Clinical Report

Intrathecal Enzyme Replacement Therapy in a Patient With Mucopolysaccharidosis Type I and Symptomatic Spinal Cord Compression

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In mucopolysaccharidosis I, deficiency of α-L-iduronidase can cause spinal cord compression (SCC) due to storage of glycosaminoglycans (GAGs) within the cervical meninges. As intravenous enzyme replacement therapy (ERT) is not likely to provide enzyme across the blood–brain barrier, standard treatment for this complication is usually surgical, which has a high morbidity and mortality risk. We report on the use of intrathecal (IT) laronidase in a MPS I patient with SCC who refused the surgical treatment. Assessments were performed at baseline, with clinical and biochemical evaluations, 4-extremity somatosensory evoked potentials, 12 min walk test and MRI studies of the CNS. Changes on these parameters were evaluated after 4 IT infusions of laronidase administered monthly via lumbar puncture. To our knowledge, this was the first MPS patient who received IT ERT. No major adverse events were observed. There were no clinically significant changes in serum chemistries. CSF GAG results revealed pretreatment values slightly above normal standards: 13.3 mg/L (NV < 12 mg/L) which after IT laronidase infusions were within normal levels (10.3 mg/L). 12MWT presented a 14% improvement, with better performance on stability and gait control. Maximum voluntary ventilation showed 55.6% improvement considering the percentage of predicted (26.7% at baseline compared to 41.9%); Maximum Inspiration Pressure improved 36.6% of predicted (26.8% at baseline to 36.7%); Pulmonary diffusion improved 17.6% of predicted %. In conclusion, although the improvement observed in this case with IT laronidase should be confirmed in further patients, this procedure seems to be a safe treatment for SCC in MPS I. © 2008 Wiley-Liss, Inc.

Key words: intrathecal treatment; lysosomal storage diseases; mucopolysaccharidosis; mucopolysaccharidosis I; Scheie syndrome; α-L-iduronidase; enzyme replacement therapy; spinal cord compression

INTRODUCTION

The mucopolysaccharidoses (MPS) are a group of inherited metabolic diseases resulting from the deficiency of lysosomal enzymes involved in the breakdown of mucopolysaccharides, also known as glycosaminoglycans (GAG). In MPS I, the deficiency of alpha-L-iduronidase (IDUA) leads to the accumulation of dermatan sulfate and heparin sulfate throughout the body. Through mechanisms that are incompletely understood, progressive storage of this material causes many ailments, including coarse
facial features with an enlarged tongue, difficulty breathing, dysostosis multiplex, joint problems, corneal clouding, hepatosplenomegaly, and neurologic dysfunction, including mental retardation in the severe form (Hurler syndrome). In the less severe forms of the disease (Hurler–Scheie and Scheie syndromes), intellectual function is near-normal to normal, but substantial neurologic morbidity can be caused by spinal cord compression from meningeal GAG storage. In all forms of MPS I, meningeal storage can also obstruct cerebrospinal fluid (CSF) reabsorption leading to high-pressure, communicating hydrocephalus and rapidly progressive developmental decline or debilitating headaches [Neufeld and Muenzer, 2001]. Specific treatment for MPS I is provided by intravenous enzyme replacement therapy (ERT) with iduronidase, a genetically engineered analogue of IDUA produced in a immortalized cell line. However, the enzyme (at least in standard doses) does not cross the blood-brain barrier in significant quantity and therefore does not treat the CNS complications of the disease [Wraith et al., 2004; Wraith, 2005; Sifuentes et al., 2006]. Treatment of these problems often requires implantation of ventricular-peritoneal shunts to relieve CSF pressure or decompression of the cord using a cervical laminectomy with removal of thickened meninges.

In 2004, Kakkis et al., used an intrathecal ERT approach to treat CNS manifestations of a canine model of MPS I, achieving very high enzyme levels and noticeable reduction of GAG storage in the spinal meninges after four weekly doses of approximately 1 mg IT iduronidase and no IV treatment [Kakkis et al., 2004]. Recently, Dickson et al. [2007] showed that IT iduronidase can not only diffuse widely throughout the CNS and treat disease there, but also that it can work effectively with a clinically feasible injection frequency and dose, on the same canine animal model for MPS I. We report on the use of intrathecal ERT in an adult patient with MPS I and symptomatic spinal cord compression.

