Long-term intrathecal baclofen therapy for severe spasticity of cerebral origin

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Object. The goal of this study was to ascertain the long-term effectiveness and safety of intrathecal baclofen (ITB) in the treatment of spasticity of cerebral origin in children and young adults.

Methods. A prospective, multicenter study was conducted in 68 patients who had been enrolled in the initial evaluation of ITB therapy and were willing to participate in long-term surveillance. Seventy-three percent of the patients were younger than 16 years of age at the time of study entry. The patients were examined at least every 3 months and were observed for an average of 70 months. At each follow-up visit, spasticity in the upper and lower extremities was evaluated by applying Ashworth scores. All adverse events and complications were recorded on standardized data forms.

Spasticity in both upper and lower extremities decreased significantly ($p < 0.005$) and remained decreased up to 10 years. The dose of ITB increased from a mean of 157 µg/day 3 months after pump insertion to 300 µg/day at 2 years postimplantation, and remained relatively stable thereafter. There were no significant differences in ITB dosage in children of different ages. Adverse events potentially related to ITB therapy occurred in 50% of patients within 2 months after pump insertion and in 50% of patients thereafter; hypotonia and lethargy were the two most common adverse events. The most common complications of surgery were catheter-related problems (31%), seromas (24%), and cerebrospinal fluid leaks (15%).

Conclusions. Intrathecal baclofen provides effective long-term treatment of spasticity of cerebral origin and its effects do not appear to diminish with time. This therapy is frequently associated with adverse side effects that usually can be alleviated by adjustments in dosage.

Key Words • spasticity • intrathecal baclofen • drug delivery • children

The effects of ITB on spasticity of cerebral origin were evaluated initially in single-institution studies. The results of those studies indicated that ITB significantly improves spasticity in both upper and lower extremities and that function improves in some patients.\textsuperscript{1,3,4,6} Data from prospective, multicenter US clinical trials subsequently confirmed the effectiveness and relative safety of ITB,\textsuperscript{8} and in June 1996, the US Food and Drug Administration approved ITB for the treatment of spasticity of cerebral origin.

Earlier publications contain descriptions of the short-term effects of ITB therapy in treating cerebral spasticity. After approval of ITB by the Food and Drug Administration, the present multicenter study was undertaken to evaluate the long-term safety, efficacy, and dosing requirements of ITB in patients with severe spasticity of cerebral origin.

Clinical Material and Methods

This is the report of a prospective, open-label, follow-up study conducted at nine US centers (Appendix). Patients eligible for the study were a subset of patients who had participated in the US clinical trials (Investigation of the Administration of Lioresal Intrathecal [baclofen injection] for the Management of Spasticity of Cerebral Origin, IND No. 39-327), which began in February 1989. Secondary inclusion criteria for enrollment in the present study included at least one of the following: 1) the patient had to be 16 years of age or younger at the time ITB treatment began; 2) the patient’s spasticity had to be a result of brain injury; or 3) the patient had to have been one of the first 10 patients to enter the IND clinical trial.

Of approximately 100 patients who were eligible for the surveillance study, 68 chose to enroll in the study. Their study group included 54 patients (79%) with spastic cerebral palsy, nine (13%) with traumatic brain injury, three (4%) with cerebral anoxia, one (1.5%) with degenerative brain disease, and one (1.5%) with transverse myelitis. At the time of the first pump implantation, 48.5% of the patients were younger than 12 years of age, 23.5% were 12 to 15 years, and 28% were 16 years of age or older. The mean age of patients at the first implantation was 12.6 years, with a median age of 12 years. Patients were followed up for a mean of 70 months (range 14.6–133.4 months) and a median of 67 months, with a total of 4761 therapy months. Reasons that the remaining 32 eligible patients did not participate in the study included the following: 1) there was no signed consent; 2) the patient was lost to follow up; 3) the patient was being followed up at another site; 4) the patient

Abbreviations used in this paper: CSF = cerebrospinal fluid; IND = Investigational New Drug; ITB = intrathecal baclofen.
TABLE 1
Ashworth scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Degree of Muscle Tone</th>
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<tbody>
<tr>
<td>1</td>
<td>no increase in tone</td>
</tr>
<tr>
<td>2</td>
<td>slight increase in tone, giving a “catch” when affected part is moved in flexion or extension</td>
</tr>
<tr>
<td>3</td>
<td>more marked increase in tone, but affected part easily flexed</td>
</tr>
<tr>
<td>4</td>
<td>considerable increase in tone; passive movement difficult</td>
</tr>
<tr>
<td>5</td>
<td>affected part rigid in flexion or extension</td>
</tr>
</tbody>
</table>

or physician was not interested in participating; 5) the patient or physician had left the participating institution; and 6) the patient was no longer receiving therapy.

