Intrathecal cyclodextrin in the treatment of Niemann-Pick disease type C

Maria Roch Santed,¹ Maria Josep Cabañas Poy,¹ Mireia Del Toro Riera,² Carme Cañete Ramírez,¹ Aurora Fernández Polo,¹ Susana Clemente Bautista¹

¹Pharmacy Department, Hospital Vall d'Hebron, Barcelona, Barcelona, Spain
²Pediatric Neurology Department, Hospital Vall d'Hebron, Barcelona, Barcelona, Spain

Correspondence to

Maria Roch Santed, Hospital Vall d'Hebron, Pharmacy department, Passeig de la Vall d'Hebron, 119-129, Barcelona, Barcelona 08035, Spain; maria24rs@gmail.com

Received 4 August 2016

Revised 7 October 2016

Accepted 19 October 2016

Published Online First

3 November 2016

EAHP Statement 3:
Production and
Compounding

ABSTRACT

Summary Case A child with Niemann-Pick disease type C was started on miglustat therapy at the age of 2 years. Intrathecal administration of hydroxypropyl- β -cyclodextrin was added 5 months later. The initial dose of 175 mg was gradually increased over the first 6 months to reach 325 mg. The drug was administered every 15 days, and the patient received 43 doses. A slight delay in progression of the disease was seen during the first year of intrathecal hydroxypropyl- β -cyclodextrin. However, additional symptoms have emerged since that time, suggesting a lack of effectiveness of the drug. Our patient has shown no drug-related adverse events.

Conclusions Intrathecal hydroxypropyl- β -cyclodextrin therapy is safe, but its efficacy seems questionable in a patient with the severe infantile form of Niemann-Pick disease type C.

of GM2 and GM3 gangliosides, glucosylceramide and lactosylceramide. The liver and brain are two of the most highly affected organs in NP-C. An accumulation of free cholesterol, sphingomyelin, phospholipids and glycolipids predominates in liver cells, whereas glucosylceramides, gangliosides and lactosylceramides additionally accumulate in the brain. This would explain why miglustat has led to reductions in the neurological progression of the disease in some cases, but has not proven to be equally effective for the cholestasis and other systemic symptoms.

Recent data suggested that hydroxypropyl- β -cyclodextrin (HPBCD) may minimise neurological damage in NP-C and could be a new line of treatment that may improve the symptoms and delay the disease progression.

The objective of this report is to describe the efficacy and safety of the intrathecal (IT) administration of HPBCD in a patient with a severe early infantile form of NP-C.

BACKGROUND

Niemann-Pick disease type C (NP-C) is a neurodegenerative disease transmitted by autosomal recessive inheritance; the main signs and symptoms include splenomegaly and neurological deterioration. NP-C, which can present from the perinatal period up to adulthood, has been classified according to the age at onset into a severe early infantile form (onset <2 years), late infantile form (onset 3–5 years), juvenile form (onset 5–16 years) and adult form (onset >16 years).¹

The disease encompasses two genotypes related to mutations in the NPC1 (95%) and NPC2 (5%) genes.¹ Changes in these genes result in an accumulation of unesterified cholesterol and glycolipids in the lysosomal system. Around 85% of patients with NP-C have hepatosplenomegaly and neurological abnormalities (eg, ataxia, dysphagia, cognitive deterioration, vertical supranuclear gaze palsy, psychiatric disorder, epilepsy). The prognosis of the condition varies, with the most severe form presenting within the first 2 years of life.

Various disability scales have been developed to evaluate the severity of NP-C and to monitor its progression and the effect of the treatment received. One example of a widely used, specific NP-C disability rating scale, and the one used in this study, is shown in figure 1.²

None of the currently available treatments can detain or reverse the course of NP-C. Therapy is based on symptomatic treatment and administration of miglustat, a glucosylceramide synthase inhibitor that reduces glycolipid synthesis in cells. In addition, miglustat decreases the cellular accumulation

CASE PRESENTATION

A 12-month-old girl was hospitalised for the first time in our centre to investigate hepatosplenomegaly and thrombocytopenia. In addition to spleen and liver enlargement, the physical examination disclosed mild bilateral inner ear involvement and a delay in acquiring normal milestone skills (eg, she did not change position or crawl, could not stand, showed deficient comprehension). She was referred to the hospital neurology department to exclude a possible metabolic disease.

