Improved gait performance in a patient with hereditary spastic paraplegia after a continuous intrathecal baclofen test infusion and subsequent pump implantation: a case report

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ABSTRACT

Objective: To show the benefits of a continuous intrathecal baclofen (ITB) test infusion in a patient with hereditary spastic paraplegia (HSP), with an improved gait performance after ITB pump implantation.

Design: Case report.

Setting: University hospital.

Participant: A 49-year old man with HSP experiencing progressive walking difficulties because of lower extremity spasticity, which did not respond to oral spasmolytics.

Interventions: A prolonged, continuous ITB test infusion was started at a low dose and increased gradually, to provide a stable dose of ITB over a prolonged period. The gradual dose increase provided the patient enough time to experience the effects of ITB, because he feared that ITB therapy might cause functional loss.

Main Outcome Measures: Modified Ashworth Scale, electromyography, muscle strength, timed Up and Go tests, and the Patient Global Impression of Change. Gait performance before and after ITB pump implantation was assessed in a motion laboratory.

Results: During the test infusion, the ITB dose was gradually increased to a continuous dose of 108 µg/d. This dose caused the spasticity to decrease, with maintenance of muscle strength. After pump implantation, gait performance was improved, resulting in increased knee flexion during the loading response and a doubled walking speed as compared with baseline.

Conclusions: Patients with HSP who have mild spasticity that does not respond to oral spasmyotics should receive a continuous ITB test infusion, to provide them with enough time to experience the delicate balance between spasmolysis and muscle strength. ITB administration is a suitable therapy to improve gait performance in patients with HSP.
INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of inherited neurodegenerative disorders characterized by progressive lower extremity spasticity and muscle weakness. Treatment is primarily symptomatic, consisting of physical therapy and the administration of spasmolytic agents. Most patients with HSP have a progressive decrease in their ability to walk that occurs over many years. During this decline, most patients use their spasticity to compensate for muscle weakness.

One of the most effective spasmolytics is baclofen, a gamma-aminobutyric acid (GABA) type B receptor agonist. However, orally administered baclofen has difficulty crossing the blood-brain barrier, necessitating high doses to achieve an adequate effect, resulting in many adverse effects. During intrathecal baclofen (ITB) therapy, baclofen is injected directly into the cerebrospinal fluid. ITB therapy has proven to be effective and safe in treating patients with severe spasticity. ITB has also been used in patients with HSP. However, most patients with HSP are reluctant to start ITB therapy because they fear that a loss of muscle strength might result in a loss of functional abilities. This is partially supported by studies that used a bolus test infusion to select patients for ITB therapy. One of these studies reported on 2 patients after an ITB bolus of 75 µg, which resulted in drowsiness without a reduction of spasticity. Another study reported that the administration of a 25 µg or 50 µg bolus of ITB had a positive effect in only 5 of 10 patients with HSP. However, 2 of these 5 patients refused ITB pump implantation because of subjective unsteadiness and weakness in the lower extremities.

This brief report describes a continuous ITB test infusion instead of a bolus infusion, where the ITB dose is slowly increased every 24 hours, providing the patient enough time to experience the effects of ITB therapy. Several tests were used to assess its effects. The effect of ITB on the patient’s ability to walk is illustrated by assessing gait performance in a motion laboratory and in a supplemental video (available online at http://www.archives-pmr.org/) showing the patient’s ability to walk before and after ITB pump implantation.
CASE DESCRIPTION

The patient is a 49-year old man (height, 169 cm; weight, 70 kg) with confirmed HSP caused by an SPG-7 gene mutation. He was seen at the neurology outpatient department because of progressive walking difficulties during the last 5 years, caused by spasticity confined to the lower extremities. He was able to walk only 100 m with assistive devices and used his wheelchair for most activities. His oral spasmyotics (baclofen, 75 mg/d; tizanidine, 12 mg/d) did not decrease spasticity, but caused drowsiness as an adverse effect. The patient was employed as an administrative assistant, but had stopped working because of the severe and increasing spasticity. The patient was considered a candidate for ITB therapy since oral spasmyotics had not been able to prevent a progression of his spasticity and functional decline. However, the patient feared a loss of functional abilities because of the spasmyotic effect of ITB. Therefore a continuous ITB test infusion was proposed. The following tests were used to monitor the effects of ITB therapy.