Patients were expected to return for evaluations and pump refills at least every 90 days for at least 3 years. At each follow-up visit, the neurological assessment, the ITB dosage requirement, and any adverse event or system-related complication were recorded on standardized case report forms. The neurological evaluation included application of Ashworth scores5 (Table 1) to the upper extremities (elbow flexors and extensors, and wrist flexors and extensors) and lower extremities (hip adduction and abduction, knee flexion and extension, and ankle dorsiflexion and plantar flexion) and the presence of spasms and clonus. System-related complications and adverse drug effects were described on surveillance data forms. Throughout the study, data monitoring was conducted on a regular basis through written correspondence, telephone calls, and site visits. Data on each patient in the study were recorded from the time of the patient’s enrollment in the IND clinical trial until patient withdrawal or study closure on July 31, 2001.

Results

Of the 68 patients, 49 (72%) were observed from pump implantation until the end of the study; two died (3%) and 17 (25%) were withdrawn from the study. The two deaths occurred 24.5 and 23.8 months after pump implantation. One death was caused by an upper airway obstruction and respiratory failure; the child’s pump and catheter were explanted. The treating physician believed that the patient’s death was not associated with the use or function of the baclofen pump.

The 17 patients who were withdrawn from the study had been followed up for an average of 57.5 months before they were withdrawn. Patients were withdrawn for various reasons: in five patients pump refills were obtained elsewhere; four patients were lost to follow up; two patients requested to leave the study; two experienced system-induced infection; and in one case each patients chose to leave the study because of a desire to cease all medications, the excessive cost/benefit ratio, catheter fracture, and difficulty with transportation for refills.

Patient spasticity was evaluated by application of Ashworth scores (Table 1). At baseline, the mean score in the upper extremities was 2.3 and that in the lower extremities was 3.1. During follow up, the upper-extremity and lower-extremity scores decreased significantly (Figs. 1 and 2). For the upper extremities, the changes from baseline to 6, 12, and 24 months are all statistically significant (p < 0.001). For the lower extremities, the decreases from baseline to every 6-month interval are statistically significant (p < 0.0001) up to 36 months. The improvements in spasticity persisted for years. The number of patients available for analysis at 7 to 10 years after the first pump implantation was too small for a statistical analysis, but the average Ashworth scores in that time frame were similar to scores in the first 6 years of follow up.

Baclofen dosage increased gradually during the first 2 years after pump implantation, from a mean of 157 µg/day 3 months after implantation to 300 µg/day at 2 years, but varied little thereafter (Fig. 3). The ITB dosages in children, adolescents, and adults were similar: mean dosages 3 months after implantation were 153 µg/day in children younger than 12 years old, 180 µg/day in those 12 to 15 years of age, and 143 µg/day in those 16 years of age or older (Fig. 4). Baclofen dosages ranged substantially at each time interval, but few patients received more than 800 µg/day (specifically, two patients at 12 months and four patients at 24 and 36 months). The lowest dosage any child received during the study was 22 µg/day and the highest was 1760 µg/day.

Adverse events that were potentially related to baclofen were listed in two groups: the titration phase, to 60 days postimplantation; and the maintenance phase, more than 60 days postimplantation. Two thirds of the 68 patients experi-
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Fig. 3. Graph showing the mean daily dosage of ITB in micrograms at different follow-up times. Dosages increased during the first 2 years and remained relatively constant thereafter.

