Infusion of intrathecal baclofen for generalized dystonia in cerebral palsy

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Generalized dystonia occurs in 15 to 25% of persons with cerebral palsy (CP) and responds poorly to medical and surgical treatments.

Object. After the authors observed a woman whose dystonic CP was dramatically improved by continuous infusion of intrathecal baclofen, they designed this pilot study to evaluate the effect of this treatment on a group of patients with dystonic CP.

Methods. The authors assessed the short-term response to intrathecal baclofen infusion in 12 patients with dystonic CP. An intrathecal catheter was inserted percutaneously and connected to an external microinfusion pump. The infusion began at a rate of 100 μg/day and was increased by 50 μg every 12 hours until the dystonia abated, adverse effects occurred, or the dose reached 900 μg/day with no improvement. Two observers, one blinded and one not blinded to the patient’s treatment status, viewed videotapes made before and after the infusions and graded the dystonia in eight body regions, using a 5-point scale. Overall and regional scores were compared by using Wilcoxon signed-rank tests.

Conclusions. Dystonia diminished in 10 of 12 patients whose average daily dose of intrathecal baclofen was 575 μg. Overall dystonia scores and scores for the extremities, trunk, and cervical regions were significantly better after infusion (p = 0.003). The two observers’ scores were not significantly different. Programmable infusion pumps were subsequently implanted in eight patients for long-term therapy and improvement was sustained in six (p < 0.05).

Intrathecal baclofen infusion is a promising treatment option for generalized dystonia associated with CP. The effects of intrathecal baclofen infusion on dystonia can be evaluated by using short-term continuous infusions.

KEY WORDS • baclofen • cerebral palsy • dystonia • movement disorder
fluoroscopic guidance, an intrathecal catheter was inserted percutaneously at L3–4 and advanced to the midthoracic level. The external end of the catheter was tunneled subcutaneously around the flank, where it exited and was connected to an external microinfusion pump. During intrathecal baclofen infusion, electrocardiographic response, respiratory rate, and pulse oximetry were continuously monitored, and the patient’s level of consciousness was assessed every 4 hours.

Baclofen, 500 μg/ml, initially was infused at a rate of 100 μg/day and was increased by 50 μg every 12 hours until dystonia was obviously decreased in the opinion of the parent or patient, the physical therapist, and the neurosurgeon. At that time, the infusion was stopped, the catheter was withdrawn, and the patient was videotaped again. If patients received 900 μg/day for 24 hours with no response or if adverse side effects attributable to baclofen (such as drowsiness or hypotonia) developed, we discontinued the infusion.

The videotapes were reviewed independently by a physical therapist (M.J.B) who was aware of the treatment status and by a pediatric neurologist (M.J.P.) who was blinded to the treatment status of each patient. They graded dystonia associated with CP and the high response rates to such infusions. Hyperkinetic movement disorders become evident during childhood as the nervous system pathways mature. Although CP is a static encephalopathy, new motor abnormalities such as dystonia may appear during the first two decades after perinatal or early childhood asphyxia.14,15,16,20 Such dystonia may begin in an extremity and progress over several years to become generalized. The pharmacological treatment of dystonia in patients with CP has had limited success. There are few reports on the use of oral baclofen to treat dystonia associated with CP. Oral baclofen was given in dosages of 40 to 120 μg/day to 16 children with idiopathic dystonia.14 Seven children improved, five dramatically so, with an average dosage of 79 μg/day. However, all patients were receiving other oral medications, such as trihexyphenidyl

