Intrathecal Baclofen for Spastic Hypertonia From Stroke

Jay M. Meythaler, JD, MD; Sharon Guin-Renfroe, RN, MSN, CRNP; Robert C. Brunner, MD; Mark N. Hadley, MD

Background and Purpose—We sought to determine whether continuous intrathecal delivery of baclofen can effectively decrease spastic hypertonia due to stroke.

Methods—Stroke patients with >6 months of intractable spasticity were screened via a randomized, double-blind, placebo-controlled crossover design of either intrathecal normal saline or 50 μg baclofen. Those who dropped an average of 2 points in either their affected lower extremity side Ashworth or Penn spasm frequency scores were then offered computer-controlled pump implantation for continuous ITB and followed prospectively for up to 12 months.

Results—In 21 stroke patients 6 hours after the active drug bolus, the average (±SD) lower extremity Ashworth score on the affected extremities decreased from 3.3±1.2 to 1.4±0.7 (P<0.0001), spasm score from 1.2±1.2 to 0.1±0.3 (P<0.0001). The average upper extremity Ashworth score on the affected extremities decreased from 2.8±1.1 to 1.8±0.8 (P<0.0001), spasm score from 0.7±1.0 to 0.2±0.4 (P=0.1544), and reflex score from 2.1±0.9 to 1.2±0.9 (P=0.0004). All active drug scores were statistically different from placebo scores at 6 hours (P<0.05).

With up to 12 months of continuous infusion of ITB in 17 implanted patients, the average lower extremity Ashworth score on the affected extremities decreased from 3.7±1.0 to 1.8±1.1 (P<0.0001), the spasm score dropped from 1.2±1.3 to 0.6±1.0 (P=0.4282), and the reflex score decreased from 2.4±1.3 to 1.0±1.3 (P<0.0001). The average upper extremity Ashworth score in the affected extremities decreased from 3.2±1.1 to 1.8±0.9 (P<0.0001), the spasm score dropped from 0.7±1.0 to 0.3±0.8 (P=0.8685), and the reflex score decreased from 2.4±0.8 to 1.5±1.2 (P=0.337). The average continuous ITB dose required to attain these effects was 268 μg/d.

Conclusions—Intrathecal infusion of baclofen is capable of maintaining a reduction in the spastic hypertonia resulting from stroke. (Stroke. 2001;32:2099-2109.)

Key Words: adult • baclofen • dystonia • muscle hypertonia • rehabilitation • spasticity • stroke

After recovery from a stroke (CVA), a patient can frequently have motor weakness on one or both sides of the body.1 Further impairing mobility and function in this patient population is spastic hypertonia. This abnormal, excessive muscle tone can cause many problems, including pain, loss of free movement of a limb, and interference with the ability to walk and perform daily activities, such as bathing or dressing.1–3 It also may cause the limb to become “fixed” or frozen in an uncomfortable position.

Spastic hypertonia encompasses a variety of conditions associated with CVA, including dystonia, rigidity, myoclonus, muscle spasm, posturing and/or spasticity.2–3 From a physiological standpoint, spasticity is defined as a motor disorder characterized by a velocity-exaggerated increase in tonic stretch reflexes (muscle tone), with exaggerated reflex responses, resulting from hyperactivity of the stretch reflex.1–5 Dystonia is defined as a persistent attitude or posture of the extremities such as an over-extension or over-flexion of the hand, inversion of the foot, or torsion of the spine associated with twisting, lateral bending, or torsion of the back.5 The increased muscle tone may be noted in all affected synergistic muscle groups following a stroke, thereby reducing functional motor activities.

The pharmaceutical management of spastic hypertonia following stroke has generally been confined to the use of approaches that diminish peripheral cholinergic activity at the neuromuscular junction (botulinum toxin), inhibit the release of calcium from the sarcoplasmic reticulum (dantrolene sodium), or those that act centrally.1–5 In this latter class, there are 3 primary medications: baclofen, diazepam, and clonidine.3–5 Ablative procedures have also been utilized, including phenol injections to the motor points or nerve blocks by injection.3 These procedures generally require repetition and have been associated with permanent weakness, dysesthesias, and causalgia.3,6

Most recently, intrathecally delivered baclofen has been established as a treatment method in acquired brain injury.7–9