Based on the findings of hepatosplenomegaly and neurological involvement, a deposition disease was suspected. MRI of the brain showed mild cerebral atrophy, with marked diffuse thinning of the corpus callosum and bilateral periventricular white matter lesions in the parietal lobes, findings that have been described in NP-C (figure 2). To confirm the diagnosis, the filipin test was carried out, and cDNA was extracted from cultured fibroblasts in order to be able to detect mutations related to this disease. The patient has two mutations in her genotype, a c.319delC mutation and a mutation at nucleotide +5 at intron 18. At that time, she was 19 months old, she had lost the capacity to stand and walk, she sat with support, manipulated with both hands, showed tremor in her upper limbs and did not speak at all; the score on the modified NP-C disability scale was 11.

At 22 months of age, miglustat therapy was started in the patient's referral hospital. Because of the lack of response after 5 months of treatment, the decision was taken to add IT HPBCD therapy

CrossMark

To cite: Roch Santed M, Cabañas Poy MJ, Del Toro Riera M, et al. *Eur J Hosp Pharm* 2017;24:185–188.

Disability scale			
1. Ambulation	Score	4. Language	Score
Clumsiness	1	Delayed acquisitions	1
Autonomous ataxic gait	2	Mild dysarthria (understandable)	2
Outdoor assisted ambulation	3	Severe dysarthria (only comprehensible to some members of the family)	3
Indoor assisted ambulation	4	Non-verbal communication	4
Wheelchair-bound	5	Absence of communication	5
2. Manipulation	Score	5. Swallowing	Score
Tremor	1	Abnormal chewing	1
Slight dysmetria/dystonia (allows autonomous manipulation)	2	Occasional dysphagia	2
Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	3	Daily dysphagia	3
Severe dysmetria/dystonia (requires assistance in all activities)	4	Nasogastric tube or gastric button feeding	4
3. Seizures	Score	6. Ocular movements	Score
Occasional seizures	1	Slow ocular pursuit	1
Seizures with antiepileptic drugs	2	Vertical ophthalmoplegia	2
Seizures resistant to antiepileptic drugs	3	Complete ophthalmoplegia	3

Figure 1 Modified disability rating scale (Pineda *et al*²), extended from the original developed by Iturriaga *et al*¹ in 2006.

Figure 2 MRI at 18 months of age. (A) Midline sagittal T1-weighted image. The image shows mild cerebral atrophy, with marked diffuse thinning of the corpus callosum (arrow). (B) Midline axial T2-weighted image. Ventriculomegaly (arrow) and bilateral periventricular white matter lesions (circles) are seen in the parietal lobes.

in our centre. She presented with generalised hypotonia, and the score on the disability scale at that time was 14. Before IT HPBCD therapy was started, a clinical report was drafted and submitted for evaluation by the committee for off-label drug use in our hospital. Following this assessment, the hospital directorate approved the use of the drug in the specific case presented, and the patient's parents provided written informed consent for the treatment.

A total of 43 IT HPBCD injections were administered. The initial HPBCD dose, 175 mg, was gradually increased over the first 6 months up to 325 mg, which was maintained until the end of treatment. The drug was administered every 15 days in the polyvalent paediatric day hospital of our centre.

At 7 months after the start of miglustat therapy, the drug was discontinued because the patient experienced diarrhoea with marked weight loss. However, it was restarted 3 months later. Her symptoms improved after administration of the first HPBCD doses (greater visual contact, improved motor function) and there was a slight retardation of disease progression in the first 12 months of therapy, with an increase of only 1 point on the disability scale (score, 15).

Nonetheless, she has shown progressive clinical deterioration since that time (development of epilepsy with uncontrolled epileptic seizures requiring changes in her antiepileptic regimen, dysphagia, and worsening motor function), indicating that HPBCD is not effective. MRI at the age of 30 months showed progression of cerebral atrophy, which was more prominent in the occipital lobe (figure 3). A year and 8 months after the start of treatment, IT HPBCD was suspended, because of general worsening, spastic tetraparesis and progressive deterioration with a disability scale of 18.

The IT formula was prepared from Trappsol Cyclo 100 mL vials containing an HPBCD concentration of 250 mg/mL (CTD Holdings, USA). To purchase this material, importation was requested through the Spanish Medicines Agency (drug management in special situations) following hospital directorate approval and confirmation of availability by the European distributor (Medical Need Europe AB).