Discussed one or more adverse events while in either the titration or maintenance phase; 34 (50%) experienced at least one adverse event during the titration phase and 34 experienced at least one adverse event during the maintenance phase. A total of 87 adverse events occurred during the titration phase and 132 during the maintenance phase. Table 2 lists adverse events by body system; it lists the events according to the titration and maintenance phases and includes all symptoms and signs reported by patients or caregivers during ITB administration that had a frequency greater than 5% during the particular phase. The most commonly reported adverse events in the titration phase were hypotonia (17.6%), somnolence (16.2%), nausea and vomiting (11.8%), and headache (10.3%). The most commonly reported adverse events in the maintenance phase were hypotonia (25%), somnolence (19.1%), and seizures (13.2%).

Complications were designated as procedure related, if they occurred within 60 days after operation or were directly attributable to human intervention, or as system related, if they occurred after 60 days or were attributable to the devices (the pump, intrathecal catheter, or programmer) whenever they occurred. A total of 128 pumps and 115 catheters were under surveillance during the study. Due to the long duration of the study, several patients required replacement of pumps and/or catheters.

The majority of complications were procedure related. The most common procedural complications were seromas around the pump (16.2%) and CSF leaks around the catheters (14.7%). The most common system-related complications were associated with the catheters, which fractured in 16.2%, kinked or occluded in 8.8%, and dislodged in 5.9% (Table 3). System-related problems were often associated with increases in spasticity and indicated a need to determine the reason for the system failure. The majority of the catheters (86%) used in the study were either the original Medtronic 8703 catheter, which was used in 23% of patients, or the thicker-walled 8703W catheter, which was used in 63% of the patients. Three pumps were explanted because of infection. Three patients withdrew from the study because of complications.

Discussion

Families often ask if ITB loses its effectiveness over time. It does not appear to do so in the majority of patients, as shown by continued long-term use of the therapy, persistent relief of spasticity, and relatively stable dosing beyond 2 years. The present data provide evidence of the long-term effectiveness of ITB in reducing spasticity in both upper and lower extremities. Average Ashworth scores (1.3–2 in the upper extremities and 1.3–2.4 in the lower extremities) were maintained for up to 11 years, with only moderate increases in the average ITB dosage over time.

In our patients the Ashworth scores in the upper extremities were significantly reduced in response to drug therapy, an observation that has been reported by others despite the fact that most intrathecal catheters were positioned in the lower thoracic region (62% were placed at T10–12, 34% at T6–9, and only 4% at T4 or above). Intrathecal baclofen infusion through catheters placed at T10–12 results in lower concentrations of baclofen in the cervical region than concentrations obtained using catheters positioned in the upper thoracic or lower cervical regions. When treating children with spastic quadriparesis and substantial upper-extremity spasticity, the catheter tip can be placed between C-7 and T-2 to obtain better effects in the upper extremities.

As shown in Fig. 3, ITB dosages increased gradually during the first 1 to 3 years of ITB therapy and then remained relatively constant thereafter. If follow-up examinations after 3 years reveal unexpected increases in Ashworth scores, the possibility of insufficient ITB infusion should be suspected and evaluated. The problem can come from pump failure (battery failure or pump stalling), catheter difficulties (kinking, fracture, or migration), or rarely, the formation of adhesions around the catheter tip. Evaluation of the problem typically includes x-ray film studies to assess cath-

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Titration Phase</th>
<th>Maintenance Phase</th>
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<tr>
<td>hypotonia</td>
<td>12 (17.6)</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td>somnolence</td>
<td>11 (16.2)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>convulsions</td>
<td>3 (4.4)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>nausea &amp; vomiting</td>
<td>8 (11.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>headache</td>
<td>7 (10.5)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>
The most commonly reported adverse events during long-term follow up, hypotonia and somnolence, can also be alleviated by reducing the ITB dosage. Convulsions were reported on the data collection forms of nine patients (13%); eight of these children had experienced seizures before ITB therapy and their seizure frequency did not appear to change during ITB therapy. The relationship between ITB and seizures has been questioned. Of the nine children who experienced seizures during the surveillance period, eight had seizures before pump implantation. The single child who experienced his first seizure after ITB treatment began suffered a brief seizure 6 months after implantation; no subsequent seizure was reported during the next 4 years.

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Medical City Dallas Hospital, Dallas, Texas; Dale Swift, M.D., Principal Investigator; eight patients.
Methodist Hospital, Indianapolis, Indiana; Michael Turner, M.D., Principal Investigator; one patient.

Disclosure
A. Leland Albright, M.D., is a consultant for Medtronic, Inc.

References

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