**CLINICAL REPORT**

**Patient**

The patient is an adult male, 8th offspring of 12 children (5 females and 7 males) born from a nonconsanguineous, young and healthy couple. One sister and one brother were also affected and already deceased. The patient was born through a nonconsanguineous, young and healthy couple. At age 23 he was diagnosed as having MPS I–Scheie syndrome. His IDUA activity was 0.3 nmol/ml/h in plasma (normal: >6.0), and 0.034 nmol/hr/mg protein in leukocytes (normal: 32–52). The molecular analysis of his IDUA gene showed he was a compound heterozygote, with a Q380R/R628P genotype. He had received a corneal transplant for corneal clouding. He had hypoacusia with chronic otitis media, hepatosplenomegaly with umbilical and inguinal hernia, severe restrictive respiratory disease and severe obstructive sleep apnea treated with continuous positive airway pressure (CPAP). His standing height is ~155 cm, weight ~50 kg, and blood pressure is 110/60 mmHg. He had a cardiac murmur due to mild aortic and mitral insufficiency (known since the age of 38 years). His pulmonary artery systolic pressure was 55 mmHg. He had multiple joint contractures with carpal tunnel syndrome and dysostosis multiplex. Neurologic examination at age 38 years identified gait ataxia, with signs and symptoms of cord compression in the upper and lower limbs including numbness, tingling and pain. Unstable and progressive cord compression was confirmed on magnetic resonance imaging (MRI). After clinical, neurosurgical and radiologic evaluation he was counseled to undertake a standard, well-accepted neurosurgical procedure to remove the thickened meninges (laminectomy). He refused this approach as he was a Jehovah’s Witness and the possibility of a blood transfusion associated to the surgical intervention could not be excluded. Since the patient presented with significant neurologic morbidity caused by spinal cord compression resulting from GAG storage and refused the standard surgical treatment, intrathecal enzyme replacement therapy (IT ERT) with recombinant iduronidase was considered as an alternative therapy.

**METHODS**

After baseline evaluations, the patient received 4 intrathecal injections of 3 ml of α-L-iduronidase (approximately 1.74 mg of enzyme) at 1-month interval. This dose is equivalent to the lower dose used in the canine model [Kakkis et al., 2004]. The patient was assessed at baseline, immediately before each of the three subsequent IT injections, and after the fourth injection. Following strict IRB guidance, this patient was evaluated by several physicians to determine that he could safely undergo the study procedures, and a detailed informed consent form was signed prior to enrollment. Counseling regarding treatment options including surgical intervention and no medical intervention, was provided. The risks of the procedure were explained, including a risk of hyperventilation, seizure, meningitis, allergic reaction, infection, other unforeseen complications, and the possibility of death. The patient was free to withdraw from the study at any time. Baseline and outcome assessments were designed to determine both safety and efficacy of the procedure. The assessments that were performed at baseline and repeated before each of the following infusions, and also after the 4th infusion included the following:

(a) Vital signs.

(b) Subjective assessment at each visit, whereby the patient was asked to identify any symptoms as to their location, duration, frequency and severity;
the use of medications was also recorded, including analgesics.

(c) Twelve Minute Walk test: was performed as a modification of the 6 minute walk test according to American Thoracic Society guidelines [ATS statement, 2002]. The distance walked by the patient along a 30 m course in a long, flat, indoor hallway in 12 minute time was recorded.

(d) Twelve Minute Walk test: was performed as a modification of the 6 minute walk test according to American Thoracic Society guidelines [ATS statement, 2002]. The distance walked by the patient along a 30 m course in a long, flat, indoor hallway in 12 minute time was recorded.

(e) Serum biochemistry and hematologic studies included alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, protein, creatinine, urea, sodium, potassium, phosphorus, chloride, magnesium, calcium and glucose.

(f) Cerebrospinal fluid (CSF) was collected at every IT injection. Approximately 9 ml of CSF were withdrawn and evaluated for protein, glucose, cell counts and GAG levels. Sulfated glycosaminoglycans were assayed at a reference laboratory (Children’s Hospital and Regional Medical Center, Seattle, WA, USA), using a dimethylene blue assay as previously published [Whitley et al., 1989].

