HHS Public Access

Author manuscript

Mol Genet Metab. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Mol Genet Metab. 2015 ; 116(0): 75–79. doi:10.1016/j.ymgme.2015.07.001.

Intrathecal 2-Hydroxypropyl-Beta-Cyclodextrin in a Single Patient with Niemann-Pick C1

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Abstract

Niemann-Pick C, Type 1 (NPC1) is a progressive autosomal recessive neurologic disease caused by defective intracellular cholesterol and lipid trafficking. There are currently no United States Food and Drug Administration approved treatments for NPC1. We undertook a study evaluating the safety, efficacy, and biomarker response of intrathecal 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) in a 12-year old subject with mildly symptomatic NPC. The subject received 200mg intrathecal HP-β-CD administered biweekly via lumbar puncture. To date the subject has received 27 intrathecal HP-β-CD injections. Intrathecal HP-β-CD has been generally safe and well tolerated in this subject. There has been improvement in vertical gaze. The subject has developed subclinical hearing loss at high frequency that is likely HP-β-CD related. Plasma 24-(S)-hydroxycholesterol, a pharmacodynamic biomarker for cholesterol redistribution in the central nervous system, was significantly increased in response to each of the first 5 drug administrations. Further dosing as well as dose escalations are needed to more completely ascertain the safety and efficacy of intrathecal HP-β-CD.

Keywords

Niemann Pick C; Cyclodextrin; Therapeutic; Ototoxicity

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1. Introduction[1]

Niemann-Pick C is an autosomal recessive condition that is caused by defective intracellular cholesterol and lipid trafficking. The incidence of NPC is estimated to be approximately 1/100,000 live births. The disorder is caused most often by mutations of the *NPC1* (about 95% of cases) or the *NPC2* genes (about 5% of cases) [1]. The clinical presentation of NPC type 1 (NPC1) is heterogeneous, with onset ranging from the perinatal period to advanced age [2]. Initial manifestations may be neurologic, psychiatric, or hepatic. Later in the disease course the neurologic manifestations predominate and consist of progressive cerebellar ataxia, dysarthria, dysphagia, dementia, and premature death [3].

There are currently no United States Food and Drug Administration (FDA) approved therapies that slow or reverse the neurologic effects of NPC1. Miglustat (Zavesca®), an iminosugar molecule that decreases the production of glycosphingolipids and is approved in more than 40 countries outside the United States, shows limited benefit in treatment of NPC disease [4,5]. Other than miglustat, only supportive and palliative therapies exist for the treatment of individuals with NPC1.

Recent data from animal model studies suggest that 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) may ameliorate the neurologic effects of NPC1. HP-β-CD is a cyclic oligosaccharide with a hydrophobic interior, which has been shown to promote redistribution of lysosomal cholesterol in NPC cells. Subcutaneous injection of high doses HP-β-CD has been shown to be effective in pre-clinical studies despite the fact that the substance has been found to cross the blood-brain barrier of mice inefficiently (~1%) [6]. Direct injection of HP-β-CD into the ventricular system of NPC1 mice had a more striking effect, mobilizing cellular cholesterol (which is in excess due to the metabolic defect), decreasing cerebellar Purkinje cell loss, reducing the clinical effects of the disease, and prolonging survival [7–10]. A more recent study found that HP-β-CD injected directly into the cisterna magna of cats prevented the onset of pre-symptomatic cerebellar dysfunction but was found to produce an increase in hearing threshold [11, 12]. Intrathecal HP-β-CD was similarly found to produce dose-dependent ototoxicity in mice as well [13]. The only published human studies of HP-β-CD involved the administration of intravenous and then intracerebroventricular HP-β-CD to Japanese patients with advanced disease. The authors found that intravenous HP-β-CD yielded only partial and transient neurologic improvements in two individuals and may have led to transient pulmonary toxicity [14]. Intracerebroventricular HP-β-CD may have prevented further neurologic deterioration in a single patient with severe disease and was not associated with pulmonary or auditory toxicity [15].

Our study seeks to evaluate the safety of twice monthly intrathecal HP-β-CD in a single patient with NPC1. We hypothesize that intrathecal HP-β-CD will stabilize or slow disease progression as based on clinical and biomarker analysis.