- The Modified Ashworth Scale was used to grade spasticity during a physical examination. The cumulative score for knee, hip, and ankle flexors and extensors, and hip abductors and adductors ranges from 0 to 40. Note that for calculation purposes, the 1+ score was converted to 2 and scores ≥2 were increased by 1; thus, scores ranged from 0 to 5.
- Electromyography was used to measure the amplitude of the maximum Hoffmann reflex (H_max) to that of the maximal muscle response (M_max) of the soleus muscle after stimulation of the tibial nerve.\(^9\)
- The Medical Research Council scale was used to grade muscle strength during a physical examination. The cumulative score for hip flexors, and knee and ankle flexors and extensors ranges from 0 to 25.
- The maximal isometric strength of the knee flexors (at 45° knee flexion) and extensors (at 90° knee flexion) was tested on a dynamometer (Biodex Medical Systems). The maximal result of 3 consecutive trials was used.
- A timed Up and Go test was used to assess functional abilities by measuring the time it took the patient to stand up from a chair, walk 3 m back and forth, and sit down.
- The patient was asked to grade the overall change in his condition compared with baseline on the Patient Global Impression of Change (PGIC) scale. Scores range from 1 (very much improved) to 7 (very much worse).
ITB test infusion

The patient received an intrathecal catheter with the catheter tip at the level of Th10, connected with an external infusion pump. (External Chrono Five infusion pump; Cane Medical Technology). The ITB infusion was started at a low continuous dose of 36 µg/d and increased in daily small steps of 36 µg/d. Baseline scores of all tests were collected before starting the ITB test infusion. All tests were repeated 24 hours after each dose change in order to retest at steady-state concentrations and to provide the patient enough time to experience the effect of ITB therapy. After retesting, the patient and physician mutually decided whether the ITB dose should be further increased. At a maximal dose of 108 µg/d the patient decided to have permanent pump implantation.

Pump implantation

The ITB pump (Synchromed II ITB pump; Medtronic) was implanted 4 months after the test infusion, at the Department of Neurosurgery of the University Medical Center Groningen. The procedure was without complications. Continuous ITB infusion was started at 105 µg/d.

The effect of ITB therapy on gait performance was assessed by measuring step length, walking speed, and knee flexion in the motion laboratory of the Department of Rehabilitation of the University Medical Center Groningen, using a Vicon Motion System 370 (Oxford Metrics). The assessments were done at baseline (1 day before) and 6 months after ITB pump implantation.

RESULTS

Test infusion

The results of the tests during the ITB test infusion are displayed in table 1.

The dose was increased up to a maximum of 108 µg/d, at which spasticity decreased as shown by a drop in the total Modified Ashworth Scale score from 20 to 6 and by a decrease of the $H_{\text{max}}/M_{\text{max}}$ ratio from 0.47 to 0.06. Muscle strength was preserved, illustrated by the stable Medical Research Council score and the increase of maximal isometric strength in both knee flexor and extensor moments. The timed Up and Go test was performed almost twice as fast. The patient rated his condition on the PGIC as “very much improved” and therefore agreed to have permanent ITB pump implantation. Except for an initial period of subjective weakness in the legs during the test-infusion, there were no side effects.
### Table 1. Results of the tests during the continuous ITB test infusion

<table>
<thead>
<tr>
<th>Test</th>
<th>ITB dose (µg / day)</th>
<th>0</th>
<th>36</th>
<th>72</th>
<th>108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS (0-40)</td>
<td></td>
<td>20</td>
<td>16</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>EMG (H&lt;sub&gt;max&lt;/sub&gt;/M&lt;sub&gt;max&lt;/sub&gt; ratio)</td>
<td></td>
<td>0.47</td>
<td>0.24</td>
<td>0.14</td>
<td>0.06</td>
</tr>
<tr>
<td>Strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC-scale (0-25)</td>
<td></td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Dynamometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee flexors</td>
<td></td>
<td>43 Nm</td>
<td>44 Nm</td>
<td>56 Nm</td>
<td>46 Nm†</td>
</tr>
<tr>
<td>Knee extensors</td>
<td></td>
<td>110 Nm</td>
<td>127 Nm</td>
<td>159 Nm</td>
<td>160 Nm</td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timed Up and Go test</td>
<td></td>
<td>32 s</td>
<td>28 s</td>
<td>25 s</td>
<td>17 s</td>
</tr>
<tr>
<td>PGIC</td>
<td></td>
<td>N/A</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

* Abbreviations: EMG, electromyography; H<sub>max</sub>, maximal Hoffman reflex; MAS, Modified Ashworth Scale; MRC, Medical Research Council; M<sub>max</sub>, maximal muscle response; N/A, not applicable.
† Results of both legs were averaged.
‡ Only left leg tested, since the right leg was painful because of an injury on the same day.

