

Use of modified cornstarch therapy to extend fasting in glycogen storage disease types Ia and Ib¹⁻³

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ABSTRACT

Background: Type I glycogen storage disease (GSD) is caused by a deficiency of glucose-6-phosphatase resulting in severe fasting hypoglycemia.

Objective: We compared the efficacy of a new modified starch with the currently used cornstarch therapy in patients with type Ia and Ib GSD.

Design: This was a randomized, 2-d, double-blinded, crossover pilot study comparing the commonly used uncooked cornstarch with the experimental starch in 12 subjects (6 GSDIa, 6 GSDIb) aged ≥ 13 y. At 2200, the subjects were given 100 g of digestible starch, and glucose and lactate were measured hourly until the subject's plasma glucose concentration reached 60 mg/dL or until the subject had fasted for 10 h. The order in which the products were tested was randomized in a blinded fashion.

Results: The matched-pair Gehan rank test for censored survival was used to compare the therapies. The experimental starch maintained blood glucose concentrations significantly longer than did the traditional therapy ($P = 0.013$) in the 2-sided analysis. Most of the benefit was found to be after glucose concentrations fell below 70 mg/dL. The currently used cornstarch resulted in higher peak glucose concentrations and a more rapid rate of fall than did the new starch.

Conclusions: The experimental starch was superior to standard therapy in preventing hypoglycemia (≤ 60 mg/dL). This therapy may allow patients with GSD to sleep through the night without awakening for therapy while enhancing safety. Additional studies are warranted to determine whether alternative dosing will further improve control in the therapeutic blood glucose range. *Am J Clin Nutr* 2008;88:1272-6.

INTRODUCTION

Glycogen storage disease (GSD) type I is a rare autosomal recessive disorder of glycogen metabolism that affects ≈ 1 in 100 000 live births (1). Mutations in the genes that encode glucose-6-phosphatase (2) and glucose-6-phosphate translocase (3) cause type Ia and type Ib GSD, respectively. Because glucose-6-phosphatase catalyzes the final step of both glycogenolysis and gluconeogenesis, abnormal glucose-6-phosphatase activity results in impaired endogenous glucose production. Severe hypoglycemia consequently occurs within 3-4 h of a meal. During infancy, children exhibit episodes of hypoglycemia, developmental delay, hepatomegaly, and poor growth. A series of metabolic derangements also result from the enzymatic defect,

because the liver remains responsive to the normal neuroendocrine responses to impending hypoglycemia. Concentrations of glucose-6-phosphate increase from glycogenolysis, and shunting into alternative pathways results in accumulation of lactic acid, triglycerides, cholesterol, and uric acid (1, 2, 4-6).

The primary goal of treatment is to maintain normal blood glucose concentrations (>70 mg/dL) throughout the day and night, which will prevent activation of counterregulatory responses. In newborns and infants, frequent feeds during the day combined with overnight infusion of dextrose or a glucose-containing formula maintain normoglycemia (7-9). In 1984, uncooked cornstarch was found to be the most effective therapy for maintaining blood glucose concentrations in the desirable range (10). Although cornstarch has dramatically improved the quality of life for patients with GSD type I, it has a limited duration of action. A previous study suggested that cornstarch therapy only prevents hypoglycemia for a median time of 4.25 h in children (11). All children must awaken in the middle of the night for therapy, and delayed administration of the therapy can be associated with the development of hypoglycemia, seizures, and neurologic injury. Even as adults, almost all patients still require therapy every 4-6 h, and overnight therapy is required in $>90\%$ of patients to achieve optimal metabolic control (19, 10-13).

The constant anxiety about avoiding hypoglycemia and the necessity to interrupt sleep to receive therapy 1 to 3 times per night is deeply detrimental for these patients and their families. The effort is exhausting, and the resulting fatigue affects the work

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and quality of life of the patients and their families. In addition, exhaustion from waking up every night eventually leads to delayed administration of a cornstarch dose, which puts children with GSD Ia at extreme risk from hypoglycemia.

An ideal food in GSD type I would be able to provide an 8-h duration of reliable blood glucose concentrations and have a low glycemic index, ie, it would avoid the rapid development of high glucose concentrations and subsequent secretion of insulin. The low glycemic index is a necessary feature of an ideal food because a high insulin concentration would not only increase the risk of hypoglycemia but would also prevent the accumulation of alternative fuels for the brain (lactate and ketones) if hypoglycemia were to occur (14–22). In addition, this food must not result in the delivery of too much undigested material to the colon, thus causing abdominal cramping and flatulence (23). The volume of food must not be too large to administer as a meal and the preparation time, storage, and costs are all important considerations.