[1]NPC1: Niemann-Pick C, Type 1
HP-β-CD: 2-hydroxypropyl-beta-cyclodextrin
IND: investigational new drug
CSF: Cerebrospinal fluid

2. Methods

2.1 Consent

Approval of the protocol was obtained from the John R. Wolf Human Subjects Committee at the Los Angeles Biomedical Research Institute at Harbor-UCLA prior to initiating treatment. The study drug was administered under an individual investigational new drug (IND) application filed with the FDA (IND 119,208). Informed consent was provided by the subject's guardians and assent was provided by the subject.

2.2 Subject

The subject is a 12 year old male who developed hepatosplenomegaly and jaundice at 6 weeks of life. A liver biopsy at that time revealed cholesterol accumulation in hepatocytes. Subsequent molecular testing confirmed the diagnosis of NPC1, revealing two pathogenic mutations in the *NPC1* gene (c.2660 C>T [P887L], c.3741_3744delACTC [L1247fs]).

The subject was evaluated at the National Institutes of Health at age 4 years 8 months, while on miglustat, and was noted at that time to have normal gross and fine motor skills, no hyperreflexia, and minor speech slurring. At 5 years 8 months he was found to have mild vertical gaze palsy and lower extremity hyperreflexia. At age 9 years, he was noted to have deficits in receptive and expressive communications. His performance in school diminished and a school psychologist found deficiencies in following directions and in concentration. At age 11 years, he was found to have dysdiadochokinesia, mild gait ataxia, vertical gaze palsy, abnormal saccades, and impairment in fine motor skills. The subject was enrolled in the study in December 2013 at age 11 years.

2.3 Study Protocol

The study protocol called for the administration of 200 mg intrathecal HP-β-CD every 14 +/− 3 days over the course of 5 years. The initial dose of 200 mg intrathecally was determined based on preclinical toxicology studies in cats and juvenile beagle dogs conducted by the Therapeutics for Rare and Neglected Diseases program, NCATS, NIH and collaborators. Dose escalations were planned based on safety and tolerability of the study drug.

HP-β-CD was formulated as a 200 mg/mL injectable solution (Janssen Research & Development, LLC, New Jersey, USA). 1 mL drug was gently mixed with 9 mL of sterile 0.9% saline (Hospira, Illinois, USA, endotoxin level ≤0.25 EU/mL, final volume 10 mL). The first intrathecal injection consisted of saline and acted as a control. Thereafter, the subject received HP-β-CD twice monthly administered intrathecally by lumbar injection.

For the study procedure, the subject was admitted to an inpatient unit of the Harbor-UCLA Medical Center for administration of the study medication and was monitored for approximately 24 hours post dosage. Sedation was provided with 0.25 mg/kg oral midazolam. For the lumbar injection the subject was placed in the right lateral decubitus position. Topical and subcutaneous lidocaine were administered. A 22-gauge needle was used to penetrate the subarachnoid space. The opening pressure was measured via manometry. Approximately 6–10 mL of cerebrospinal fluid was removed to accommodate

the HP-β-CD solution and for laboratory and biomarker evaluations. HP-β-CD was then administered via slow push over 3–5 minutes. Vital signs were monitored until the subject fully recovered from sedation.

2.4 Toxicity

Toxicity was monitored before and after each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (version-4). Audiograms were carried out by an audiologist approximately 24 hours following each administration of the study drug. Electrocardiograms were obtained both pre and post HP-β-CD dosing for each drug administration.

Our protocol called for a discussion with the subject's guardians about the potential risk of continuation should grade I or II acute ototoxicity develop, given the known connection between HP-β-CD and ototoxicity. In the event of a grade III CTCAE event, dose de-escalation and consideration of study withdrawal were to be considered.

2.5 Assessments

2.5.1 Medical History and Physical/Neurological Examination—Interval history and physical examination were performed at baseline and with each subsequent treatment with intrathecal HP-β-CD. The subject also received assessments of interval history and physical examinations 24 and 72 hours post HP-β-CD dosing to determine whether adverse events had occurred.

2.5.2 NPC1 Severity Scale—Measurement of the NIH NPC1 severity scale was carried out semiannually. Briefly described, this validated scoring system consists of clinical signs and symptoms in nine major domains (ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, and swallowing, scored 0–5) and eight minor domains (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, and respiratory problems, scored 0–2). The value of this score is expected to increase linearly with age [16].

2.5.3 Audiologic Testing—Pure tone audiometry assessments were performed at baseline and then at every dosing visit, or sooner if there was concern of hearing loss. Brainstem auditory response was performed at baseline and every 6 months after initiation of dosing.