The following evaluations were done at baseline and repeated after the 2nd and 4th injections. The patient underwent a baseline MRI of the brain and spine performed with a 1.5 T clinical MRI scanner. It was performed with standard protocols in the sagittal, transverse and coronal planes, with roughly a 5 mm slice thickness. T1-weighted, T2-weighted and FLAIR images were obtained. The degree of cord compression as a percentage of the spinal canal diameter was assessed and recorded as the length of the compression and spinal segments involved. Brain abnormalities were graded in similar fashion as described by Seto et al. [2001].

Procedure

The patient was taken to a surgery unit and was placed on a cardiorespiratory monitor and continuous pulse oximetry. A peripheral intravenous catheter was placed in a superficial arm vein for administration of medication. The patient was premedicated with hydrocortisone, tenoxicam and promazine (~30 min prior to IT injection). A local anesthetic (lidocaine) was administered into the L4–L5 interspace. Roughly 9–10 ml of CSF was collected for laboratory evaluations through a lumbar puncture and a dose of 3 ml (~1.74 mg) of recombinant α-l-iduronidase plus 6 cm³ Elliotts B® artificial CSF solution (for a total volume of 9 ml) was administered (immediately following mixing) slowly over ~2 min via lumbar puncture into the L4–L5 interspace. The patient was monitored during enzyme administration for any adverse clinical reactions. After enzyme administration, the patient remained supine for a period of 1 hr with monitoring. He was observed overnight following the first IT infusion to monitor for possible adverse events or unexpected reactions.

After IT infusions 2–4 he was observed for a few hours after treatment. Recovery was uneventful for all infusions.

RESULTS

Safety Evaluations

A progressive increase in baseline heart rate during the 12MWT was noticed throughout the study. During the 4th IT laronidase dose, lumbar puncture was particularly difficult and minor bleeding was observed. No other adverse events were observed or reported during or following IT ERT with laronidase. CSF opening pressure was normal on all occasions; the highest value was at baseline (130 mmH₂O) and it, decreased to 90 mm by the third LP (lowest) (Table I). No clinically significant changes were noticed on serum chemistries or CSF protein, glucose, or cell count (Table I). Blood levels of bilirubin, which were increased at baseline, normalized at the end of observation period.
Clinical Results

At baseline, this patient reported significant gait disturbances, lower limb and lumbar pain, for which he used 900 mg of sodium dipirone daily, and numbness and tingling of all four extremities. He reported frequent falls requiring permanent assistance with walking. He reported difficulty rising from a seated position and with activities of daily living.

After four IT laronidase treatments, he reported improvement in cord compression symptoms, including decreased numbness and tingling, increased stability when rising from a chair and when walking, and decreased need for pain medication (300 mg of sodium dipirone). Before IT ERT, neurological exam showed a mild paraparesis, of lower limbs. Muscle strength of hip flexion and knee extension were graded as 4; at Mingazzini tests, both lower limbs fell down 60° in 60 sec with a fall to 10 cm above the bed in 60 sec. Diffuse spasticity was seen, with bilateral ankle and right wrist clonus and absence of the cutaneo-plantar response. There was a total loss of vibration sense in both legs, with reduction in touch, pain and temperature sensations in the feet.

Following treatment with IT laronidase, his consistent right ankle clonus disappeared after the last IT infusion. Temperature sensation showed improvement following the 3rd and 4th IT infusions. The remainder of the neurologic examination was unchanged. Kurtzke FSS and EDSS did not vary during the study period (Table II). His 12 MWT showed modest improvement from 509 m at baseline to 580 m after four IT infusions, and 14% improvement at 6 months from baseline. He also showed better performance on stability and gait control (Table III).

Other Results

The CSF GAG level before treatment was 13.3 mg/L, which is above the upper limit of normal (<12 mg/L) [Dickson P, personal information on local lab reference values]. The CSF sample retrieved immediately before the 4th IT laronidase infusion showed a normal GAG level at 10.3 mg/L.

Pulmonary function tests were performed at baseline and at the end of observation period (Table IV).

