Safety and Efficacy of Chronic Extended Release Cornstarch Therapy for Glycogen Storage Disease Type I

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Abstract *Background:* Glycogen storage disease type I (GSD I) causes severe hypoglycemia during periods of fasting since both glycogenolysis and gluconeogenesis are impaired. Primary treatment in North America consists of cornstarch therapy every 3–4 h. Waxy maize extended release cornstarch was introduced for maintaining overnight glucose concentrations, but no studies have assessed long-term safety and efficacy of the product.

Objective: To demonstrate the safety and efficacy of modified cornstarch in GSD I.

Design: An open-label overnight trial of extended release cornstarch was performed. Subjects with a successful trial (optimal metabolic control 2 or more hours longer than with traditional cornstarch) were given the option of continuing into the chronic observational phase. Subjects were assessed biochemically at baseline and after 12 months.

Results: Of the 106 subjects (93 GSD Ia/13 GSD Ib), efficacy was demonstrated in 82 patients (88%) with GSD Ia and 10 patients (77%) with GSD Ib. The success rate for extending fasting was 95% for females and 78% for males. Of the patients who entered the longitudinal phase, long-term data are available for 44 subjects. Mean duration of fasting on traditional cornstarch prior to study for the cohort was 4.1 and 7.8 h on the extended release cornstarch

($P < 0.001$). All laboratory markers of metabolic control have remained stable in the chronically treated patients.

Conclusion: Extended release cornstarch appears to improve the quality of life of patients with GSD I without sacrificing metabolic control. Avoiding the overnight dose of cornstarch should enhance safety in this population.

Abbreviations

ALT Alanine aminotransferase
AST Aspartate aminotransferase
GSD Glycogen storage disease

Introduction

The hepatic glycogen storage diseases are a group of inherited disorders characterized by the abnormal storage or release of glycogen (Wolfsdorf and Weinstein 2003). The inability to release glycogen as glucose during periods of fasting results in marked hypoglycemia. In glycogen storage disease type I (GSD I), hypoglycemia is severe since all endogenous glucose production is impaired, and the shunting of glucose-6-phosphate into alternative pathways results in the accumulation of uric acid, triglycerides, and lactate (Kishnani et al. 2014).

The primary goal of treatment for both GSD Ia and Ib is to maintain a normal blood glucose concentration to prevent neuroglycopenia and the associated acidosis by ameliorating the counter-regulatory response. In the early 1980s, uncooked cornstarch was introduced as a treatment for maintaining normoglycemia (Chen et al. 1984), and it has remained the mainstay of therapy in North America (Koeberl et al. 2007). While cornstarch has dramatically improved the quality of

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life and clinical outcome for patients with GSD I, it has a limited duration of action. A previous study suggests that it only prevents hypoglycemia for a median time of 4.25 h in children (Weinstein and Wolfsdorf 2002). All children must wake up in the middle of the night for therapy, and delayed administration of the cornstarch can be associated with development of hypoglycemia, seizures, neurologic injury, and death. Even as adults, almost all patients still require therapy every 4–5 h, and overnight administration of cornstarch is required in over 90% of patients to achieve optimal metabolic control (Weinstein and Wolfsdorf 2002).

We previously reported on the efficacy of an extended release cornstarch preparation for maintaining glucose concentrations during the overnight period (Correia et al. 2008). In 2009, the extended release waxy maize cornstarch Glycosade® (Vitaflo International Ltd, Liverpool, England) was approved in the United Kingdom for treatment of GSD I, and it was released as a medical food in the United States in 2012. While this extended release formulation has been used for several years, there have not been any publications reporting the long-term safety and efficacy of the product. We now describe our long-term, overnight experience with the extended release cornstarch in a cohort of patients with GSD I.

Subjects and Methods

Subjects

Patients followed by the University of Florida Glycogen Storage Disease Program with genetically proven GSD I were eligible to participate. Inclusion was limited to patients 5 years of age and older based upon the recommendations for use of the product in the United States. From 2012–2013, patients were given the option of trying the extended release cornstarch overnight. A total of 106 eligible subjects ranging from 5 to 60 years of age chose to participate. This cohort consisted of 93 subjects with GSD Ia (43 males/50 females), 13 with GSD Ib (7 males/6 females). Patients who clinically did well on the extended release formulation were given the option of participating in a longitudinal study. 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, was obtained prior to enrollment in this study.

