Original Article

SAFETY AND EFFICACY OF THE NONSYSTEMIC CHEWABLE COMPLEX CARBOHYDRATE DIETARY SUPPLEMENT PAZ320 ON POSTPRANDIAL GLYCEMIA WHEN ADDED TO ORAL AGENTS OR INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: Our primary objective was to evaluate the effect of the dietary supplement PAZ320 on postprandial glucose excursion. PAZ320 is derived from glucomannan and acts by blocking carbohydrate hydrolyzing enzymes and by binding to ingested polysaccharides. Endpoints included area under the curve during postprandial glucose excursion (gAUC) and adverse reactions.

Methods: In an open-label, sequential dose-escalation, prospective study, we examined the efficacy and safety of PAZ320 in 24 subjects with type 2 diabetes treated with oral agents and/or insulin. Subjects consumed 75 g jasmine rice alone or with low-dose (8 g) or high-dose (16 g) PAZ320. A real-time blinded continuous glucose monitor (CGM) was used to assess 3-hour postprandial glycemia.

Results: We found that 45% of subjects responded to high-dose PAZ320 as evidenced by a decrease in gAUC of 40% compared to baseline in a dose-dependent manner. The effect of PAZ320 does not correlate with duration of diabetes and seems to work regardless of concurrent diabetes medications. The responders had higher postmeal glucose elevation at baseline, while the nonresponders showed no effect or paradoxic glucose response to PAZ320. There was no severe hypoglycemia, and the gastrointestinal side effects were mild.

Conclusions: PAZ320 may be useful as an adjunct to decrease postprandial glycemia in type 2 diabetes, although patients should verify its effect on postprandial glucose due to a possible paradoxic response. Its safety profile is reassuring. Further study is required to determine its long-term effects on glycated hemoglobin (HbA1c) and to further define which subpopulation may respond to PAZ320. **(Endocr Pract. 2013;19:627-632)**

Abbreviations:
ANOVA = analysis of variance; **BMI** = body mass index; **CGM** = continuous glucose monitoring; **gAUC** = glucose area under the curve; **GI** = glycemic index; **GLP-1** = glucagon-like peptide 1; **PGX** = PolyGlycopleX

INTRODUCTION

Type 2 diabetes is a growing concern given its rising prevalence (1). As uncontrolled diabetes can lead to macro- and microvascular complications, tighter but safe glycemic control is imperative, including control of postprandial glucose excursions (2,3). In addition, it has been shown that a gradual loss in daytime postmeal glycemic control occurs in type 2 diabetes prior to deterioration in fasting glycemia (4,5).

This study was designed to assess the efficacy and safety of the nonsystemic chewable complex carbohydrate-based compound PAZ320 on postprandial glucose excursion. PAZ320 is readily available to patients as over-the-counter SUGARDOWN® tablets, but its effect has not been formally tested in patients with type 2 diabetes. It is derived from glucomannan and acts by blocking the key carbohydrate-hydrolyzing enzymes, such as amylase, maltase, lactase, and sucrase in the gastrointestinal tract. It also acts to bind to ingested polysaccharides and slow their absorption with each meal, thereby reducing the post-

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prandial glucose excursion. Due to this, patients have increased satiety but may also have gastrointestinal-related side effects, including flatulence and bloating (6). However, by providing a convenient way to control postprandial glucose, it may assist diabetic patients in better control throughout the day.

Glucomannans have been shown to lower postprandial glucose, and their individual unit is mannose, which can be isolated from guar, locust bean, fenugreek, barley, or konjac (7). In a single-blind, placebo-controlled, crossover study conducted in Thailand, glucomannan was given to half of the participants with type 2 diabetes during an oral glucose tolerance test. It was noted that the group receiving glucomannan had lower area under the glucose curve (8). In a randomized controlled trial, PolyGlycopleX (PGX), a viscous polysaccharide that acts in similar fashion to glucomannan, was evaluated for its ability to reduce postprandial glucose (9). Ten normal subjects consumed high-glycemic index (GI) foods with a sprinkling of PGX, and it was demonstrated that postprandial glucose excursions were reduced and GIs were lowered. Similarly, Zucker diabetic rats showed improved glucose control after receiving PGX (10).