### TABLE 1

<table>
<thead>
<tr>
<th>Site of Dystonia</th>
<th>Blinded Rater Pre-infusion</th>
<th>Blinded Rater Post-infusion</th>
<th>Nonblinded Rater Pre-infusion</th>
<th>Nonblinded Rater Post-infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>overall</td>
<td>22.9</td>
<td>15.6</td>
<td>24.3</td>
<td>13.3</td>
</tr>
<tr>
<td>eyes</td>
<td>1.8</td>
<td>1.5</td>
<td>1.7</td>
<td>1.3</td>
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<tr>
<td>mouth</td>
<td>2.7</td>
<td>2.1</td>
<td>2.8</td>
<td>1.6</td>
</tr>
<tr>
<td>neck</td>
<td>3.1</td>
<td>2.2</td>
<td>3.0</td>
<td>1.9</td>
</tr>
<tr>
<td>trunk</td>
<td>3.1</td>
<td>2.2</td>
<td>3.4</td>
<td>1.8</td>
</tr>
<tr>
<td>lt upper extremity</td>
<td>3.2</td>
<td>2.7</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>lt lower extremity</td>
<td>2.9</td>
<td>1.2</td>
<td>3.2</td>
<td>0.8</td>
</tr>
<tr>
<td>rt upper extremity</td>
<td>3.4</td>
<td>2.8</td>
<td>3.8</td>
<td>2.7</td>
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<tr>
<td>rt lower extremity</td>
<td>3.0</td>
<td>1.2</td>
<td>3.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Possible scores for each area ranged from 0 (best) to 4 (worst); potential overall scores, a total of the area scores, ranged from 0 to 32. Overall scores were significantly lower after infusion of intrathecal baclofen (p = 0.003, blinded rater and p = 0.0002, nonblinded rater). With the exception of the eyes, all area scores were also significantly (p < 0.05) lower after treatment. Blinded rater = observer blinded to treatment status; nonblinded rater = observer not blinded to treatment status.

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Generalized dystonia was reduced during the screening infusions in 10 of the 12 patients. Another patient’s dystonia improved in his lower extremities, but not in his upper extremities or in his facial or cervical regions. The overall dystonia scores were significantly lower (that is, better) at the end of the infusions than at the start. The rater who was blinded to treatment status noted a mean decrease in overall dystonia scores of 7.3 points (p = 0.003) and the rater who was not blinded to treatment noted a mean decrease of 11 points (p = 0.0002) (Table 1). Scores for the patient’s neck, trunk, and all extremities also improved significantly after administration of baclofen (p < 0.05). There was no significant difference between the two raters in their assessment of overall dystonia scores (p = 0.62) and the probability-of-concordance test result was significant (p = 0.004). Dystonia in most patients did not improve until the baclofen dosage was in the range of 350 to 750 μg/day; that is, after 4 to 7 days of infusion.

Meningitis developed in two patients, in one during the infusion trial and in the other 1 day after the infusion catheter was withdrawn. Both patients’ dystonia had not responded to the infusion and both were treated successfully with antibiotic therapy. The technique for catheter insertion was altered to minimize cerebrospinal fluid leaks and no infections occurred in the subsequent 10 patients.

Programmable subcutaneous pumps were implanted in eight of the 10 patients who responded to the screening infusions. These patients have been followed for 11 to 24 months (mean 15.6 months) during which time they have received continuous intrathecal baclofen doses of 185 to 625 μg/day (mean 441 μg/day). Improvements in dystonia that were observed during the short-term infusions have been maintained during long-term therapy in six of eight children. The mean overall dystonia scores of the eight patients decreased from 25 prior to pump implantation to 14.6 12 months afterward (p < 0.05).

**Discussion**

We have described the use of continuous short-term infusion of intrathecal baclofen in persons with generalized dystonia associated with CP and the high response rates to such infusions. Hyperkinetic movement disorders become evident during childhood as the nervous system pathways mature. Although CP is a static encephalopathy, new motor abnormalities such as dystonia may appear during the first two decades after perinatal or early childhood asphyxia.14,15,16,20 Such dystonia may begin in an extremity and progress over several years to become generalized. The pharmacological treatment of dystonia in patients with CP has had limited success. There are few reports on the use of oral baclofen to treat dystonia associated with CP. Oral baclofen was given in dosages of 40 to 120 μg/day to 16 children with idiopathic dystonia.14 Seven children improved, five dramatically so, with an average dosage of 79 μg/day. However, all patients were receiving other oral medications, such as trihexyphenidyl
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hydrochloride, in addition to the baclofen. Patients improved gradually over weeks and were treated for a mean of 3.8 years, with sustained improvement. Narayan and coworkers were the first to treat dystonia with a continuous infusion of intrathecal baclofen. They described improvement of axial dystonia in an 18-year-old patient who received 825 μg/day, with no adverse effects. Penn and colleagues treated five adults with dystonia, primarily focal dystonia, with intrathecal baclofen and observed mixed results. Their patients’ responses to baclofen were screened by bolus injections, after which pumps were implanted and the patients were given 500 to 960 μg/day of baclofen. We recently reported positive responses to intrathecal baclofen in three patients with dystonic CP, but observed negative responses in two children with dystonia associated with Hallervordan–Spatz disease.

