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BRIEF REPORT

Treatment of cystinosis with delayed-release cysteamine: 6-year follow-up

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Abstract
Background Patients with nephropathic cystinosis are required to take 6-hourly immediate-release cysteamine (Cystagon®) to reduce disease progression. This arduous regimen affects quality of life, disrupts sleep, and may result in non-compliance with therapy. Enteric-coated cysteamine bitartrate (EC-cysteamine) was developed as a "proof-of-concept" formulation for twice-daily ingestion. Previous reports have shown this therapy to be effective up to a mean of 14 months.
Case-Diagnosis/Treatment Two subjects (aged 13 and 15 years) received EC-cysteamine for 5–6 years at 60–65 % of their previous total daily dose of immediate-release cysteamine given at 6-h intervals. White blood cell (WBC) cystine levels were monitored every 1–3 months.
Conclusion The administration of EC-cysteamine did not result in any change in mean trough WBC cystine levels or any deterioration in the estimated glomerular filtration rate, thyroid, or liver function, suggesting that delayed-release, twice-daily EC-cysteamine is an effective long-term treatment alternative to immediate-release cysteamine given at 6-h intervals.

Introduction

Nephropathic cystinosis, a disorder characterized by the intralysosomal accumulation of cystine, is associated with progressive renal failure and, without specific therapy, renal transplantation before 10 years of age [1]. To date, the only specific treatment for cystinosis that lowers intracellular cystine throughout the day is treatment with 6-hourly cysteamine bitartrate (Cystagon®; Mylan, Morgantown, WV) [2]. Lifelong cysteamine therapy reduces the rate of deterioration of renal and thyroid failure and improves growth in children [3–5]. Cysteamine has been associated with gastric-acid hypersecretion, gastrointestinal symptoms, halitosis, and body odor [6, 7]. For these reasons it is not surprising that poor compliance with therapy may ensue, leading to earlier transplantation, poor growth, and perhaps to irreversible motor dysfunction in older patients [8, 9].

In an earlier study, Dohil et al. [10] showed that cysteamine delivered directly into the small intestine (SI) through a tube improved drug absorption and resulted in sustained suppression of white blood cell (WBC) cystine levels (a surrogate marker of drug efficacy with an optimum level of <1 nmol half-cystine/mg protein) [10]. Based on these results, we hypothesized that the targeted release of cysteamine in the SI may require fewer daily doses and developed a "proof of concept" delayed-release formulation [11, 12]. We recently reported the effective use of a twice-daily enteric-coated cysteamine (EC-cysteamine) for the treatment of cystinosis in children. Although intended initially to last for only 1 month, the same study now continues into its sixth year. We report the outcomes for two patients who remain in this study.

Methods

The University of California at San Diego (UCSD) Human Research Protection Program approved this study, and informed consent was obtained for each participant.

Subjects

Two children with cystinosis who had participated in a previous study chose to remain on EC-cysteamine therapy indefinitely. Patients were able to swallow capsules, and relevant clinical

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data (growth parameters, WBC cystine levels, chemistry, thyroid, and liver function tests, blood count, and urinalysis) were obtained every 2–3 months. Serum creatinine was measured and used to estimate the glomerular filtration rate [eGFR; calculated using a length of 0.413 (cm)/plasma creatinine (mg/dl)] [13].

Enteric-release cysteamine bitartrate

Commercially available immediate-release cysteamine bitartrate capsules (50 and 150 mg) were altered so they would disperse at pH 5.5–6. This was achieved by coating the capsules with Eudragit L30D 55 (Rohm GmbH & Co KG, Darmstadt, Germany) at The Coating Place Inc. (Verona, WI) using the Model 600 Wurster unit, producing EC-cystamine capsules. Fresh batches of cysteamine capsules were coated every year and expired capsules were discarded.

WBC cystine

White blood cell cystine levels were measured 11–12 h post-EC-cysteamine every 1–3 months. Leukocytes were prepared locally and shipped to the UCSD Cystine Determination Laboratory. WBC cystine levels were measured using tandem mass spectroscopy (API 4000 LC/MS/MS; Applied Biosystems, Foster City, CA) [14].

