

Investigation of an Amylase Inhibitor on Human Glucose Absorption after Starch Consumption

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Abstract: Inhibition of carbohydrate metabolism or absorption can decrease calorie intake to promote weight loss and combat obesity. It is also a mechanism for reducing hyperglycemia in diabetic subjects. A concentrated northern kidney bean extract was found to be an effective *in vitro* amylase inhibitor, thus potentially affecting the absorption of starch carbohydrates. This product was tested in two single dose human studies. Eleven fasting subjects were given 4 slices of white bread and 42 g of margarine with or without 1.5 g of bean extract. Absorption as measured by the area under the plasma glucose-time curve was inhibited 66%. A full meal study with 7 subjects and 0.75 g of extract caused a non-significant 28-41% reduction in absorption. There was a dose-response decrease in glucose absorption by the extract. The bean extract has *in vivo* efficacy for inhibition of starch absorption and may prove beneficial in weight reduction in individuals consuming large amounts of starch. It also may inhibit starch-induced hyperglycemia in normal and diabetic subjects.

Key Words: Glucose, starch, amylase inhibitor, bean extract.

INTRODUCTION

The most common nutritional disorders in the USA are overweight and obesity. The prevalence of obesity has increased more than 75% since 1980 [1]. A 2006 survey by the Centers for Disease Control found that an average of 37% of Americans were overweight [2]. These findings are in agreement with trends seen elsewhere in the world. The number of children and adolescents considered overweight has more than doubled in the US since 1976 [3]. In 1999, over \$300 million was spent in the USA for prescription medicines to treat obesity [4]. Being obese increases the risk of arthritis, dyslipidemia, hypertension, diabetes and coronary artery disease. Compounding these health risks, obese individuals have a lower quality of life than those who are not obese [5]. Medications currently approved for weight loss can be divided into two categories based on mechanism: (a) reduction of appetite or increasing satiety, and (b) inhibition of nutrient absorption [6]. There are numerous side effects of these medications, which limit their utility. On the plus side, there is evidence that even modest weight loss (5% of body weight) will decrease the risk of the chronic diseases such as diabetes and cardiovascular disease [7].

The major source of carbohydrates in the US diet is starch and over consumption of carbohydrates is frequently associated with obesity [8]. This idea has been made popular by the low-carbohydrate diet popularized by Atkins and others. White kidney bean (*Phaseolus Vulgaris*) has documented salivary and pancreatic amylase inhibitory effects [9, 10]. The theory behind starch blockers has been explained by Preuss and co-workers [11]. Digestion of starch begins

with salivary amylase in the mouth followed by amylase and other pancreatic enzymes in the duodenum. The end result of digestion is the production of mono and disaccharides that are absorbed in the small intestine. The final conversion of disaccharides to monosaccharides occurs during absorption. Slowing of the rapid absorption of carbohydrates would favorably influence the insulin system and in turn lead to lesser fat accumulation [12].

A 2008 search in the National Library of Medicine Database reveals that there are 1552 articles concerning amylase inhibition. A comprehensive experimental investigation found that the major reason commercial amylase inhibitors have failed to influence starch digestion in humans is their low amylase inhibitor activity [13]. We thus investigated a new commercial product for blocking carbohydrates from starch consumption *in vivo*.

MATERIALS AND METHODOLOGY

Phase 2, a concentrated white kidney bean extract (Pharmachem Labs, Kearney, NJ) is in the form of a tan powder. It was found to be a potent *in vitro* amylase inhibitor, 5300 ± 1052 U amylase activity/g using a standard assay done in triplicate at pH 6.8 with potato starch as the substrate and pancreatin as the enzyme source (Lycoming Analytical Laboratories Standard Operating Procedure Revision 5, 2003).

Two random double-blind, crossover human pilot studies were conducted after obtaining approval from the University of Scranton Institutional Review Board and informed consent from the volunteers.

Study 1

There were eleven normoglycemic subjects (6 females and 5 males, aged 21 to 57) who appeared after an overnight fast. After an initial blood draw, they consumed a week apart

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either 4 large slices of white bread with 3 tablespoons of soybean oil margarine (610 calories from 60.5 g carbohydrates, 36.5 g fat, and 10.5 g protein) and 4 g of Sweet N'Low™ with or without 1.5 g of Phase 2 which was mixed with the margarine. Blood was drawn before eating and then every 15 minutes for 2 hours. Plasma glucose measured using an automated clinical procedure.

Study 2

A second pilot study with seven subjects (aged 23 to 43, 4 females and 3 males) included a lower dose of Phase 2 (0.75 g) with a full meal taken after an overnight fast. The subjects consumed a Hungry Man™ frozen dinner of country fried steak with gravy, mashed potatoes, green beans and cherry-apple pie containing 630 calories from 64 g carbohydrate (6 g of dietary fiber, 19 g of sugars, and 39 g of starch), 29 g of fat, and 29 g of protein or a control without added Phase 2. The Phase 2 was mixed with the gravy and the subjects were given the dinners blinded. Blood was drawn every 10 minutes for 60 minutes then periodically until 2 hours. For both studies statistical analysis was performed using a paired t test.