2.5.4 Speech and Swallowing Evaluation—Evaluations of functional speech, swallowing and eating abilities were conducted at baseline and every 6 months. In addition, a fluoroscopic swallowing study was obtained and obtained at baseline and every 6 months by an otolaryngologist.

2.5.5 Laboratory and Biomarker Assessment—Complete blood counts with differential, chemistry panels, liver function panels, lipid panels, and coagulation studies were measured at baseline and prior to each dosing of intrathecal HP-β-CD.

Biomarker analysis included plasma and cerebrospinal (CSF) 24-(S)-hydroxycholesterol, plasma and CSF oxysterols, CSF protein biomarkers, CSF markers of inflammation, CSF markers of oxidative stress, and CSF markers of neuronal damage. These biomarkers have been previously shown to be altered in NPC1 animal models and humans [7, 17–19]. Measurement of 24-(S)-hydroxycholesterol was carried out as previously described [20].

2.5.6 Imaging Assessment—3.0 Tesla magnetic resonance imaging (MRI) of the brain, magnetic resonance spectroscopy and diffusion tensor imaging were performed at baseline and every 6 months during therapy using a General Electric Discovery MR scanner. The MRI utilized a 16-channel transmit-receive head coil. Sequences acquired included 3-dimensional fast-spoiled gradient recalled-echo, axial proton density, axial T2, axial fluid attenuated inversion recovery, MR spectroscopy and diffusion tensor imaging. Measurements were compared to age-matched normative controls.

3. Results

To date our subject has received 27 treatments with 200mg intrathecal HP-β-CD over the course of 1.5 years. The results of routine chemistry tests, serum lipid measurements, complete blood counts, and liver function studies have remained unchanged from baseline. HP-β-CD has been generally safe and well tolerated (Table 1). The adverse events have included headache, nausea and vomiting. The headache is typical of a post-lumbar puncture headache and typically resolves with the subject lying flat.

The subject has developed an increase in hearing threshold at 8 kHz bilaterally, more significant in the right ear than the left (Figure 1). This increase in hearing threshold meets criteria for a grade I adverse event. Similar effects were not observed at lower frequencies of hearing. The subject and his parents have not reported subjective hearing changes or audiologic symptoms since the beginning the treatment.

There has been improvement in the subject’s vertical gaze. Vertical saccades, which were not present at the initiation of the study due to vertical gaze paralysis, became present but were slow. The horizontal saccadic eye movements were present, but slow at baseline and showed intermittent improvement. Otherwise the subject’s neurologic exam remains unchanged. The gait ataxia persists. The imaging findings, auditory brainstem response, and speech and swallow function are unchanged.

The NPC1 severity score has improved from 7, prior to the initiation of treatment, to 6, measured after 14 months of study enrollment (Table 2). These values indicate mild disease. The subject had a 1 point improvement in eye movement. The subject experienced hearing loss, which would normally prompt an increase in the NPC severity score by one point. However, the high frequency hearing loss that was observed bilaterally was felt by the investigators to be due to the study drug rather than progression of the subject’s underlying disease. As a result no points were recorded for this category of scoring on follow up examinations. Scores for the other categories of this scale remained unchanged.

Our biomarker analysis consists of measurement of plasma 24-(S)-hydroxycholesterol in the initial treatment with saline as well as the first 5 administrations of HP-β-CD. This

pharmacodynamic biomarker increased significantly following dosing of HP-β-CD when compared to the baseline saline infusion, indicative of target engagement and cholesterol redistribution in the central nervous system (Figure 2).

Discussion

The goals of our study were to determine the safety, efficacy, and biomarker response of intrathecal HP-β-CD in a single subject with NPC1. To date our subject has received 27 infusions of semimonthly 200mg intrathecal HP-β-CD. Our initial results are significant for improvements in his supranuclear gaze palsy. There was a 1 point improvement in the NPC1 severity scale, once drug-related hearing loss was excluded from the score. The study drug was suspected to cause high frequency hearing loss that was subclinical. Plasma 24-(S)-hydroxycholesterol was elevated following the first 5 drug administrations.

Impairment of vertical gaze is a manifestation often noted early on in the course of NPC1. The vertical gaze in our subject was noted to be improved 3 months into treatment with HP-β-CD. However, the improvement was not noticed by the parents or the subject, and therefore it is difficult to interpret the clinical significance of this finding. Also we cannot exclude the possibility that the improvement is the effect of practice. Improvement in extraocular movements has also been observed in NPC1 patients treated with miglustat [4].

