± 0.4	6.4 ± 0.5	5.6 ± 0.3‡	5.1 ± 0.2‡
90	5.9 ± 0.4	5.5 ± 0.4	5.4 ± 0.1	5.8 ± 0.3	5.5 ± 0.3	5.0 ± 0.2
120	5.2 ± 0.5	5.3 ± 0.3	5.0 ± 0.2	5.4 ± 0.2	5.1 ± 0.2	5.0 ± 0.1
150	4.6 ± 0.5	5.2 ± 0.2	4.4 ± 0.4	5.4 ± 0.2‡	5.0 ± 0.1	4.8 ± 0.2
180	3.8 ± 0.4	5.0 ± 0.2‡	4.5 ± 0.2	5.0 ± 0.2†	4.8 ± 0.2†	4.9 ± 0.1
			Plasma insulin (mU/l)			
−30	14 ± 3	12 ± 3	14 ± 3	17 ± 4	14 ± 3	19 ± 7
0	12 ± 3	9 ± 1	13 ± 3	17 ± 6	13 ± 6	15 ± 8
15	44 ± 7	22 ± 5‡	54 ± 12	43 ± 7	25 ± 6†	22 ± 6
30	51 ± 8	31 ± 7	61 ± 10	42 ± 8	25 ± 2†	23 ± 6‡
45	59 ± 10	33 ± 6‡	69 ± 5	45 ± 8‡	28 ± 6†	22 ± 7†
60	62 ± 9	33 ± 5†	61 ± 4	38 ± 7	30 ± 10‡	25 ± 6†
90	45 ± 4	26 ± 4‡	34 ± 3	34 ± 7	27 ± 6	23 ± 10
120	34 ± 4	23 ± 4	35 ± 6	28 ± 9	22 ± 8	20 ± 7
150	27 ± 5	21 ± 4	27 ± 10	23 ± 8	18 ± 5	17 ± 6
180	16 ± 5	19 ± 3	19 ± 8	16 ± 6	17 ± 5	15 ± 5

Significantly different from GBR alone: *$p < 0.001$, †$p < 0.01$, ‡$p < 0.05$.

subjects reported symptoms of intestinal discomfort (flatulence, colic) between five and eight hours after the test meal containing 50 mg Acarbose powder. None of the subjects reported symptoms after any of the other test meals, nor were there any increases in breath hydrogen (Table 2). In parallel with the glucose and insulin responses, the postprandial GIP responses to ground rice were reduced by Acarbose in a dose-dependent manner (**Table 3**). The metabolic results are summarized in Table 3 as areas under the incremental curves (AUC) for the first hour after meal ingestion. Presenting the data as AUC's during the absorptive phase of the meal highlights the clear dose-dependent nature of the Acarbose inhibition of starch digestion.

In five subjects a comparison was made between the effects of Acarbose administered as a powder uniformly distributed through a starch meal (as done in the present study) and Acarbose taken as a tablet with the first mouthful of the meal (as suggested by the distributors of the preparation). The results are presented in **Figure 1.** Distributing the α-glucosidase inhibitor uniformly through the meal made it about four times as potent as when taken as recommended in the form of a tablet. The responses to the tablet tended to be more variable than those to the powder.

Discussion

The major finding in this study was the considerably greater potency of Acarbose

TABLE 2
Area under the breath hydrogen curve for 3 hours following the test meals. Mean ± SEM (n = 6)

	Breath hydrogen *ppm hr*
OGTT	1.0 ± 1.0
Brown rice	2.4 ± 2.4
Ground brown rice (GBR)	3.4 ± 3.0
GBR + 12.5 mg Acarbose powder	3.4 ± 3.0
GBR + 25 mg Acarbose powder	0.6 ± 0.4
GBR + 50 mg Acarbose powder	3.2 ± 3.2

TABLE 3
Incremental area under the glucose, insulin and GIP curves for the first hour after the test meals. Mean ± SEM (n = 6)

	Glucose	Insulin	GIP
	mmol L^{-1} hr	*mU L^{-1} hr*	*ng L^{-1} hr*
OGTT	1.96 ± 0.33	35.1 ± 7.5	671 ± 128
Brown rice	1.07 ± 0.16*	14.7 ± 4.5†	251 ± 71‡
Ground brown rice (GBR)	2.22 ± 0.21	48.8 ± 5.2	767 ± 171
GBR + 12.5 mg Acarbose	1.22 ± 0.23‡	23.8 ± 3.5‡	345 ± 142
GBR + 25 mg Acarbose	0.68 ± 0.18†	12.3 ± 1.13*	104 ± 22‡
GBR + 50 mg Acarbose	0.44 ± 0.05*	5.4 ± 1.5	12 ± 3†

Statistics: Different from GBR alone, *p < 0.001, †p < 0.01, ‡p < 0.05.