Study Design

The overnight challenge was performed using the protocol outlined by Correia et al. (2008). Since dosing standards for the extended release cornstarch have not been established,

the dose of the product for the overnight challenge was calculated by replacing the carbohydrate load from traditional cornstarch with a comparable amount of the new waxy maize formulation. An in-dwelling intravenous catheter was placed, and hourly monitoring of glucose and lactate was performed using a YSI 2300 STAT Plus™ Glucose & Lactate Analyzer (YSI Incorporated, Yellow Springs, Ohio) until glucose concentrations fell to 70 mg/dL or patients fasted for 12 h. Lactate concentrations over 5 mmol/L were also established as criteria for ending the trial, but these stop criteria were never reached.

Following completion of the overnight trial, patients were given the option of staying on the product chronically during the overnight period. For inclusion in the follow-up safety and efficacy studies, the extended release cornstarch needed to be consumed at least 3 nights per week. All patients remained on their baseline cornstarch therapies throughout the day. Doses of both the daytime and overnight cornstarch preparations were titrated over the course of the year based upon home glucose monitoring as per standard GSD I care to maintain glucose concentrations over 75 mg/dL (4.2 mmol/L). The following laboratory data were collected at baseline and twelve months: aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol, triglycerides, uric acid, total protein, and albumin.

Statistical Analysis

For the overnight trial, success was defined as maintaining glucose concentrations above 70 mg/dL at least 2 h longer than with traditional uncooked cornstarch with comparable markers of metabolic control. Statistical analysis was performed using paired two-tailed *t*-tests to determine whether there were differences between the metabolic markers before treatment and after 12 months. *P* values <0.05 were considered statistically significant.

Results

Overnight Challenge

A total of 106 patients (50 males/56 females) participated in the overnight challenge. Efficacy for extending fasting for 2 h beyond baseline was demonstrated for 88% patients (82/93) with GSD Ia and 77% (10/13) with GSD Ib. The success rate for extending fasting was 95% (53/56) for females and 78% (39/50) for males.

Long-Term Safety and Efficacy Follow-Up

Of the initial 106 patients who underwent the overnight fasting challenge, 77 patients chose to be followed as part of

Fig. 1 Outcome of participants who attempted waxy maize cornstarch

a protocol aimed at determining long-term efficacy and safety of the extended release cornstarch (67 GSD Ia, 10 GSD Ib). Of the subjects who entered the longitudinal phase of the study, long-term data are available for 44 subjects; 26 subjects remained on the waxy maize cornstarch, but long-term data could not be obtained; 6 subjects dropped out of the study (1 GSD Ia and 5 GSD Ib) due to discontinuation of the experimental product; and 1 person with GSD Ia died during the study after missing the waxy maize dose and going all night with no therapy. Fourteen subjects were not included in the chronic phase of the study after failing the initial overnight challenge (11 GSD Ia, 3 GSD Ib), and 15 subjects who passed the overnight challenge opted not to participate in the longitudinal phase (Fig. 1). Gastrointestinal intolerance or exacerbation of inflammatory bowel disease and hypoglycemia were the reasons provided by the GSD Ib patients who dropped out, while worsening metabolic control was the primary reason for withdrawing in the GSD Ia population. Figure 2 shows the total duration of fasting increase on waxy maize compared with uncooked cornstarch. The mean duration of overnight fasting on traditional cornstarch prior to the study for the cohort was 4.2 and 7.8 h on the extended release cornstarch for both the GSD Ia and Ib populations ($P < 0.001$ for all types; Figs. 3 and 4). All laboratory markers of metabolic control have remained stable in the chronically treated patients (Tables 1 and 2).