RESULTS

Study 1

The bread consumption results are shown in Fig. (1). The Phase 2 group experienced a lower change in glucose C_{max} and the glucose returned to baseline earlier than the control (62 vs. 80 min.). The area under the curve (calculated from baseline to when the curve returns to baseline after consumption) for Phase 2 (0 to 62 min) was 66% lower ($p < 0.05$) than for the control (0 to 80 min.). This result indicates only 1/3 of the carbohydrates in the bread were absorbed with Phase 2.

Study 2

The full meal study data are shown in Fig. (2). Again Phase 2 caused an earlier return to baseline (58 vs. 70 min).

With this dose the average area under the curve was 28% lower, indicating 2/3 of the carbohydrates in the meal were absorbed. This is in fact a conservative estimate, since the label of the frozen dinner meal lists 19 g of the carbohydrates are sugars that are not inhibited from absorption. Assuming all the sugars are glucose and that it is completely absorbed, the maximum inhibition would be 41% of the carbohydrates consumed. The changes in glucose and areas under the curves were not significantly different between the two groups.

DISCUSSION

The product is sold commercially as tablets or in a capsule. We added the product to the meal as a powder to eliminate any effects of an excipient, which could contain starch. Consumption of 0.75g of Phase 2 produced a calculated 28 to 41% inhibition and with 1.5g there was a 66% inhibition of starch absorption as glucose. Thus there was a dose-response inhibition of starch absorption in spite of difference in nutrient consumption between the two meals. The low dose was about 1/2 as effective as the high dose so the effect was linear. However the low dose of Phase 2 did not result in any significant effect perhaps due to small number of subjects. Our results can be compared to a 1987 Mayo Clinic study with a 650-calorie meal in which 2.9 g of an in-house prepared bean extract but not 2.0g reduced postprandial glucose [14]. Also corroborating our single dose results is a study in which fasting subjects consumed 50 g of carbohydrates as white bread plus capsules containing Phase 2 at doses from 1500 to 3000 mg by Udani (personal communication). Reductions in area under the blood glucose-time curve occurred at all doses with a maximal decrease of 34% at the highest dose ($p < 0.05$). The Phase 2 product seems to be much more potent, allowing lower doses to be used. In our single dose study there were no side effects during the day of the study such as flatulence as indicated by questioning the subjects. In the 5 long-term human studies

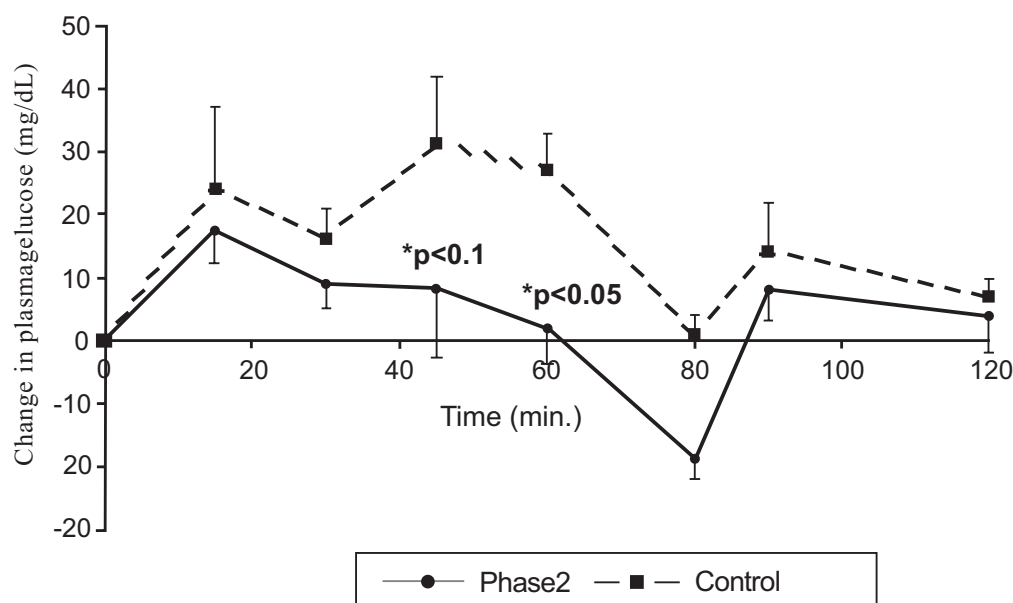


Fig. (1). Comparison of 1.5 g of Phase 2 vs. control on changes in plasma glucose after consumption of 4 slices of white bread and margarine (mean $\pm$ standard error of mean). *Significance vs. control.