Results

At the time of writing, two patients with cystinosis, one female and one male, had received EC-cysteamine for 70 and 57 months, respectively. After initial dose titration, we determined that 60–65 % of the previous total daily dose of 6-hourly immediate-release cysteamine was required to maintain a WBC cystine level of <1 nmol half-cystine/mg protein. It was not necessary to change the drug dosage thereafter. Both patients took regular electrolyte replacement therapy, but neither took thyroxine. Twice-daily therapy was more manageable than 6-hourly cysteamine for both patients, who also reported better sleep patterns and less disruption during their daily routines in order to take cysteamine.

Patient no. 1

A 21-year-old female who has not undergone renal transplantation entered the study at 15 years of age. She was diagnosed with cystinosis at 1 year of life, and genotyping revealed her to be compound heterozygous for the 57-kb deletion and the nonsense mutation in exon 7 (c.414G>A- p.Thr138X) [15]. With these severe mutations she is unlikely to produce any cystinosin. She had previously been compliant with immediate-release cysteamine therapy, but had complained of nocturnal enuresis and mild intermittent abdominal pain. The abdominal pain was perimublical, unrelated to the timing of medication ingestion and may have been related to stress. Her symptoms did not respond to acid-suppression therapy. A diagnosis of irritable bowel syndrome was made. Parents regularly noticed body odor and halitosis. Before entering the study she took immediate-release cysteamine 500 mg every 6 h. Following initial dose titration she was treated with EC-cysteamine 600 mg twice daily for almost 6 years. About 25 months into the study she developed Henoch–Schönlein purpura (HSP) with associated immunoglobulin A (IgA)-associated mesangial proliferative glomerulitis. She commenced steroid therapy and her renal function gradually returned to baseline levels. During the 6-year treatment with EC-cysteamine her mean pre-dose WBC cystine level was 0.61 (standard error of the mean±0.1; n=27) nmol half-cystine/mg protein (see Fig. 1). For the 4-year period before entering the study, while on 6-hourly immediate-release cysteamine therapy, her pre-dose WBC cystine level was 0.6 (±0.1; n=8). Her eGFR and thyroid stimulating hormone (TSH) levels in 2006 and 2012 were 54 and 53 ml/min/1.73 m^2 and 0.99 and 1.14 uIU/ml, respectively (reference range 0.45–4.5 uIU/ml). Urinary protein level shortly before the HSP event in 2008 was 17 mg/dl (reference range 0–15 mg/dl); in 2012 it was 64.7 mg/dl. Liver function remained normal and her menstruation was regular. Her parents felt that her odor and halitosis were less noticeable (see Table 1). This subject had never received growth hormone and her height remained unchanged at 158 cm throughout the duration of the study. Her weight gain had been satisfactory until she moved away from home for college.

Patient no. 2

An 18-year-old male was diagnosed with cystinosis at 5 years of age and had undergone renal transplantation at

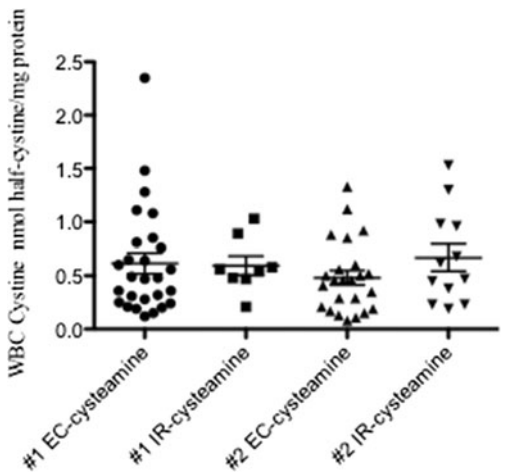

Fig. 1 White blood cell (*WBC*) cystine levels in both subjects during treatment with enteric-coated (*EC*) cysteamine for 5–6 years and immediate-release (*IR*) cysteamine for 4 years before entering the study

Table 1 Parents'/subjects' impressions on how the twice-daily formulation has impacted their lives

- Uninterrupted sleep has had positive effect on a number of different levels: physical, alertness, academic performance.
- A heightened awareness of control and influence over his schedule.
- We believe the emotional/psychological benefits are equal to, if not more, than the physical benefits.
- Have not noticed a significant reduction in odor, but there seems to be a lessening in terms of intensity over a period of time.
- Taking medications twice daily also reduces the number of occasions when the odor is strongest.