Recently, scientists at the starch research laboratory based at Glasgow Caledonian University (Glycologic Ltd, Glasgow, UK; international patent WO2005044284) developed a controlled heat-moisture processing of a high-amylopectin-containing cornstarch (24) that is more amenable to digestion by intestinal enzymes than other forms of starch. Initial investigations performed in England showed that this experimental cornstarch improved maintenance of glucose concentrations in 20 patients with GSD tested during the day. The study was limited, however, by several confounding variables including duration of fasting, activity, and variable treatment strategies that are inherent during the day (24). The aim of this double-blind, crossover study was to determine whether the new modified cornstarch could maintain normoglycemia longer than the standard cornstarch in a cohort with type I GSD during an overnight fast.

SUBJECTS AND METHODS

Subjects

All subjects followed by the University of Florida Glycogen Storage Disease Program with a proven diagnosis of type I GSD established either biochemically or by liver biopsy were eligible to participate, and the diagnosis of type Ia or Ib was proven by mutation analysis. These studies were approved by the Institutional Review Board of the University of Florida, and informed consent (and assent from the child when under the age of 18 y) was obtained before enrollment in this study. A total of 12 participants over 13 y of age were enrolled (6 subjects with GSDIa and 6 subjects with GSDIb). All subjects were treated with uncooked cornstarch therapy around the clock at baseline.

Test products

For these investigations, the experimental heat-moisture processed cornstarch Glycosade (VitaFlo International Ltd, Liverpool, United Kingdom) was compared with uncooked Argo brand cornstarch, the standard starch preparation used in the United States (ACH Food Companies Inc, Memphis, TN). The characteristics of these products are summarized in **Table 1**. All starch products were delivered to the institutional metabolic kitchen where the products were measured and distributed. The investigators, subjects, and research team were blinded with regard to the starch preparation. All starch doses were administered

TABLE 1

Characteristics of the conventional and experimental starches examined in the study¹

	Conventional starch	Experimental starch
Moisture content (%)	10.9	11.9
Amylopectin content (%)	72.8	99.5
Total carbohydrate, wet base (%)	87.5	82.5
Resistant starch (%)	60.5	67.7
Glycemic index (GI units)	70	30

¹ Conventional starch was Argo (ACH Food Companies Inc, Memphis, TN); experimental starch was Glycosade (VitaFlo International Ltd, Liverpool, United Kingdom).

as a 100 g of digestible starch dose in 177 mL (6 ounces) of an artificially sweetened, carbohydrate-free, lemon-raspberry drink (Crystal-Light; Kraft Foods Inc, Northfield, IL) to mask the taste. The dose was taken orally or through a gastrostomy tube if requested by the participant.

Study design

The study was a double-blinded, randomized, 2-d, crossover pilot study comparing the standard cornstarch product with the experimental starch preparation. The study was a consecutive, 2-night, in-patient stay at the General Clinical Research Unit at the University of Florida. At 2200, the subjects were given 100 g of carbohydrate starch (either the conventional or experimental preparation), and glucose and lactate were measured hourly through an in-dwelling intravenous line until the subject's plasma glucose concentration reached 60 mg/dL or the subject had fasted for 10 h. All glucose and lactate determinations were assayed in a CLIA-approved laboratory housed on our research unit by using a YSI Analyzer (YSI Incorporated, Yellow Springs, OH). Venous pH was measured every other hour in the CLIA-approved hospital laboratory. A venous pH <7.25 or lactate concentrations >10 mmol/L were established criteria for stopping the study, but these abnormalities never developed in any of the subjects. The alternate starch was administered on the second night of the study. The participants were asked to be sedentary for 4 h before administration of the cornstarch, and the same meal was served for dinner both nights of the study to minimize possible confounders.

Statistical analysis

The primary outcome analysis of the trial was the time to reach a plasma glucose concentration of 60 mg/dL. This was analyzed in an actuarial manner, because not all subjects were able to reach this level during their time on the trial, making them right censored. Because the trial was a crossover protocol, we used the Gehan (25) ranks in a match pair set-up. This is a close analogue of the Wilcoxon's sign rank test (26). Qualitatively, we used Kaplan-Meier curves to plot the time-to-event outcome data (27). The numerous unknown factors prevented a prospective power analysis. Key unknown ingredients included degree of correlation between the paired observations and the degree of censoring. The data from this pilot study can now provide estimates of these unknown factors for planning future studies.