Dose-dependent ototoxicity has been observed in several NPC1 animal studies receiving HP-β-CD. Auditory dysfunction is also seen along the natural course of NPC1 [21]. As a result it may be difficult to determine with certainty whether ototixicity is HP-B-CD induced or rather a manifestation of the underlying disease. Our group believes that our subject's hearing loss was due primarily to HP-β-CD for two reasons. First, the high frequency hearing loss coincided with the initiation of intrathecal cyclodextrin therapy. Second, King et al. report that the severity of auditory dysfunction associated with NPC1 appears to correlate linearly with disease severity as measured by the NPC1 severity score. In their study, hearing impairment greater than 50dB at 8kHz was not seen in individuals with a NPC severity score less than 6.

In our subject two administrations of HP-β-CD were temporarily held (after doses 4 and 14) due to concerns of high frequency hearing loss. No significant improvement was seen on measurements of pure tone audiometry to suggest that postponing a dose had a significant effect on hearing threshold. The mechanism underlying HP-β-CD mediated ototoxicity is multifactorial, and based on mouse studies includes outer hair cell loss and more subtle changes to the architecture of the cochlear membrane [22]. This mechanism shares some qualities of aminoglycoside-induced ototoxicity. Therefore, an area of future investigation may include determining if otoprotective strategies, such as inhibition of apoptosis or neutralization of reactive oxygen species (both shown *in vitro* to be effective in preventing aminoglycoside mediated ototoxicity), are effective in mitigating HP-β-CD related hearing loss [23].

The mechanism by which HP-β-CD exerts its clinical effect remains incompletely understood. The accumulation of unesterified cholesterol in late endosomes and lysosomes,

which is characteristic of NPC1 cells, underlies the neurodegenerative phenotype [24]. Both *in vitro* and *in vivo* studies have shown that HP-β-CD restores the transport of cholesterol from the lysosome to endoplasmic reticulum [7, 25].

Ideal dosages, dosing intervals, and infusion rates of HP-β-CD remain undetermined. While the pharmacokinetics of intracerebroventricular HP-β-CD delivery in human NPC1 subjects has been studied, less is known regarding intrathecal delivery [26]. Our dosing interval of every two weeks and dosage of 200mg intrathecally were based on animal studies. Higher intrathecal doses are currently being administered in an ongoing NIH study. Higher infusion rates may be associated with pulmonary toxicity when cyclodextrin is administered intravenously [27–28]. We observed no pulmonary toxicity in our subject. A more complete understanding of the behavior of HP-β-CD in the central nervous system will be needed to determine the safest and most efficacious dosing.

A future direction into cyclodextrin-based therapies will focus on the safety and efficacy of structurally different cyclodextrins in NPC1. In a recent publication, 2-hydroxypropyl-gamma-cyclodextrin was found to more efficiently reduce the cholesterol accumulation and restore the functional abnormalities in induced pluripotent stem cell lines from NPC1 patients [29]. Preclinical studies have not yet been reported on this compound.

Conclusion

Our individual investigational new drug study contributes to our understanding of the use of HP-β-CD in human NPC1 subjects. We have shown that intrathecal HP-β-CD stabilized or possibly improved disease associated outcomes when administered intrathecally over 1.5 years in a single patient. Further dosages and dose-escalation of HP-β-CD are needed to more clearly ascertain the safety and efficacy of this drug in our patient. An ongoing Phase I trial at the NIH is examining the safety and exploring the efficacy of this compound across disease phenotypes and will assist in paving the way for a Phase II/III study that will determine the ideal dosage and efficacy for this therapy.

Acknowledgments

We are thankful for the assistance from Nathalia Cressey, Jun Zozobrado, Patricia Trejo, Daisy O'Brien, Cassandra Morris, Roxanne Tanoviceanu, Arlette Nazariansthe, and the Harbor UCLA pediatric nursing staff throughout the study. This study would not have been possible without the gracious cooperation of our study subject and his family.