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From the Department of Physical Medicine and Rehabilitation and the Division of Neurological Surgery (M.N.H.), University of Alabama at Birmingham School of Medicine.
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Correspondence to Jay M. Meythaler, MD, JD, University of Alabama at Birmingham, R157 Spain Rehabilitation Center, 619 19th St South, Birmingham, AL 35249-7330. E-mail JMeythaler@uab.edu
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Baclofen, 4-amino-3-(p-chlorophenyl) butyric acid, is structurally similar to gamma aminobutyric acid (GABA) and binds to presynaptic GABA-B receptors within the brain stem, dorsal horn of the spinal cord, and other central nervous system (CNS) sites.\textsuperscript{3,5,10,11,15–22} The intrathecal infusion of baclofen through chronically placed catheters has been reported to be useful in treating spastic hypertonia in adults with spinal cord injury, multiple sclerosis, cerebral palsy and acquired brain injury.\textsuperscript{7,8,10,12–14} The delivery system consists of a subcutaneously placed pump with a reservoir attached to an intraspinal catheter. The pump is programmable to deliver various rates of medication via a catheter that enters at the lumbar spinal level into the subarachnoid space of the spinal canal. The central side effects of oral baclofen such as drowsiness or confusion appear to be minimized with intrathecal administration.\textsuperscript{7,8,10,12–14} The intrathecal delivery of baclofen concentrates the medication in the cerebrospinal fluid (CSF) at much higher levels than those attainable via the oral route.\textsuperscript{15,16}

Recently, the intrathecal delivery of baclofen over a relatively short 3-month period has been reported to reduce the tone and spastic hypertonia of adults who have suffered a CVA.\textsuperscript{9} However, a detailed systemic randomized study with blinding has yet to be reported in this patient population. This study describes the initial experience of a double-blind randomized crossover trial of bolus ITB in adults with spastic hypertonia from stroke. This was followed by a continuous delivery trial via a computer controllable pump for 1 year in patients who underwent surgery for the placement of an implanted pump to deliver ITB.

Subjects and Methods

Subjects

The prospectively recruited patient population consisted of 22 CVA patients with intractable spastic hypertonia who are >6 months out from the onset of their CVA. Patients were recruited in a consecutive manner. The spastic hypertonia functionally interfered with their activities of daily living, sleep, mobility and positioning or was causing significant contractures or pain. All patients had failed to respond to treatment or had untoward side effects related to cognition or alertness with various oral antispasticity medications including a trial of orally delivered baclofen. The protocol is similar to those previously reported by our group.\textsuperscript{7,10,13,17}

Inclusion Criteria

After the initial screening evaluation, patients were enrolled in the study if they met all of the following criteria: (1) >16 years of age, (2) diagnosis of severe chronic spastic hypertonia in the lower extremities (although the upper extremities could also be involved) of at least 6 months’ duration that was defined by an average Ashworth score\textsuperscript{14} of at least 3 in one affected extremity or an average spasm score\textsuperscript{14} of at least 2 in the affected extremities at the day of the first screening, and (3) failure to respond satisfactorily to treatment with the maximum recommended doses of oral antispasticity medications (including baclofen and possibly diazepam, clonidine, tizanidine, and/or dantrolene sodium) or occurrence of unacceptable side effects at effective treatment dosages.

Screening

Evaluation Procedure

The following parameters were assessed before a double-blind bolus trial was performed: (1) a complete physical examination and neurological assessment and a thorough history of spasticity, includ-

<p>| TABLE 1. Definition of Ashworth, Penn Spasm Frequency, and Reflex Scale Scores |
|-----------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashworth Scale</td>
<td>No increase in tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in tone, giving a “catch” when affected part is moved in flexion or extension</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in tone, but affected part easily flexed</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in tone; passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Affected part rigid in flexion or extension</td>
</tr>
<tr>
<td>Penn Spasm Frequency Scale</td>
<td>No spasms</td>
</tr>
<tr>
<td>0</td>
<td>Mild spasms induced by stimulation</td>
</tr>
<tr>
<td>1</td>
<td>Infrequent full spasms occurring &lt;1/h</td>
</tr>
<tr>
<td>2</td>
<td>Spasms occurring &gt;1/h</td>
</tr>
<tr>
<td>3</td>
<td>Spasms occurring &gt;10/h</td>
</tr>
<tr>
<td>Reflex Scale</td>
<td>Reflexes absent</td>
</tr>
<tr>
<td>0</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>1</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Mild hyperreflexia</td>
</tr>
<tr>
<td>3</td>
<td>3 or 4 beats clonus only</td>
</tr>
<tr>
<td>4</td>
<td>Clonus</td>
</tr>
</tbody>
</table>

ing treatments and medications used to manage the spasticity; (2) the 5-point Ashworth (rigidity) scale (Table 1) to assess muscle tone in both the lower extremities (hip abduction, hip flexion, knee flexion, and ankle dorsiflexion) and the upper extremities (shoulder abduction, elbow extension, elbow flexion, and wrist extension); (3) a 4-point scale (Table 1) reflecting the number of spontaneous sustained flexor and extensor muscle spasms per hour; and (4) a 5-point scale documenting deep tendon reflexes at the biceps, patella, and Achilles (Table 1).