age 9 years. He entered the study at 13 years of age and required EC-cysteamine 650 mg twice daily. He had previously taken immediate-release cysteamine 500 mg every 6 h and was asymptomatic. Two months after entering the study he developed humoral rejection with positive donor-specific antibodies to the kidney. He responded initially to immunemodulation and plasmaphoresis therapy, but his baseline creatinine levels remained mildly elevated. He continued to take EC-cysteamine. About 2 years after entering the study he developed hypertension and increasing creatine levels, which culminated in him undergoing repeat kidney transplantation. EC-cysteamine therapy was stopped for a 3-month period during this time and restarted in June 2010. During almost 5 years of treatment with EC-cysteamine his mean pre-dose WBC cystine level was 0.48 (±0.07; n=24) nmol half-cystine/mg protein, while for 4 years before the study, while taking immediate-release cysteamine, his pre-dose mean WBC cystine level was 0.67 (±0.13; n=12) (see Fig. 1). His eGFR and TSH levels in 2007 and 2012 were 63 and 62 ml/min/1.73 m^2 and 1.89 and 1.64 uIU/ml, respectively. Urinary protein level in 2007 and 2012 was 17 and 12 mg/dl, respectively. His liver function tests remained normal. This subject received growth hormone therapy for 5 years up until his first renal transplant. He grew 13.2 cm (final height 165 cm). Before and during the study period the subject had not complained of gastrointestinal pain and did not require acid-suppression therapy. Body odor and halitosis were problems which were more frequently noticeable on immediate-release cysteamine than with EC-Cysteamine (see Table 1).

Discussion

Although the initial "proof of concept" study using twice-daily EC-cysteamine was intended to last for only 1 month, two subjects requested to have the study prolonged and are still being treated 5–6 years later. Both subjects have reported an improvement in quality of life on twice-daily cysteamine and are sleeping throughout the night. Neither subject has reported significant gastrointestinal symptoms related to therapy. The female subject started college 3 years ago and also has a diagnosis of mild irritable bowel syndrome. Twice-daily cysteamine has made her cystinosis therapy more manageable since leaving home. The younger male subject will start college soon and will hopefully also be able to manage his own cystinosis therapy. Twice-daily cysteamine has improved the likelihood of compliance with therapy in these young adults, particularly as they transition to full independence.

Unfortunately, subject no. 2 developed humoral rejection of his transplanted kidney 2 months after starting the study and did eventually require repeat transplantation 2 years later. Despite this, his growth during the 5 years of EC-cysteamine therapy has been very good. Although cystinosis is not thought to occur in the transplanted kidney, the disease does continue to involve other body organs, which was the primary reason for continuing EC-cysteamine therapy.

Although twice-daily EC-cysteamine has proven effective in maintaining low WBC cystine levels, the actual process of producing enterically coated cysteamine capsules for the purpose of this study has been laborious and expensive. Fresh batches of EC-cysteamine were coated every year. Typically during each coating process the integrity of over 40 % of the capsules would be breached, rendering the capsule useless. These damaged capsules were individually picked out by hand from the batches before being dispatched from the coating facility. Ingestion of mildly damaged capsules that are not identified may result in abnormal drug bioavailability and inadequate WBC cystine control. A new twice-daily microspheronized "bead" cysteamine bitartrate delayed-release formulation has recently been developed and shown in a clinical study to be as effective as immediate-release 6 hourly cysteamine in depleting WBC cystine levels [16]. These "beads" will be ingestible by all age groups (or placed through a gastrostomy tube) and not just by patients who are able to swallow whole capsules. They will also deliver cysteamine in a more "controlled" fashion to the small intestine than we believe is possible with the proof-of-concept EC-cysteamine formulation.

Body odor and halitosis are commonly reported in those patients who receive regular cysteamine therapy and is thought to be due to dimethylsulfide (DMS) production. The peak DMS levels usually follow peak plasma cysteamine levels [17]. A recent study compared DMS levels in four subjects following ingestion of immediate-release cysteamine and cysteamine bitartrate delayed-release administered as microspheronized beads. Although the plasma cysteamine concentration/time area under curve (AUC) estimates were the same for both formulations, the DMS concentration/time AUC was lower following the ingestion of cysteamine bitartrate delayed-release beads [18]. This study helps to explain why halitosis and body odor were less apparent in patient no. 1.

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Conflict of interest statement The University of California, San Diego has a financial interest in Raptor Pharmaceutics, the company sponsoring this research. Dr Dohil and the University of California may financially benefit from this interest if the company is successful in developing and marketing a cysteamine product for the treatment of cystinosis. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. Betty Cabrera does not have any conflict of interest.

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