For the past 7 years, we have evaluated continuous intrathecal baclofen infusion in patients with spasticity of cerebral origin, primarily that associated with CP. Intrathecal baclofen appears to improve spasticity by acting at the spinal cord level, inhibiting the release of excitatory neurotransmitters from afferent nerve endings in the superficial layers of the spinal cord. Baclofen inhibits the uptake of calcium that is required for glutamate release. Within 2 hours after infusion of a single intrathecal baclofen dose of 50 to 100 μg, lower-extremity spasticity is reduced and remains so for 6 to 8 hours. In previous studies of patients with mixed spastic–dystonic CP, single intrathecal baclofen boluses (50–100 μg) have reduced the spasticity, but have had no effect on the dystonia. After initiation of continuous intrathecal baclofen infusion by means of either an external or implanted pump, dystonia generally does not improve for 2 or 3 days, a sufficient time for baclofen to enter the intracranial subarachnoid space. Because dystonia is not affected by single intrathecal baclofen boluses but is reduced by continuous infusion, we infer that baclofen’s site of action in dystonia may be intracranial. In the model of basal ganglia function developed by DeLong, et al., and Alexander and coworkers, motor output is modulated by the corticobasal gangliothalamocortical circuit, which contains a direct and an indirect pathway. Lesions in the direct pathway typically result in hypokinetic movement disorders such as parkinsonism. Lesions in the indirect pathway, which includes the subthalamic nucleus, result in hyperkinetic movement disorders. Patients with secondary dystonia associated with CP often have lesions in the striatum, primarily in the putamen. The putamen normally inhibits the external globus pallidus, which inhibits the subthalamic nucleus. If the putamen were damaged by a perinatal insult, the deficient inhibition of the external globus pallidus (disinhibition) would result in excessive output from the subthalamic nucleus and, ultimately, in excessive stimulation of the premotor and supplementary motor cortices, causing hyperkinetic movements such as dystonia. Continuous infusion of intrathecal baclofen might improve dystonia by inhibiting the excessively stimulated supplementary motor cortex and premotor cortex.

Assessing dystonia is difficult, especially in persons with CP, because they may also have weakness, spasticity, lack of motor control, difficulty in communication, or cognitive deficits. We modified the Fahn–Marsden scale, a dystonia scale that rates patients according to provoking factors and severity factors. In CP, however, there is often no provoking factor: dystonia is present both at rest and with volitional movement. Determining whether a movement is volitional is also challenging in patients with cognitive impairments. On the Fahn–Marsden scale, the severity factors are primarily based on function. Because most of the patients in our study were unable to perform functional tasks, we expanded the severity factors to include the severity of involuntary movements and posturing of the trunk and extremities. We believe the revised scale is a more appropriate measure for our patients.

The quantified improvements in dystonia during continuous infusion of intrathecal baclofen were accompanied by qualitative improvements in several patients: general level of comfort, sleeping, and ease of positioning in wheelchairs commonly improved. We did not evaluate function before and after intrathecal baclofen infusion because only two patients were capable of self-care.

Intrathecal baclofen infusions are associated with risks from the screening trial, pump implantation, and long-term therapy. The primary risk of the screening trial and pump implantation is meningitis or infection. Meningitis occurred in 4% of 51 patients in a multicenter study of continuous intrathecal baclofen infusion to treat cerebral spasticity (data on file, Medtronic, Inc.). During long-term therapy, overdoses may occur but are rare. They are almost always associated with either inaccurate programming of the pump or infusion of a bolus dose.

The results of this pilot study indicate that continuous infusion of intrathecal baclofen reduces generalized dystonia in some patients with CP. Thus far we cannot identify factors that might predict the response of dystonia to intrathecal baclofen. Additional investigations are being conducted to evaluate long-term responses and functional and quality-of-life outcomes.

References


Manuscript received April 3, 1997. Accepted in final form July 15, 1997. This study was supported in part by Grant No. 5M01-R00084 from the National Institutes of Health General Clinical Research Center, Bethesda, Maryland, and by Medtronic, Inc., Minneapolis, Minnesota, who provided the baclofen. Address reprint requests to: A. Leland Albright, M.D., Department of Neurosurgery, Children’s Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, Pennsylvania 15213.