Screening Bolus Trial

Patients were randomized before the bolus to either 50 μg baclofen or preservative-free normal saline via a coin toss. All boluses were at least 72 hours apart. Patients who had a partial drop (<2 points) in the mean Ashworth scores or Penn spasm frequency scores but did not meet criteria for pump placement were given the option of a 75- to 100-μg bolus trial, which was not blinded. If, after this trial, they qualified, then pump placement was offered. Both the raters and the patient were blinded until after the second bolus. Before the bolus all patients were weaned off antispasticity medications. All patients except 2 were screened via a randomized double-blind bolus injection of 50 μg baclofen intrathecal. A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 cc was injected. Data for the Ashworth scale, spasm score, and deep tendon reflex score were then collected by the same investigator at 1, 2, 4, and 6 hours after injection for the limbs (extremities) with abnormal motor tone or increased spasm frequency. Criteria for consideration for continuous ITB delivery via programmable pump and intrathecal catheter were given to patients who had a reduction of muscle tone of at least 2 points on the Ashworth scale or had experienced a reduction of 2 points in the Penn spasm frequency scale in the affected limbs, as determined by the spasm frequency scale with the active agent, without untoward side effects.

1 Two patients who were on anticoagulants such as warfarin sodium, aspirin, clopidogrel, or ticlopidine had their dosage held at
least 3 days or the length of time required to drop their prothrombin time under 1.6 INR. These patients were then screened by using a 25-gauge spinal needle rather than the usual 22-gauge spinal needle. The patients and/or their guardians were informed of the risks versus the benefits of holding the anticoagulants.

Setting
All patient screenings via a lumbar puncture were performed in an outpatient rehabilitation clinic setting, which is part of a single, tertiary-care university medical center. Follow-up clinical visits were performed in the same outpatient clinic for dose adjustments and pump refills. Blinding was performed per protocol of the experimental pharmacy section at UAB Hospital.

Implantation
The continuous-infusion pump and intraspinal catheter system were implanted under general anesthesia with the patient in the lateral decubitus position. The programmable pump was placed in a lower abdominal wall subfascial pocket; the catheter was placed into the lumbar subarachnoid space via a percutaneous technique with a 14- or 15-gauge Touhy needle. The catheter placement, which was premeasured before insertion or placed under fluoroscopic guidance, was threaded up to the midthoracic area (approximately T6) in all patients for improved upper extremity effects.7,8,18 The intraspinal catheter was then tunneled into the subcutaneous space to the programmable pump, thus completing the procedure.

Postoperatively, all patients received 24 to 36 hours of intravenous fluids, vancomycin, and gentamicin for prophylaxis of infection. They were kept supine for 24 hours to reduce the incidence of postoperative headaches. All patients were admitted the day of their surgery and discharged from the hospital 72 hours later unless there were significant rehabilitation therapy goals secondary to the reduction of the spastic hypertonia.

For patients on warfarin sodium or other anticoagulants, the anticoagulants were withheld for 1 week before surgery and were not restarted until 5 days after surgery. The patients and/or their guardians were informed of the risks versus the benefits of withholding the anticoagulants.

Follow-Up
After implantation of the continuous-infusion device, patients were followed on an outpatient basis for refilling and dosage adjustment. All subjects initiated treatment of ITB at 100 \( \mu \)g/d. Dose increases were performed at the 1-month, 3-month, 6-month, 9-month, and 12-month intervals, and as requested by the patient or therapist. These dose increases can be performed within 24 hours of the previous dose adjustment. The goal was to reduce the Ashworth score and/or the Penn spasm frequency score to as close to normal as possible and was dependent on improving, or at least not reducing, the functional status of the patient. The maximum refill interval currently recommended by the manufacturer is 90 days, but, depending on the dosage and drug concentration, patients may be seen more or less frequently.