METHODS

We recruited adults with type 2 diabetes who were patients at Dartmouth-Hitchcock Medical Center. Eligibility criteria included: type 2 diabetes, age 18-75 years, use of oral agents or insulin, body mass index (BMI) 25 to 45 kg/m^2, HbA1c ≤9.0%, and the ability to comply with study procedures and provide informed consent. The exclusion criteria were use of medications that affect glucose or galactose metabolism (other than diabetes medications), use of acetaminophen-containing products (due to potential interaction with glucose sensor), lactose or galactose intolerance, history of eating disorder, food allergy, pregnant or lactating females, use of high-dose sulfonylureas (glyburide>20 mg/day, glimepiride>8 mg/day, or glipizide>20 mg/day), use of alpha-glucosidase inhibitors, or use of meglitinides. The protocol was approved by the Committee for Protection of Human Subjects, and subjects provided informed consent.

Study Design

Recruitment occurred from September 2011 to May 2012. This was a single-center, open-label, sequential dose-escalation, prospective study of 24 patients with type 2 diabetes treated with oral agents and/or insulin. Each subject took part in the control arm and then started additional treatment with PAZ320 (lot#41842, Boston Therapeutics, Manchester, NH) at a low dose (8 g) and then high dose (16 g). Subjects were monitored over 4 study visits over a 7-day period. The first visit included signing consent, verifying demographics, and obtaining medical history. At the 2nd through 4th visits, patients were instructed to arrive fasting (≥10 hours) and took their usual medications with the exception of the morning dose of sulfonylurea (if applicable, they took it just before eating rice). Subjects were blinded to the continuous glucose monitor (CGM) readings during the study.

At visit #2 for the control monitoring day, a Dexcom SEVEN+Plus™ CGM was inserted subcutaneously to measure interstitial fluid glucose levels every 5 minutes. After the CGM was in place for 2 hours, 2 fingerstick glucoses were performed for calibration. Subjects then consumed 75 g (dry weight, 60 g carbohydrate) of cooked jasmine rice (White Gold brand, manufacturing date 7/28/2011). Jasmine rice was chosen due to its high GI of 109, compared to glucose with GI of 100 (generally, high GI foods have a GI≥70) (11,12). Subjects consumed the rice within 20 minutes and remained sedentary throughout the 3-hour observation session without additional food or drink (except water). Subjects were instructed to check their fingerstick blood glucose prior to each meal and enter the result into the CGM to maintain calibration. They recorded meal content and timing in a food diary. At visit #3 for the low-dose test, subjects chewed two tablets of PAZ320 (8 g) and then consumed 75 g of rice 10 minutes later. They also took 2 PAZ320 tablets 10 minutes prior to each of their usual meals that day. At visit #4 for the high-dose test, they chewed 4 PAZ320 tablets (16 g) before they consumed 75 g of rice and before each meal. Upon completion of the 3 arms, subjects returned the CGM, and glucose levels were evaluated for the 3-hour period after rice consumption. Adverse effects were noted at each visit. Meals prepared at home were not controlled for carbohydrate content. They were intended to be used to keep PAZ320 in steady state in the gastrointestinal tract and also to evaluate for side effects outside the study laboratory.

Statistical Analysis

A sample size of 12 subjects allowed 80% power to detect a 20% difference in 3-hour glucose area under the curve (gAUC) at the 5% significance level. A responder was defined as subject who showed a significant decrease in gAUC of greater than 20% with ingestion of PAZ320 at either dose. To determine whether subject characteristics were different between the responder and nonresponder groups, Fisher's exact test was used for gender, and *t*-tests were used for continuous variables.

One-way repeated measures analysis of means was used to determine if the 3 outcomes measures showed a difference among the 3 interventions. In the likelihood that the outcomes were not normally distributed, the Friedman test was also done. If the analysis of variance model indicated a difference, then a post-hoc one-way repeated measures analysis of variance (ANOVA) was conducted to compare rice alone to low-dose PAZ320, low-dose to high-dose PAZ320, and rice alone to high-dose PAZ-320™. A

$P<.017$ was considered significant (this value is used to account for the need to repeat the statistical test 3 times, thus reducing the likelihood of a Type 1 error). All statistical tests were done using STATA (version 8, StataCorp., College Station, TX).

Fisher's exact tests were used to determine if adverse events were associated with an intervention. To ascertain whether any adverse event was associated with a group (responder or nonresponder), a logistic model was used.

RESULTS

Twenty-four subjects with type 2 diabetes participated in the study. One subject did not schedule their visits, and another had a protocol violation; therefore no data were collected for the 3 interventions for these 2 subjects. Among the other 22 subjects, there were 2 who responded well to low-dose PAZ320 but experienced gastrointestinal side effects and withdrew from the high dose arm. Their information regarding side effects was reported, but the comparison of low- and high-dose PAZ320 could not be analyzed.