Fig. 2 Duration of fasting increase on waxy maize cornstarch compared with uncooked cornstarch (mean = 3.7 ± 0.9 h)

Discussion

Prior to the description of continuous glucose therapy for treatment of GSD I, most patients with glycogen storage disease did not survive (Crigler and Folkman 1977). With the introduction of cornstarch therapy in 1982, the prognosis for children and adults with GSD I improved, but dosing every 3–5 h has been required to achieve optimal metabolic

Fig. 3 Duration of fasting with uncooked cornstarch (mean = 4.2 ± 0.5 h) and waxy maize cornstarch (mean = 7.9 ± 0.8 h) for glycogen storage disease type Ia

Fig. 4 Duration of fasting with uncooked cornstarch (mean = 4.2 ± 0.6 h) and waxy maize cornstarch (mean = 7.8 ± 0.9 h) for glycogen storage disease type Ib

control (Weinstein and Wolfsdorf 2002). Extended release waxy maize cornstarch was introduced in 2009 as the first new treatment for the hepatic GSDs, but the product was approved as a medical food based solely upon short-term

studies (Bhattacharya et al. 2007). Long-term complications in GSD I can be delayed or prevented with achievement of optimal metabolic control (Beegle et al. 2015; Minarich et al. 2012; Tsilianidis et al. 2013; Wang et al. 2011). It is therefore imperative that outstanding metabolic control is maintained, and it is reassuring that the biochemical studies have remained stable in this cohort chronically treated with the new therapy.

As with traditional cornstarch, therapy with the extended release formulation must be individualized. Not all patients responded well when challenged with the extended release formulation. In fact, 10 (9 GSD Ia/1 GSD Ib) patients developed hypoglycemia within 5 h during the initial challenge, and therefore initiation of the therapy is recommended in an in-patient setting where close monitoring can occur. GSD Ia patients that failed typically were in the pubertal growth spurt. Active inflammatory bowel disease in both GSD Ia and Ib was also found to be associated with treatment failure, but it is not clear if this was due to abnormal absorption or increased metabolic demand. Exacerbations of inflammatory bowel disease with increased stool frequency and worsening inflammatory markers were the primary cause of treatment failure and discontinuation of the waxy maize cornstarch in the GSD Ib population. The increase in gastrointestinal problems contributed to the worse outcome in GSD Ib when compared with the GSD Ia population.

It is important to note that none of the published studies to date have investigated use of the extended release cornstarch in children under 5 years of age. Hypoglycemia in younger children has been associated with increased neurologic sequelae (Flykanak-Gantenbein 2004), and use in this vulnerable population cannot be recommended until a study has been performed. Similarly, there have been very limited data published to date on daytime use of the waxy maize cornstarch (Bhattacharya et al. 2015). Formal investigation of daytime use is warranted since higher energy demands during the day may not be adequately covered with the slower release therapy.

The extended release cornstarch appears to improve quality of life without sacrificing metabolic control. Since the middle-of-the-night dose of cornstarch is avoided, fewer episodes of overnight hypoglycemia may result and should improve compliance in teenagers and young adults who historically have struggled with transitioning to independence (Storch et al. 2008). While the therapy appears to be safer than traditional cornstarch, administration of the product is critical, and missed therapy can have dire consequences as occurred with the death of a 13-year-old young man followed as part of this study. His death occurred after he missed his overnight dose of the waxy maize therapy, and he experienced severe hypoglycemia the next morning which led to seizure and ultimately his

Table 1 Glycogen storage disease type Ia metabolic markers before and after extended release cornstarch therapy

	Pre-therapy [mean $\pm$ SD (<i>n</i> = 41)]	Pre-therapy median	Pre-therapy range	Post-therapy (12 months) [mean $\pm$ SD (<i>n</i> = 41)]	Post-therapy median	Post-therapy range	<i>P</i> - value
AST (U/L)	29.7 $\pm$ 10.9	26	16–65	32.0 $\pm$ 17.7	29	9–97	0.43
ALT (U/L)	27.0 $\pm$ 17.0	22	7–89	31.9 $\pm$ 25.9	24	7–153	0.23
Cholesterol (mg/dL)	179.6 $\pm$ 42.5	177	95–285	187.1 $\pm$ 43.8	188	99–279	0.18
Triglycerides (mg/dL)	265.2 $\pm$ 147.3	235	77–732	293.8 $\pm$ 166.8	272	66–745	0.28
Uric acid (mg/dL)	6.2 $\pm$ 1.7	6.1	3.2–10.5	6.2 $\pm$ 1.7	6	3.1–10.5	0.96
Protein (g/dL)	7.2 $\pm$ 0.5	7.2	6.0–8.1	7.2 $\pm$ 0.4	7.2	6.6–8.9	0.98
Albumin (g/dL)	4.4 $\pm$ 0.3	4.3	3.7–5.0	4.4 $\pm$ 0.3	4.4	3.5–5.1	0.31