### Table 2. Effect of ITB-therapy on gait performance at own comfortable walking speed

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>ITB therapy (105 µg / day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step length (m)</td>
<td>0.42</td>
<td>0.61</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>0.22</td>
<td>0.94</td>
</tr>
<tr>
<td>Knee flexion*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial contact (deg)</td>
<td>12.4 ± 1.5</td>
<td>12.4 ± 2.1</td>
</tr>
<tr>
<td>Loading Response (deg)</td>
<td>10.1 ± 0.8</td>
<td>21.5 ± 1.4</td>
</tr>
<tr>
<td>Midstance (deg)</td>
<td>11.0 ± 1.5</td>
<td>10.3 ± 1.3</td>
</tr>
<tr>
<td>Terminal Stance (deg)</td>
<td>8.9 ± 0.6</td>
<td>8.8 ± 1.6</td>
</tr>
<tr>
<td>PGIC</td>
<td>N/A</td>
<td>1</td>
</tr>
</tbody>
</table>

* Knee flexion was measured in the sagittal plane, and results of both legs were averaged.

NOTE: Values are mean ± SD or as otherwise indicated.
Abbreviation: N/A, not applicable.
**Effect of ITB on gait performance**

Table 2 shows the changes in gait performance between baseline and 6 months after ITB pump implantation. This is further illustrated by supplemental video, showing the ability to walk at these moments. Step length and walking speed increased. Knee flexion increased from 10.1° to 21.5° during the loading response, while it was unaffected during the other stance phases. Six months after ITB pump implantation the patient was able to walk 200 m without any assistive devices, although for longer distances he used a wheelchair. He was able to work again, as well as drive a car and ride a bicycle. All of these improvements had a significant effect on his personal well-being, which was reflected by the PGiC (very much improved).

**DISCUSSION**

This case shows the positive effects of a continuous ITB test infusion, reflected by decreased spasticity, increased muscle strength, and improved functional abilities. The positive effects of long-term ITB therapy were supported by an increase in walking speed, step length, and knee flexion, which are probably a result of decreased spasticity and muscle tone normalization. The isolated increase of knee flexion during the loading response is likely a reflection of the increased force of the knee extensor muscles, which is necessary to achieve this increased flexion. This is also supported by the increased knee extensor moments during the test infusion (see table 1). These data are supported by previous studies on ITB therapy in patients with HSP, showing that a reduction in spasticity was correlated with increases in walking speed (from 0.73 to 1.31 m/s), step length (from 0.40 to 0.70 m), and range of motion.5,10

However, the most important lesson of this case is that appropriate selection of possible candidates for ITB therapy, who still have a walking capability, ideally should take place by means of a continuous test infusion. A bolus test infusion causes the intrathecal baclofen concentration to rise too quickly, resulting in a rapid and large spasmolytic effect. This may cause adverse effects such as drowsiness and subjective feelings of unsteadiness, as well as weakness in the lower extremities.5,8 Because of these adverse effects, ITB therapy may be withheld from some patients who could benefit from it. A continuous test infusion will prevent these unwanted adverse effects, since it delivers a stable dose of baclofen during the day.
Study limitations
The limitation of this case report is that only one patient is described. However, there is a clear logic behind the presented data. Nevertheless, these results should be considered exploratory.

Conclusions
Patients with spasticity who do not respond to oral spasmolytics and who still have the ability to walk should be offered a continuous ITB test infusion. A continuous infusion appears to cause fewer adverse effects and provides sufficient time to explore the effects of ITB on the patient, likely leading to a higher rate of positive responders as compared with testing with an ITB bolus infusion.
REFERENCES