The project described was supported by the National Center for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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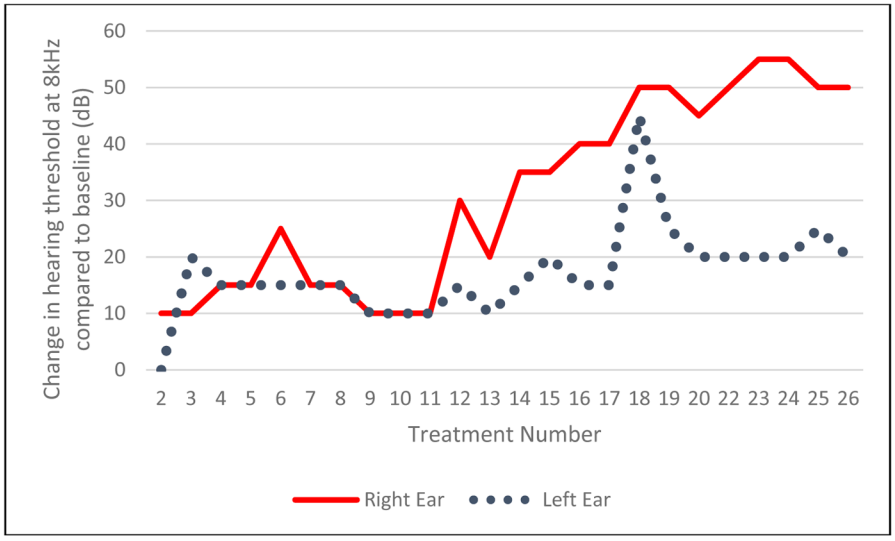

Figure 1.

Change in hearing threshold (in dB) at 8kHz compared to baseline. Audiometric evaluations were performed approximately 24 hours post HP-β-CD dosing. [1 column]

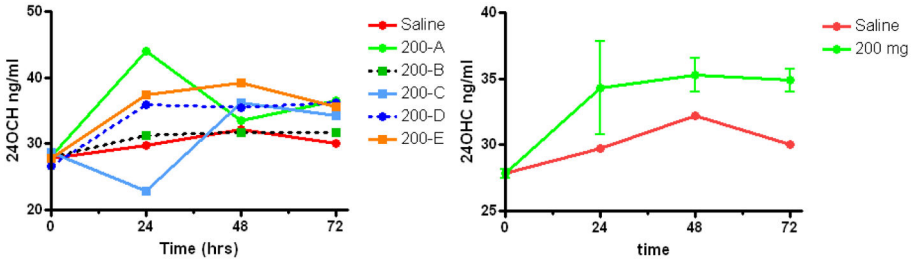

Figure 2.

24-(S)-hydroxycholesterol (24OCH) in plasma. Plasma was drawn at time=0 (pre-dose), 24, 48 and 72 hours post-dose. The first dose is 200-A, second dose 200-B, etc. Right, mean and standard deviation for plasma 24-OCH measurements across doses.

$AUC_{cyclodextrin} - AUC_{saline} = 243$ [2 columns]

Table 1

Adverse events over 27 treatments with IT HP-β-CD [1 column]

Adverse Event	Related to HP-β-CD?	Related to study procedure?	CTCAE grade	Outcome
Vomiting	Not related	Yes	I	Resolved
Headache when upright	Not related	Yes	I	Resolved
Epistaxis	Not related	No	I	Resolved
Headache	Not related	Yes	I	Resolved
Increased sleepiness	Probably not related	No	I	Resolved
Low platelet count (138,000 per mm3)	Probably not related	No	I	Resolved
Upper respiratory infection	Not related	No	I	Resolved
Abrasions on back	Not related	No	I	Resolved
Hearing loss > 20 dB at 8kHz in right ear	Probably	No	I	Ongoing
Hearing loss > 20dB at 8kHz in left ear	Probably	No	I	Ongoing
Buttock pain during lumbar puncture	Possibly related	Yes	I	Resolved
Chipped tooth and lip laceration	Not related	No	I	Resolved

Table 2

NPC1 severity scale at baseline compared to the most recent evaluation. ABR: auditory brainstem response. [1 column]

	12/17/2013	2/25/2015
Eye Movement	2	1
Speech	1	1
Fine Motor		
Skills	1	1
Hearing	0	0*
Seizure	0	0
Ambulation	1	1
Swallow	0	0
Cognition	1	1
Memory	0	0
Gelastic		
Cataplexy	0	0
Narcolepsy	0	0
Behavior	0	0
Psychiatric	0	0
Hyperreflexia	1	1
Incontinence	0	0
ABR	0	0
Respiratory	0	0
Total	7	6

* High frequency hearing loss was observed bilaterally, but this was felt by the investigators to be due to the study drug rather than progression of NPC1.