The average age for the 20 subjects was 59 years, and the responders were almost a decade older than the nonresponders (Table 1). There was no association between response and gender. All subjects were Caucasian, except one who identified as Asian. The subjects' average BMI was 33 kg/m^2 and was not different between response groups. The number of years since type 2 diabetes diagnosis was 10 years with an average HbA1c of 7.5%, and these were not different between groups. The response to PAZ320 did not appear to be dependent on any concurrent diabetes medications, including various treatment regimens of oral agents and/or insulin.

Responders Compared to Nonresponders

Table 2 contains the responder and nonresponder summary statistics for the outcome measures for the 3 interventions, and examples of CGM tracings for both responder and nonresponder are shown in Figure 1. In the responder group, the gAUC was the lowest for the high-dose PAZ320 intervention, with an approximately 40% reduction of gAUC compared to the control rice alone. Posthoc repeated ANOVA showed that high-dose PAZ320 was significantly different from rice alone. Time-to-peak blood glucose and peak blood glucose were not significantly different. In the nonresponder group, the gAUC was significantly lower for rice alone compared to low- and high-dose PAZ320. Again, time-to-peak blood glucose was not statistically different, but the peak glucose level was significantly higher for high-dose PAZ320 among the nonresponders.

Table 1
Subject Characteristics for All Subjects (Data for All 3 Interventions), Responders and Nonresponders to PAZ320

	All subjects n = 20	Responders[a] n = 9	Nonresponders n = 11	*P* value
Age–mean in years, (SD)	59 (9.8)	64 (8.1)	55 (9.6)	.045
DM diagnosis-mean in years, (SD)	10 (6.4)	12.2 (7.4)	8.8 (5.2)	.240
HbA1c–mean %,(SD)	7.5 (0.66)	7.5 (0.63)	7.4 (0.70)	.660
BMI–mean in kg/m^2,(SD)	33 (5.5)	32 (6.1)	33.6 (5.1)	.615
% Males–(n)	55% (11)	67% (6)	27% (3)	.175
Medication				
Monotherapy				
Met (n)	3	2	1	.348
SU (n)	2	0	2	.290
Combination Therapy				
Met + SU (n)	3	0	3	.145
Met + DPP4 or GLP (n)	3	1	2	.434
Met + SU ± DPP4 or GLP1 ± TZD (n)	3	3	0	.074
Insulin + Met (n)	2	1	1	.521
Insulin + SU ± Met ± GLP1 (n)	3	1	2	.434

Abbreviations: BMI = body mass index; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase 4 inhibitor; GLP1 = glucagon-like peptide-1 analog; = HbA1c = glycated hemoglobin; insulin = either basal and/or bolus insulin; Met = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
[a] The responders had a significant decrease in gAUC greater than 20% after ingestion of PAZ320).

Table 2
Summary Statistics for the 3 Outcome Measures Across Interventions for Responders and Nonresponders to PAZ320

	Responders			Nonresponders		
	Baseline	Low-dose	High-dose	Baseline	Low-dose	High-dose
gAUC, mean (mg × min/dL)	9,413	8,890	5,775[a]	5,368	8,422	9,604[b]
gAUC, SD (mg × min/dL)	5,625	5,581	5,065	2,169	3,390	3,506
Time to peak, mean (min)	104	73	89	113	107	105
Peak glucose (mg/dL)	227	245	219	195	229	235[c]

Abbreviations: gAUC = glucose area under the curve; SD = standard deviation.
[a] *P* value (ANOVA) across interventions = .012
Post-hoc repeated one-way ANOVA: Baseline versus high-dose *P* = .001
[b] *P* value (ANOVA) across interventions = .014
[c] *P* value (ANOVA) across interventions = .005
Post-hoc repeated one-way ANOVA: Baseline versus high-dose *P* = .001

For both the responders and nonresponders, the gAUC for control rice alone was different from that observed with high-dose PAZ320. In Figure 2, it is apparent that both the responders and nonresponders had a different response to the 3 interventions. The nonresponders had a lower gAUC for rice alone and had a higher gAUC for high-dose PAZ320, while the responders had the opposite response of high gAUC with rice alone with the anticipated decrease in gAUC for the high-dose PAZ320 intervention. Only high-dose PAZ320 was effective in the responder group. For rice alone, a *t*-test was performed to determine whether the average gAUC was significantly higher for responders compared to the nonresponders, and *P* -values (1 or 2-tail) were significant (*P* = .025, 2-tail *P* = .0498). For high-dose PAZ320, the nonresponders had a significantly higher average gAUC (*P* = .035) compared to the responders. Both groups had a different response to rice alone, which was the control. Therefore, it would not be valid to group the responders with nonresponders because they had different responses to the control intervention.