Among all parameters under analysis, three showed important improvements; Maximum Voluntary Ventilation (VVM) increased 55.6% of predicted (26.7% at baseline compared to 41.9%), Maximum Inspiration Pressure (MIP) improved 36.6% of predicted (26.8% at baseline to 36.7%), and pulmonary diffusion improved 17.6% of predicted % (TLCOcSB). SSEP studies demonstrated similar results when comparing baseline and post-IT ERT treatment evaluations.

Baseline MRI studies of the CNS showed severe lesions diffusely involving the white matter and multiple dilated perivascular spaces in the basal ganglia bilaterally (Fig. 1a). Hydrocephalus and brain atrophy were absent. Spinal MRI showed severe canal stenosis and cord compression (Fig. 1b). Follow-up studies performed during the

<table>
<thead>
<tr>
<th>Finding</th>
<th>Baseline</th>
<th>1st month and 2nd month</th>
<th>3rd month</th>
<th>4th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended upper limbs: fall of 30° in 60 sec. Muscle strength graded 5</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Mingazzini test: fall of 60° in 60 sec. Muscle strength graded 4</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Tonus and reflexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spasticity, hyperactive reflexes, bilateral ankle clonus</td>
<td>=</td>
<td>=</td>
<td>Right ankle clonus has disappeared</td>
<td></td>
</tr>
<tr>
<td>Sensitive tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vibratory sensation loss in lower limbs; and reduction in tactile sense: unable to discriminate thermal stimuli in right limbs</td>
<td>=</td>
<td>Improvement of thermal sensation (able to discriminate 90% of thermal stimuli in all limbs)</td>
<td>Improvement continues</td>
<td></td>
</tr>
<tr>
<td>FSS for pyramidal functions</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>FSS for cerebellar functions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FSS for sensory function</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>FSS for bowel and bladder function</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Kurtzke Functional System Scores (FSS) were performed throughout. Only system scores of interest were presented (the others have scored zero). (=) unchanged.
2nd and 4th months showed no progression in white matter lesions or spinal stenosis.

**DISCUSSION**

Although preliminary, this pioneer intrathecal ERT treatment yielded promising results, as there were no significant adverse events, and some clinical and functional improvements were documented. Adverse events included a minor bleeding in the last lumbar puncture and an increase in baseline heart rate during 12MWT. There was no concomitant sign or symptom of cranial hypotension. All the other parameters—clinical, biochemical and imaging studies—were stable, indicating safe follow-up. Some results suggested that IT ERT was associated with both subjective and objective improvements. The patient had improvement in his gait and ability to rise when seated. Improvement in the 12MWT was notable for increased distance walked from 509 to 580 m (a 14% improvement), which was also noted at the 6 minute mark (251 m compared to 289 m). The increased baseline heart rate was not associated with abnormal arterial blood pressure changes measured before and after each IT infusion. Transthoracic Doppler echocardiogram and ECG did not show abnormalities other than mitral valve insufficiency. No oxygen desaturation was recorded. Motivational drive should be taken into account since patient was very committed and excited with treatment results (Fig. 2).

Gait improved during treatment, and was steadier and less ataxic. Additionally, a reduction in joint and/or neuropathic pain was reported, along with a reduced need for pain medication. There were improvements in pulmonary diffusion tests and disappearance of right ankle clonus, a well-known sign of pyramidal dysfunction. Its disappearance (after being registered 4 times) can be interpreted as reduced spinal cord compression, due perhaps to less thickened and/or more flexible meninges. Less easily understandable are the lung diffusion results in the present case. They usually reflect either a direct effect on gas exchange in the alveoli or an increase in alveolar volume, which may be related to improvement in pulmonary mechanics. It is unlikely that intrathecal laronidase had reached the alveoli. The more likely interpretation is that improvement in lung diffusion was the result of an increase in the motor strength of respiratory muscles. However, the physiopathology of these findings remains to be understood.

Regarding serum chemistry values, the patient had a bilirubin level which was above normal at baseline. After the fourth IT ERT dose, this value normalized. This finding might have been due to a prior episode of chemical hepatitis secondary to pain medication, which was eventually resolved with the reduced intake. Alternatively, a possible small systemic circulation of the enzyme, injected through the lumbar puncture, and acting on liver tissue, should be considered. If this systemic circulation occurred it could be the result of a minimal blood–brain barrier crossing, or even entering through the needle tract. These are remote possibilities that can not be established, as pharmacokinetic studies during IT procedures were not performed.