when it was administered as a powder mixed uniformly through the meal than when it was given in the recommended manner as a tablet with the first mouthful of the meal. In the powdered form Acarbose caused a significant flattening of the postprandial glucose, insulin and GIP responses to the starch load at a dose as low as 12.5 mg. This effect was observed consistently in all subjects. Increasing the dose to 25 mg delayed the digestion and absorption of carbohydrate from ground rice more than when the rice was consumed in its natural whole grain form, but did not produce any symptoms of intestinal discomfort associated with carbohydrate malabsorption. However such symptoms were reported by half of the subjects at the highest dose employed in this study (50 mg) which resulted in almost completely flattened postprandial metabolic responses to ground rice. These observations suggest that for breath hydrogen measurements to be used to detect starch malabsorption following delayed digestion, measurements should be taken over a time period considerably longer than the three hour test to allow for the slower intestinal transit. For this reason, in the present study the symptoms reported must be taken as the major indicator of malabsorption. Thus, these results demonstrate that it is possible to markedly delay the digestion and absorption of starch with a dose of Acarbose (25 mg) which does not cause carbohydrate malabsorption if the drug is administered as a powder uniformly mixed through the carbohydrate load. Even in cases where it is not possible to mix the α-glucosidase inhibitor through the food (eg baked goods) administration in the form of a powder sprinkled over the meal would be more likely to achieve uniform distribution than if it were given as a tablet. This study also confirms previous observations that GIP secretion is strongly influenced by the *rate* of carbohydrate ab-

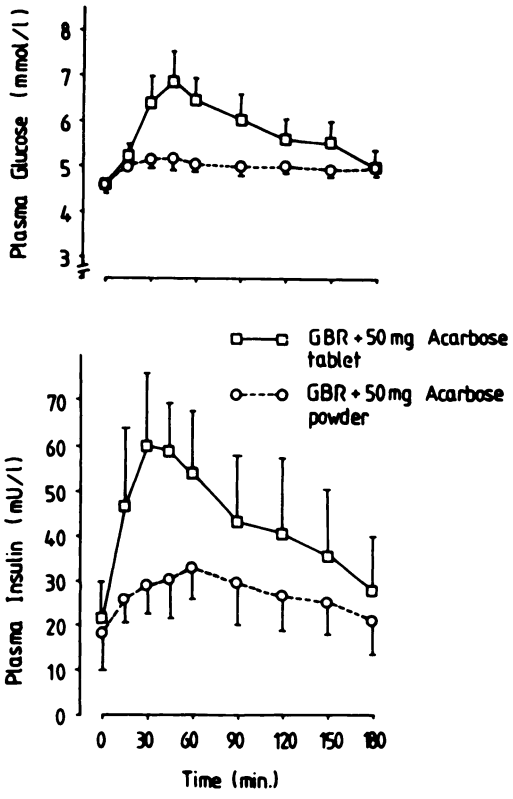

FIG 1. Comparison of postprandial glucose and insulin concentrations following 75 g starch (ground brown rice) in the presence of 50 mg Acarbose either dispersed uniformly through the meal as a powder (- - -) or eaten with the first mouthful as a tablet (——). *Statistics:* Tablet > powder; Glucose: 30, 45, 60 mins (p < 0.05); Insulin: 30 (p < 0.05), 45, 60 mins (p < 0.02).

sorption (14, 15). The trend towards higher glucose, insulin and GIP levels following ground brown rice compared with oral glucose may have been due to the presence of some protein in the rice in addition to the carbohydrate.

This greatly improved effectiveness of Acarbose in the powdered form relative to the tablet form is not unexpected if its mechanism of action as a competitive inhibitor of intestinal glucosidases is considered. As a tablet taken with the first mouthful of food, Acarbose is unlikely to be uniformly distributed through the food in the intestine even if it was chewed thoroughly. As a result of this non-uniform distribution it is possible that the early part of a meal may be malabsorbed, due to high local concentrations of the inhibitor, while the latter part of the meal may be absorbed almost normally due to low or absent amounts of the inhibitor. Under such circumstances, at the extreme it is possible to envisage symptoms of malabsorption occurring in the face of very little metabolic benefit.

Animal studies with Acarbose have been much more successful than clinical studies in terms of predictable metabolic responses and effective treatment of obesity, diabetes and hyperlipidemia (1, 4–6). This success may well be due to the mode of administration. In animal studies it has been uniformly mixed through the food and shown to have significant beneficial effects at doses as low as 10 mg/100 g chow (5). In contrast, up to 200 mg Acarbose has been administered in tablet form with a single meal in human studies, often followed by extremely unpleasant symptoms of intestinal discomfort due to carbohydrate malabsorption (2, 7–10). In the present study, Acarbose was administered in a manner analogous to that used in the successful animal studies with similar results: effectiveness at low doses (25 mg) which do not produce malabsorption. This dose is considerably lower than that recommended by the manufacturers for the tablets. The delay in digestion and absorption which is achieved by adding Acarbose to sucrose or starch loads is comparable to that resulting from eating certain unrefined carbohydrates (17, 18) or adding viscous fibre supplements to refined carbohydrate (19, 20). Although the mechanisms by which absorption is delayed differ in these three situations the net metabolic consequences are the same. The reduced postprandial glucose and insulin levels are of immediate direct benefit to diabetics by lowering their insulin requirement and improving metabolic control (4, 20).

In conclusion, the results of the present study highlight the importance of uniform distribution of Acarbose (or similar inhibitors) through a carbohydrate meal in order to achieve maximum effectiveness in delaying digestion and absorption while not promoting carbohydrate malabsorption. In practical terms, the major implication of these results is that Acarbose (or any similar preparations) should be marketed as a powder rather than a tablet so that it can be distributed as uniformly as possible through the carbohydrate components of a meal. Alternatively, patients could crush the tablet into a powder and mix it through a meal. However, the greatly increased potency of Acarbose in the powder form may complicate this latter approach since the effective dose would be considerably lower.

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