Adverse Effects of PAZ320

Adverse events analysis was done for all 23 subjects, whether or not they completed all 3 interventions. No severe hypoglycemic episodes were observed. Three mild hypoglycemic episodes requiring treatment with glucose tablets were recorded. Flatulence was the most common adverse reaction, it was noted in 26% of patients with low-dose PAZ320 and 18% of patients with high-dose PAZ320, which was significant compared to baseline (*P* = .022). There was no significant difference in adverse events between responders and nonresponders.

DISCUSSION

The current study demonstrates that a subset of patients with type 2 diabetes do have improved postprandial glycemia in a dose-responsive manner following PAZ320. PAZ320 improved the gAUC only at the high dosage in 45% of the subjects. This suggests that PAZ320 may be an effective tool for helping to control postprandial blood glucose in diabetic patients, particularly in those who have significant postmeal hyperglycemia at baseline. Based on the mechanism of action, we predicted that time-to-peak blood glucose would be delayed, but there was no statistically significant change observed in our study.

Interestingly, the responders and nonresponders had significantly different responses to the rice alone, and the average gAUC at baseline after eating the control rice was significantly higher for the responders compared to the nonresponders. Therefore, it would not be valid to group the responders with nonresponders because they have different responses to the control rice intervention. There was no significant difference between the responders and nonresponders in terms of BMI, duration of diabetes, baseline HbA1c, or concomitant diabetes medications.

We were not able to discern baseline differences between responders and nonresponders, other than older age and higher initial gAUC with the control rice alone in the responders. It would seem that the initial response to the control rice alone predicts who will then respond to PAZ320. The responders could be easily identified by checking 1- to 2-hour postmeal glucose, with a significant reduction in postmeal glucose levels in a dose-dependent manner, while the nonresponders showed persistently high