The formula was prepared by the hospital pharmacy department under aseptic conditions in a horizontal laminar flow cabinet (ISO class 5) to ensure a sterile preparation free from pyrogens. Trappsol Cyclo first underwent filtration through a 0.22 µm pore size filter. Depending on the dose prescribed, the required volume of this material was then diluted with physiological saline solution (0.9%) to reach a final volume of 3 mL.

Figure 3 MRI at 30 months of age. (A) Midline sagittal T1-weighted image. (B) Midline axial T2-weighted image. The figure shows progression of the cerebral atrophy, which is more prominent in the occipital lobe.

The pH and osmolality of Trappsol Cyclo (250 mg/mL) in the initial preparation used (175 mg/3 mL) and the final preparation (325 mg/3 mL) were determined. The pH values obtained were 6.6, 5.7 and 5.8, respectively, and osmolality values were 312, 284 and 286 mOsm/kg, respectively, indicating that the pH of the preparations did not significantly differ from that of cerebrospinal fluid (CSF) (7.32) and the osmolality was comparable to that of CSF (292–297 mOsm/kg). As Trappsol Cyclo does not contain excipients or preservatives, the possibility of neurotoxicity due to one of the components was ruled out. These factors make IT administration of the preparation a viable option. To guarantee sterility, the IT HPBCD preparation is considered stable for 8 hours at room temperature when protected from light.

INVESTIGATIONS

The first report of IT HPBCD administration in humans emerged in 2009 in the USA, when it was used in twins, 7 years of age; subsequently, approval for compassionate use of this therapy was requested from the Food and Drug Administration (FDA).³ Since then, three additional NP-C cases treated by IT HPBCD have been reported, one in a 2-year-old girl,⁴ another in a 6-year-old girl,⁵ and the last in a 12-year-old boy.⁶ In all cases, the disease stabilised during the time patients were receiving HPBCD.

HPBCD was granted orphan drug status in 2010 by the FDA and in 2013 by the European Medicines Agency for the treatment of NP-C.

Cyclodextrins are macrocycle compounds composed of α -D-bound glucose units (1,4) that are highly soluble in water and form an apolar internal cavity allowing inclusion of hydrophobic molecules. The mechanism of action that makes cyclodextrin a potentially good option for the treatment of NP-C is its ability to decrease cholesterol accumulation within the cell. However, cyclodextrins do not cross the blood–brain barrier; hence, this treatment would fail to resolve the neurological symptoms. Because of this limitation, IT administration of HPBCD was proposed.

TREATMENT

Given the failure of therapy with miglustat, the Pharmacy Service along with the Pediatric Neurology Service searched for other therapeutic alternatives in the literature. Data from studies in animal models^{7,8} and limited use in humans^{4–6} suggested that HPBCD may minimise neurological damage in NP-C.

Our patient had no adverse effects related to HPBCD treatment or the administration route. Before IT HPBCD was

administered, the same volume of CSF as the amount of drug to be administered was extracted and analysed. The biochemical variables of CSF remained stable, and no infectious agents were detected in any sample.

OUTCOME AND FOLLOW-UP

During the first year of IT HPBCD therapy in our patient, a slight delay in disease progression was noted. Nonetheless, after that time, clinical worsening was observed, which suggested a lack of treatment efficacy in this severe infantile form of NP-C.

DISCUSSION

Therapy with HPBCD has been used in several patients with NP-C, achieving neurological improvement particularly in juvenile-onset or later forms of the condition. However, limited information is available for the severe form.

IT HPBCD administration seemed to have little effect in our patient. Nevertheless, it is hard to know to what degree the medication succeeded in reducing the severity of the existing symptoms or in prolonging the time before the development of new ones. On the other hand, IT administration of HPBCD was found to be safe, as has been reported in the clinical cases described in the literature. The only reported adverse event probably related to IT HPBCD was loss of hearing,⁶ which was not documented in our patient.

The optimal HPBCD dose and administration interval are unknown. Dosage was based on the results of experimental studies in animals^{7,8} and published clinical case reports, in which HPBCD doses ranged from 175 mg at the start of treatment up to 450 mg, usually administered every 15 days.