Table 2 Glycogen storage disease type Ib metabolic markers before and after extended release cornstarch therapy

	Pre-therapy [mean $\pm$ SD (<i>n</i> = 3)]	Pre-therapy median	Pre-therapy range	Post-therapy (12 months) [mean $\pm$ SD (<i>n</i> = 3)]	Post-therapy median	Post-therapy range	<i>P</i> - value
AST (U/L)	19.0 $\pm$ 5.6	18	14–25	18.3 $\pm$ 4.9	16	15–24	0.69
ALT (U/L)	8.7 $\pm$ 3.8	7	6–13	8.7 $\pm$ 0.6	9	8–9	1.00
Cholesterol (mg/dL)	98.3 $\pm$ 4.5	98	94–103	113.5 $\pm$ 21.9	114	98–129	0.40
Triglycerides (mg/dL)	95.7 $\pm$ 43.0	88	57–142	78.0 $\pm$ 24.0	78	61–95	0.17
Uric acid (mg/dL)	8.4 $\pm$ 1.1	8.6	7.2–9.4	7.1 $\pm$ 0.6	6.8	6.7–7.7	0.30
Protein (g/dL)	8.1 $\pm$ 0.6	8.1	7.5–8.7	7.5 $\pm$ 0.4	7.45	7.2–7.7	0.64
Albumin (g/dL)	4.0 $\pm$ 0.5	4.1	3.5–4.4	3.9 $\pm$ 0.4	4.1	3.5–4.2	0.42

demise. There is no difference between missed doses of traditional therapy and the extended release therapy, but the longer duration between doses increases the risk. The higher cost of the new therapy must also be considered as the extended release formulation is about 15 times more expensive than regular cornstarch (approximately \$8.00 per night compared with \$0.56 per night for regular cornstarch). However, an emergency department visit due to a missed overnight cornstarch dose would be more expensive than several years of the extended release formulation.

In conclusion, patients benefited from the extended release cornstarch by avoiding the overnight dose while maintaining metabolic control. Future studies are warranted, however, on daytime use and in younger children. Even with this reassuring experience, patients should continue to be followed closely until more experience has been gained with this therapy.

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Compliance with Ethics Guidelines

Conflict of Interest

Katalin M. Ross, Laurie M. Brown, Michelle M. Corrado, Tayoot Chengsupanimit, Latravia M. Curry, Iris A. Ferrecchia, Laura Y. Porras, Justin T. Mathew, and David A. Weinstein declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki

Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Details of the Contributions of Individual Authors

Katalin Ross designed the research study, conducted the research, and contributed to the data collection, data analysis, writing of the manuscript, and approval of the final content of manuscript.

Laurie Brown conducted the research, data analysis, data collection, writing of the manuscript, and approval of the final content of manuscript.

Michele Corrado designed the research study and data analysis and contributed to the data collection, writing of the manuscript, and approval of the final content of manuscript.

Tayoot Chongsupanimit contributed with the data analysis, writing of the manuscript, and approval of the final content of manuscript.

Latravia Curry contributed to the data collection, data analysis, writing of the manuscript, and approval of the final content of manuscript.

Iris Ferrecchia contributed to the data collection, data analysis, writing of the manuscript, and approval of the final content of manuscript.

Laura Porras contributed to the data collection, data analysis, writing of the manuscript, and approval of the final content of manuscript.

Justin Mathew contributed with the statistical analysis, writing of the manuscript, and approval of the final content of manuscript.

David Weinstein designed the research study, conducted the research, and contributed to the data collection, data analysis, writing of the manuscript, and approval of the final content of manuscript.

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