TABLE 2Clinical characteristics of the subjects enrolled in the study¹

Subject	Age	Sex	GSD	Mutation	UCCS	UCCS daily	BMI
	y				doses/24 h	g·kg ⁻¹ ·24 h ⁻¹	kg/m ²
01	32	M	Ia	R83C/R83C	6	5.6	21.3
02	15	M	Ia	F117C/Q347X	8	3.8	26.1
03	24	M	Ia	R83C/R83C	6	8.5	24.3
04	25	M	Ia	R83C/R83C	8	2.8	32.5
05	15	F	Ia	R83C/R83C	6	4.9	22.1
06	34	F	Ia	R83C/R83C	6	4.6	29.8
07	30	F	Ib	R28C/G339C	6	6.3	31.2
08	19	M	Ib	G339C/1042delCT	5	3.9	33.5
09	24	F	Ib	G339C/1042delCT	5	4.6	23.3
10	23	M	Ib	G68K/1103ins12	6	6.1	22.1
11	19	F	Ib	G ⁺ toT (550 + 1)/ C183R	4	3.9	20.7
12	14	M	Ib	G ⁺ toT (550 + 1)/ C183R	4	5.7	18.4
Mean	23	—	—	—	6	5	25
SD	7	—	—	—	1	2	5

¹ GSD, glycogen storage disease; UCCS, uncooked cornstarch.**RESULTS**

The clinical characteristics of the subjects are summarized in **Table 2**. There was a sex distribution of 5 females and 7 males, and the subjects ranged in age from 14 to 34 y with a mean age of 22.8 y. All patients were in fair to good metabolic control at the time of the studies (**Table 3**).

The baseline mean blood glucose measurement obtained immediately before the 2200 dose of the test starch was consistent from day 1 to day 2 and for both the experimental and the control arms of the study. The mean (\pm SD) blood glucose concentration across all subjects at time zero was 77 ± 14 mg/dL. All subjects stopped the daily protocol because of reaching the stop criteria of hypoglycemia (blood glucose < 60 mg/dL) or because 10 h had elapsed from the time of the starch dose. None of the subjects became acidotic during the protocol, and the stop criteria of a lactate concentration equal to 10 mmol/L was not reached.

In the 2-sided analysis, the experimental cornstarch preparation was found to maintain blood glucose concentrations significantly longer than the currently used cornstarch preparation

($P = 0.013$). The Kaplan-Meier curve for duration above 60 mg/dL is depicted in **Figure 1**. Although the experimental starch maintained blood glucose concentrations significantly longer than the standard starch, most of the benefit was after glucose concentrations fell below 70 mg/dL. The standard cornstarch was found to have a higher peak glucose concentration and a more rapid rate of fall when compared with the experimental starch (**Figure 2**). No significant difference was found in the time maintained above 70 mg/dL or for lactate concentrations (**Figure 3**).

DISCUSSION

Although current cornstarch therapy has eased the daily management of GSD and has markedly improved these patients' quality of life for the past 25 y, the limited duration of action of the currently used cornstarch preparation necessitates finding an improved substance that will allow for fewer doses throughout the day and night. In this study, we showed that the experimental

TABLE 3Biochemical characteristics of the subjects enrolled in the study¹

Subject	AST	ALT	Triglyceride	Cholesterol	Uric acid	ESR
	U/L	U/L	mg/dL	mg/dL	mg/dL	mm/h
01	39	23	316	161	3.8	29
02	22	20	321	144	6.9	4
03	29	23	770	319	5.7	14
04	44	48	425	256	7.8	15
05	26	25	286	182	9.9	19
06	49	37	324	155	7.3	32
07	20	10	250	161	5.2	44
08	29	21	84	93	7.5	31
09	41	31	90	79	9.9	76
10	68	61	551	176	8.5	120
11	17	11	75	88	7.2	66
12	26	19	Not reported	Not reported	7.8	27
Mean	34	27	317	165	7	40
SD	15	15	210	72	2	33

¹ Baseline laboratory results were obtained at the time of enrollment in the study with intravenous line placement. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate.

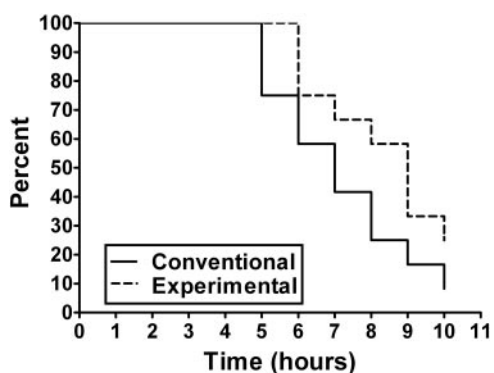


FIGURE 1. Kaplan-Meier curves depicting subject survival for maintenance of glucose concentrations >60 mg/dL for the experimental (Glycosade; Vitaflo International Ltd, Liverpool, United Kingdom) and the conventional (Argo; ACH Food Companies Inc, Memphis, TN) starches ($n = 12$). The experimental starch maintained blood glucose concentrations significantly longer than did the conventional cornstarch ($P = 0.013$, Gehan ranks test in a match pair set-up).