Two clinical trials investigating IT HPBCD, now in the preliminary stages in the USA, are seeking to determine whether the drug can improve, delay or minimise the symptoms of NP-C.^{9,10} Enrolment is underway in the first study. It is an open, phase I, single-centre non-randomised trial, based on a cohort of three patients who will receive IT HPBCD twice a month at an initial dose of 200 mg, which will be increased to 300 mg, 400 mg and 900 mg. The main objective of the study is to evaluate the safety, tolerability and pharmacokinetics of HPBCD and determine the active dose. Patients younger than 2 years and older than 25 years will be excluded.⁹

The second study, which has not yet started, plans to enrol 51 patients. It is a prospective, multicentre randomised, double-blind, phase II/III clinical trial, designed to determine the optimal dosage and evaluate the efficacy and safety of HPBCD. Patients younger than 6 years and older than 21 years will be excluded.¹⁰

One future line of research in cyclodextrin therapy will focus on the safety and efficacy of structurally different cyclodextrins. In a study performed in induced pluripotent stem cell lines derived from NP-C patients exposed to 2-hydroxypropyl- γ -cyclodextrin, the authors concluded that this cyclodextrin may be more effective than HPBCD in reducing cholesterol accumulation and restoring functional abnormalities.¹¹

In Spain, a clinical trial to investigate arimoclole therapy for NP-C patients will soon be initiated.¹² In November 2014, arimoclole citrate was designated an orphan drug for the treatment of NP-C. In stressed cells, arimoclole increases production of heat shock proteins, which stabilise the lysosomal membrane and boost the capacity of lysosomes to fractionate certain lipid molecules.

As in other genetic diseases, gene therapy may provide the definitive cure for NP-C, enabling long-term expression of

Learning points

- Therapy with hydroxypropylcyclodextrin has been used in several patients with NP-C, achieving neurological improvement particularly in juvenile-onset or later forms of the condition.
- Its efficacy seems questionable in a patient with the severe infantile form of Niemann-Pick disease type C.
- Intrathecal administration of hydroxypropyl- β -cyclodextrin was found to be safe in our patient, as has been reported in other clinical cases described in the literature.
- More studies are needed to find the optimal dose and to assess the efficacy of the treatment in all of the disease forms, but especially in the severe infantile form the patients with which are currently excluded from ongoing trials.

the defective gene, although issues such as safety, efficacy and the development of related antibodies will have to be resolved.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Iturriaga C, Pineda M, Fernández-Valero EM, *et al.* Niemann-Pick C disease in Spain: clinical spectrum and development of a disability scale. *J Neurol Sci* 2006;249:1–6.
- 2 Modified disability rating scale (Pineda *et al.*, 2010), extended from original developed by Iturriaga *et al.* in 2006. <http://www.niemann-pick-c.com/HCP/Management/Monitoring-progression-of-Niemann-Pick-type-C-disease> (accessed Jun 2015).
- 3 Addi and Cassi Fund. <http://addiandcassi.com/> (accessed Jun 2015).
- 4 Cruz-Pardos S, García-Poza P, Sánchez-García FJ. [Treatment with cyclodextrin for Niemann Pick disease]. *Farm Hosp* 2013;37:271–2.
- 5 Matsuo M, Shraishi K, Wada K, *et al.* Effects of intracerebroventricular administration of 2-hydroxypropyl- β -cyclodextrin in a patient with Niemann–Pick type C disease. *Mol Genet Metab Rep* 2014;1:391–400.
- 6 Maarup TJ, Chen AH, Porter FD, *et al.* Intrathecal 2-hydroxypropyl-beta-cyclodextrin in a single patient with Niemann Pick C1. *Mol Genet Metab* 2015;116:75–9.
- 7 Liu B. Therapeutic potential of cyclodextrins in the treatment of Niemann-Pick type C disease. *Clin Lipidol* 2012;7:289–301.
- 8 Ottinger EA, Kao ML, Carrillo-Carrasco N, *et al.* Collaborative development of 2-hydroxypropyl- β -cyclodextrin for the treatment of Niemann-Pick type C1 disease. *Curr Top Med Chem* 2014;14:330–9.
- 9 Hydroxypropyl Beta Cyclodextrin for Niemann-Pick Type C1 Disease. <https://clinicaltrials.gov> (accessed Sep 2015).
- 10 Study of 2-hydroxypropyl- β -cyclodextrin (VTS-270) to Treat Niemann-Pick Type C1 (NPC1) Disease. <https://clinicaltrials.gov> (accessed Sep 2015).
- 11 Soga M, Ishitsuka Y, Hamasaki M, *et al.* HPGCD outperforms HPBCD as a potential treatment for Niemann-Pick disease type C during disease modeling with iPS cells. *Stem Cells* 2015;33:1075–88.
- 12 Arimoclomol Prospective Study in Patients Diagnosed With Niemann Pick Disease Type C. <https://clinicaltrials.gov> (accessed Sep 2015).