The enzyme dose and the infusion intervals used for this pioneer laronidase IT ERT treatment were ~1.74 mg of enzyme (~3 ml of laronidase)

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**TABLE IV. Pulmonary Function Tests Before and After 4 Monthly Intrathecal Laronidase Injections in a MPS I Patient Presenting Cord Compression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline results (% predicted)</th>
<th>Post-treatment result (% predicted)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>1.62 (43.6)</td>
<td>1.82 (49.1)</td>
<td>+0.2 (12.3)</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>1.47 (45.6)</td>
<td>1.55 (48.4)</td>
<td>+0.08 (5.4)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>90.61 (106.8)</td>
<td>85.18 (100.6)</td>
<td>+5.45 (6.0)</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>3.36 (67.9)</td>
<td>3.38 (64.2)</td>
<td>−0.18 (5.4)</td>
</tr>
<tr>
<td>RV (l)</td>
<td>1.72 (137.1)</td>
<td>1.41 (110.5)</td>
<td>−0.31 (18)</td>
</tr>
<tr>
<td>ITGV (l)</td>
<td>2.62 (115)</td>
<td>2.35 (103.1)</td>
<td>−0.27 (10.3)</td>
</tr>
<tr>
<td>IC (l)</td>
<td>0.75</td>
<td>0.83</td>
<td>+0.08 (10.7)</td>
</tr>
<tr>
<td>TLCOC SB (ml/min/mmHg)</td>
<td>9.01 (31.7)</td>
<td>12.15 (43)</td>
<td>+3.14 (34.9)</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>56.2 (26.7)</td>
<td>56.36 (41.9)</td>
<td>+0.16 (5.7)</td>
</tr>
<tr>
<td>MIP (kPa)</td>
<td>2.95 (20.8)</td>
<td>4.03 (36.7)</td>
<td>+1.08 (35.6)</td>
</tr>
<tr>
<td>MEP (kPa)</td>
<td>5.93 (42)</td>
<td>6.04 (42.9)</td>
<td>+0.11 (1.9)</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV1, forced expiratory volume after 1 sec; TLC, total lung capacity; RV, residual volume; ITGV, intrathoracic gas volume; IC, inspiratory capacity; TLCOC SB, single breath carbon monoxide transfer factor; MVV, maximum voluntary ventilation; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure.
at monthly intervals. Using this approach, this patient achieved a CSF GAG reduction of 22.5% and his CSF GAG levels normalized. CSF opening pressure was normal on all occasions, but it is noteworthy that the highest level was recorded at the first IT treatment, with values of 130 mmH2O (~9.5 mmHg), and subsequently decreased, reaching the lowest pressure at the third IT treatment (90 mmH2O or ~6.6 mmHg) (Table I). This decrease could mean that as the GAG storage on meninges was reduced, the CSF circulating area was increasing slightly allowing for lower pressure values. CSF glucose and protein values, as well as cell count, did not show significant changes. The high cell count on the fourth IT treatment was attributed to a difficult lumbar puncture accompanied by minor bleeding. The first dogs treated with IT ERT had developed an asymptomatic, moderate meningitis found on necropsy that was associated with a lymphocytic and plasmocytic infiltrate confined to the meninges, elevated CSF leukocyte counts, and elevated IDUA antibody levels. Two of these dogs suffered seizures, which responded to dialyzing the formulation buffer [Kakkis et al., 2004]. Using less frequent and/or low dose IT laronidase reduced or prevented the meningitis in dogs, and diluting laronidase 1/3 by volume in Elliotts B artificial CSF solution, prevented seizures, hyperventilation, or twitching that had occurred when using undiluted rhIDU solution [Dickson et al., 2007]. There was no evidence of meningitis, seizures, hyperventilation, twitching or any other adverse event in the present patient, who received diluted enzyme on a monthly basis.

In conclusion, although there are likely residual risks for complications in the absence of surgery, intrathecal laronidase injections through lumbar puncture is an emerging new therapy which appeared to be effective in this adult patient with attenuated MPS I in alleviating some signs and symptoms of spinal cord compression.

REFERENCES