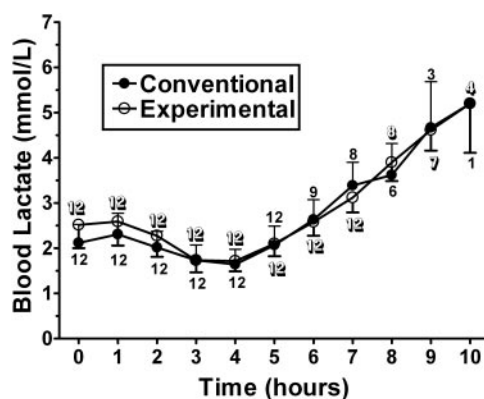


FIGURE 3. Mean (\pm SD) lactate concentrations after administration of 100 g of the conventional (Argo; ACH Food Companies Inc, Memphis, TN) or experimental (Glycosade; Vitaflo International Ltd, Liverpool, United Kingdom) starch. The numbers located at the data points represent the n for that product at the given time point. No significant difference was found in lactate concentrations when comparing the 2 starches.

starch was superior to the standard therapy at preventing hypoglycemia during the overnight period.

A previous study similarly evaluated this starch against standard therapy during the day (24). Although that study also suggested that the modified experimental starch was superior to conventional therapy, the benefit was limited to the rate of glucose fall. This apparent difference can be explained by changes in the study design. Our study evaluated subjects with type I GSD, who have a more consistent biochemical fasting profile than do a combination of type I and III subjects (4). Fasting times for the 2 different forms of GSD are not comparable. Performing the study at night also allowed standardization of activity, replicable meals, and a consistent fasting time before commencement of the study. Removing the aforementioned confounders allowed for more consistent data to be collected and likely contributed to the improved duration of action shown with the experimental product.

Our study showed improved prevention of hypoglycemia, a slowed rate of increase in blood sugar, and a slowed rate of blood glucose fall with the experimental cornstarch compared with the

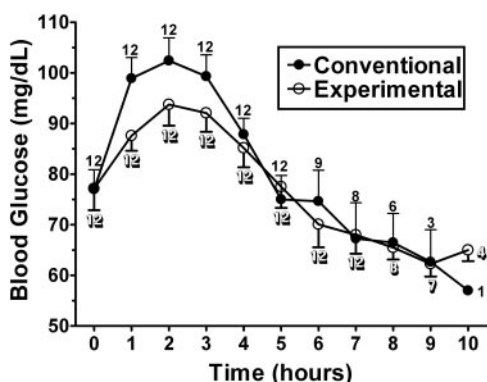


FIGURE 2. Mean (\pm SD) glucose concentrations after administration of 100 g of the conventional (Argo; ACH Food Companies Inc, Memphis, TN) or experimental (Glycosade; Vitaflo International Ltd, Liverpool, United Kingdom) starch. The numbers located at the data points represent the n for that product at the given time point. The conventional starch had a higher peak glucose concentration and a more rapid rate of fall than did the experimental starch.

currently used product. Although the therapeutic range for glucose is > 70 mg/dL, the new product may add safety by slowing the drop of glucose once 70 mg/dL is reached. This added protection will lessen the impact of a missed cornstarch dose because the slower rate of fall of glucose allows lactate concentrations to increase. Lactate can be used directly by the brain as a fuel in the setting of hypoglycemia (15, 28), and the experimental product should decrease the risk of seizures and neurologic injury in this population. Of note, it has been reported that hypoglycemia lessens with age because of the production of glucose-6-phosphatase beta (29). This was not found in the present study, and all participants developed hypoglycemia during the overnight fast with traditional therapy.

Although the new product appears encouraging regarding safety and glucose control, no significant difference was found in lactate concentrations between the cornstarch preparations. Lactate increases in GSD with counterregulation, and it will be critical to maintain glucose concentrations above the 70-mg/dL threshold for this product to be used to extend the duration between doses. Lactate concentrations have been associated with long-term complications in type I GSD, and near normal lactate concentrations are achieved with optimal therapy (11). In this study, only one dose of the experimental product was studied. Future studies are warranted to determine whether alternative dosing will improve control in the therapeutic range.

In conclusion, the newly created modified cornstarch, Glycosade, is a promising alternative to traditional cornstarch preparations and may improve quality of life and safety in this population. This therapy, in particular, offers the potential for patients with GSD to sleep through the night without awakening for therapy. Future studies are needed to learn the appropriate dosing of this promising product and to determine whether the product will release glucose at a rate sufficient to meet daytime needs.

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protocol; GPAS: involved in study conception and design; DAW: contributed to study conception and design, conducted study, drafted the manuscript, and secured funding for the study. All authors participated fully in critically revising the manuscript and approved the final version of the manuscript to be published. None of the authors had a personal or financial conflict of interest.

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