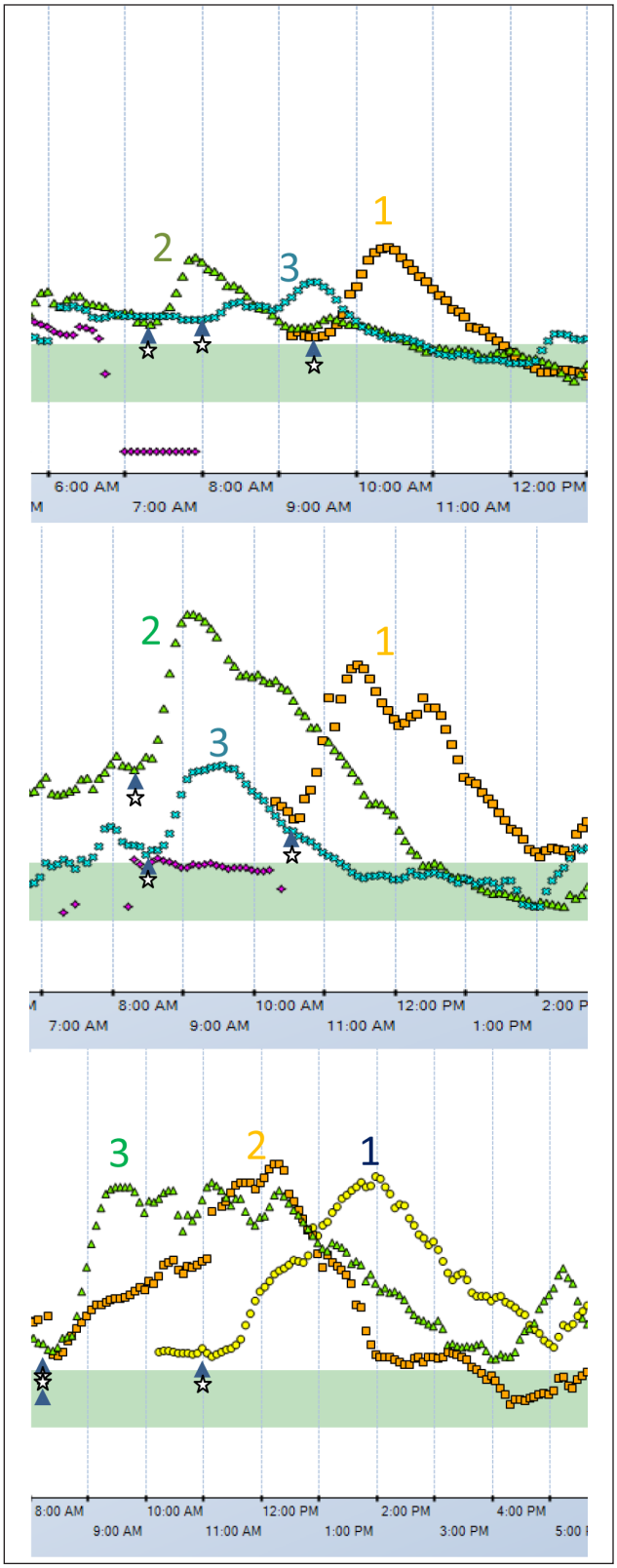

Fig. 1. Examples of CGM tracings for the responder to both low and high doses of PAZ320 (top), to only high dose (middle), and the nonresponder (bottom). *1* = control rice alone; *2* = low-dose PAZ320; *3* = high-dose PAZ320; *star* = time rice was consumed.

glucose trends. We interpret this as follows: those subjects who make less endogenous insulin in response to a carbohydrate meal respond with lower postprandial glycemia when PAZ320 is added.

Several studies have shown that other dietary factors, including gastrointestinal motility and dietary protein, fat, and fiber content, affect postprandial glycemia (13,14). Most of the subjects in our study had type 2 diabetes for approximately 10 years, and thus may have had some subclinical diabetic gastroparesis, which may have interfered with the efficacy of the supplement.

Notably, PAZ320 did not significantly increase the risk of occurrence of hypoglycemic episodes. Flatulence was common but usually mild.

Several limitations of the study must be acknowledged. This is the first feasibility study to look at the short-term efficacy and safety of PAZ320 (SUGARDOWN® dietary supplement) in diabetic patients. PAZ320 was given for a short time at varying doses, and the results analyzed were only for a single carbohydrate-controlled meal. It is possible that the high glycemic index of jasmine rice overwhelmed PAZ320's ability to delay absorption and that a lower glycemic carbohydrate or mixed meal may show better efficacy of PAZ320. Mixed meal results from home were not analyzed as they could not be accurately controlled for carbohydrate amount and were highly variable. The study was open label, so some side effects of PAZ320, such as flatulence after eating rice, could be overreported without comparison to the placebo as a baseline. The CGM glucose reading does "lag" behind real-time blood glucose but has been shown to be a useful tool to monitor glucose trends and have clinical accuracies for measurement of glucose of 95.5 to 98.9% (15). In addition, there are no data on subjects' subsequent HbA1c, and a longer study to examine the overall glycemic effect should be performed. The majority of our subjects were Caucasian with longstanding diabetes, so a larger multicenter study is required to evaluate the effects of PAZ320 in a more diverse group, including those with early or prediabetes.

CONCLUSION

It is reassuring to observe a beneficial effect in about half of diabetic patients, even in late stage, at a more advanced age, and already on a wide variety of medications (including oral agents, GLP-1, and/or insulin), without significant side effects or hypoglycemia. Further mechanistic studies should be performed to characterize which diabetics respond to PAZ320. Optimal postprandial glucose control is one of the most difficult goals to achieve as type 2 diabetes progresses, and PAZ320, a nonsystemic chewable complex carbohydrate-based compound, may be helpful for achieving this goal in a subset of patients.

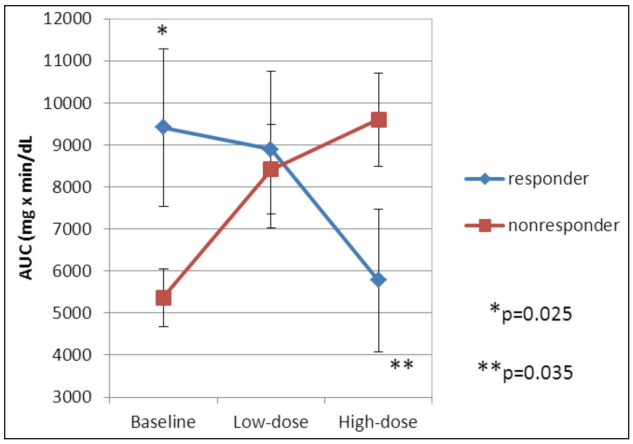

Fig. 2. Average AUC for the 3 interventions (control rice alone, with low-dose and high-dose PAZ320) for responders and nonresponders.*P = .025, ** P = .035.

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DISCLOSURE

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