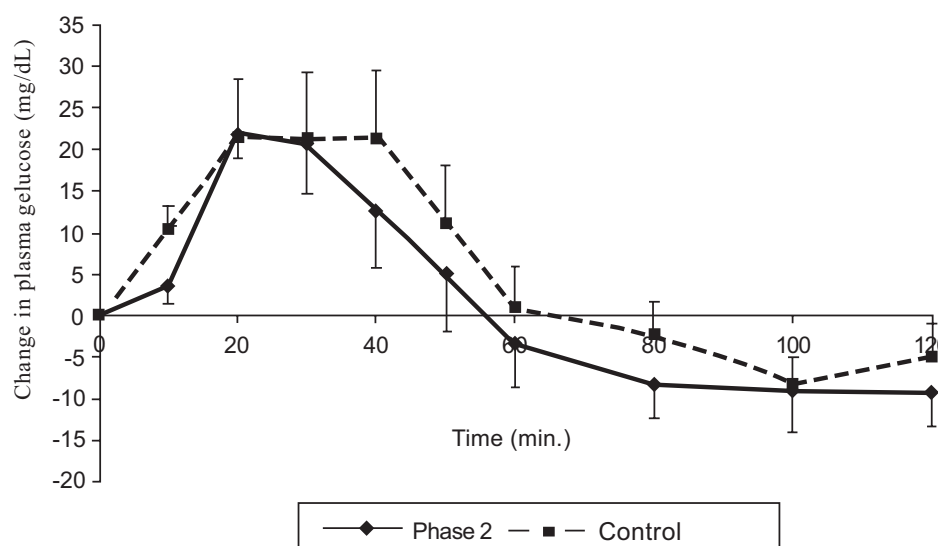


Fig. (2). Comparison of 0.75 g of Phase 2 vs. control on changes in plasma glucose after consumption of a full meal (mean $\pm$ standard error of mean). *Significance vs. control.

and an animal study discussed below there were no also no reports of side effects with Phase 2.

A recent animal toxicity study examining acute and sub-chronic dosing of Phase 2 at 0.5 to 5 g/kg body weight showed no toxicity, no adverse reactions, and no effect on renal and hepatic function [15]. A purified white bean extract was shown to decrease plasma glucose in both normal and type 2 diabetic rats [16]. The extract significantly decreased weight gain and food intake in normal animals after 3 weeks and significantly decreased food intake, water intake and body weight gain in the diabetic animals. The extract also normalized the elevated disaccharidases maltase and sucrase in the diabetic groups. The amylase inhibitor might be beneficial to prevent starch-induced hyperglycemia in diabetic subjects which is a contributing factor to the development of cardiovascular disease and diabetic complications [17].

The first paper describing a human study using Phase 2 was in 2000 [18]. The two arm study lasted 12 weeks with 40 obese volunteers produced significant reductions in weight (3.5 kg), body fat and BMI in the Phase 2 group vs. a placebo. Four hundred mg of Phase 2 at each meal were administered in combination with two other extracts so the results are not directly attributable to the Phase 2. An eight-week human placebo-controlled trial with obese subjects given 1500 mg of Phase 2 twice daily with lunch and dinner produced a moderate non-significant weight loss of 0.5 pounds/week compared to the placebo with no adverse effects [19]. The product also produced a reduction of 26 mg/dL in the subjects' plasma triglycerides. A more recent study by the same group included a program of dietary modification, exercise and behavioral intervention [20]. It was a shorter study of 4 weeks with 1000 mg twice per day and showed the highest weight loss of 8.7 pounds in the subjects who consumed the most carbohydrates vs. the placebo group who lost 1.7 pounds ($p < 0.05$) and also a significant reduction in waist size ($p < 0.01$) occurred in the active group. This result best demonstrates the efficacy of the product for inhibiting carbohydrate absorption for those subjects consuming a large amount of carbohydrates. The weight loss

from Phase 2 is similar to that found for Orlistat (4 pounds) after 12 weeks [21]. A Japanese group investigated 750 mg of Phase 2 plus several other ingredients given twice per day for 8 weeks [22]. They found a significant reduction in weight, hip, waist, body fat, blood pressure and BMI and a significant increase in basal metabolism for the 10 subjects. The largest and most recent study was a randomized, double-blind, placebo-controlled study conducted on 60 pre-selected, slightly overweight volunteers, whose weight was stable for at least six months. They were divided into two groups, homogenous for age, gender, and body weight. The active product was a table of 445 mg of Phase 2 taken once per day for 30 days before a main meal rich in carbohydrates. There was an average weight loss of 3 kg in the active group and -0.4 kg in the placebo group ($p < 0.001$), a loss of fat mass in active group of 2.4 kg ($p < 0.001$) and a loss of 3 cm in waist circumference and a loss of 1.5 cm in hip circumference ($p < 0.001$). Also adipose tissue thickness taken by a skin echogram decreased 4.2 mm ($p < 0.001$) [23].

The Phase 2 bean extract inhibits starch absorption with normal subjects given either bread or a full meal as a source of carbohydrates. The bean extract also increases the rate of clearance of glucose. Therefore it might also prove to be efficacious for decreasing meal-induced hyperglycemia in diabetic subjects. In November 2006 the FDA in a letter stated that for Phase 2 it was allowed to use the following structure/function claims: "May assist in weight control when used in conjunction with a sensible diet and exercise program" and "May reduce the enzymatic digestion of dietary starches". Long-term weight loss studies (a year in duration) in both overweight and obese normal and diabetic subjects are indicated from these results of this study and published studies.

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