Follow-Up Evaluation Procedures
(1) Patients were scheduled for data collection at the following times; initial score on the day of bolus with active medication, 1 month, 3 months, 6 months, 9 months, and 1 year after pump placement. The data for limbs with a motor deficit were analyzed separately from that obtained from limbs with normal motor function and tone.
(2) The 5-point Ashworth (rigidity) scale7,8,18 (Table 1) was used to assess muscle tone in both the lower extremities (hip abduction, knee flexion, knee extension, and ankle dorsiflexion) and the upper extremities (shoulder abduction, elbow flexion, elbow extension, and wrist extension).
(3) A 4-point scale7,8,14 (Table 1), which reflected the number of spontaneous sustained flexor and extensor muscle spasms per hour, was used.
(4) A 5-point scale documenting deep tendon reflexes was used at the biceps, patella, and Achilles7,10 (Table 1).

(5) The current 24-hour infused dosage at the time of the data collection was also recorded at the scheduled data collection times.
(6) Data with regard to untoward complications, including cognitive dysfunction, urological problems, infections, problems regarding physical and occupational therapy, as well as equipment malfunction, were noted.

Statistical Analysis
The statistical study design is an A-B single case control design with each patient used as his or her own control. Because muscle tone, spasm, and reflex scores were measured on ordinal level scales, overall changes over time were analyzed using the Friedman test, the nonparametric equivalent of a repeated-measures ANOVA with a single group.19 Data with regard to drug dosage were analyzed via ANOVA and paired Student t tests. The Wilcoxon signed rank test was also used to test the significance of observed differences between set periods of time in the continuous treatment. A value of \( P \leq 0.05 \) was considered significant. Although nonparametric tests were used, data are presented as averages with standard deviations to facilitate the interpretation of the magnitude and clinical significance of the results presented. Rather than consider each muscle separately, average scores for muscle tone, spasms, and reflexes were averaged for the upper extremities or the lower extremities for each patient.

Data are reported to the rounded-off 0.1 decimal level.

Statistical analysis was performed with Abacus Concepts, Stat View 4.5 (1997) for Macintosh.

Protocol Review
The study was reviewed and approved by The University of Alabama at Birmingham Health Sciences Human Investigation Committee (new drug and device investigations). Each patient signed an informed consent form prior to testing, after being familiarized with the experimental method and the potential risks as well as the potential benefits of the procedure.

Results
Bolus Trial
Twenty-one subjects (average age 53 years; range 16 to 86 years of age) were screened via a double-blind bolus trial. (Subject 22 refused the second injection after the first bolus and requested that the bolus trial be unblinded as she felt she had been given the active drug.) She had been given the active drug and had had a dramatic drop in the Ashworth score so the subject went on to implantation. Two patients in this study who failed a bolus of 50 \( \mu \)g ITB did not respond to a larger bolus of 100 \( \mu \)g. One patient who had a significant response to the active drug in the bolus trial elected not to have a pump placed for continuous delivery of ITB. There were no adverse effects from the bolus other than a headache in 2 patients that lasted 24 to 48 hours. No patient suffered any serious adverse effects from withholding any oral antispasticity medications before the bolus.

Lower Extremities
Overall, the average (±SD) lower extremity Ashworth score decreased 1.9 points, from 3.3±1.2 before treatment to 1.4±0.7 6 hours after a 50-\( \mu \)g intrathecal bolus of baclofen (\( P<0.0001 \), Friedman test). Figure 1A shows the average lower extremity Ashworth score at each time period after both treatment and placebo administration. Although no trend was observed after placebo administration, a highly significant reduction in average lower extremity score on the Ashworth scale was observed over time with the active drug administration, with the maximum effect occurring 6 hours.
after injection. No significant baseline difference was observed in average lower extremity Ashworth score between active drug or placebo administration \((P>0.05)\). There were significant differences noted between the active drug and placebo at 4 hours \((P<0.0001)\) and 6 hours \((P<0.0001, \text{Wilcoxon signed rank test})\) after administration.

A response pattern similar to that shown in Figure 1A was observed for both lower extremity spasm scores (Figure 1B). The average \((\pm \text{SD})\) spasm score for the lower extremities decreased 1.1 points, from \(1.2 \pm 1.2\) before treatment to \(0.1 \pm 0.3\) 6 hours after treatment \((P=0.0224, \text{Wilcoxon signed rank test})\). No significant baseline difference was observed in the average lower extremity spasm score between active drug or placebo administration \((P>0.05, \text{Wilcoxon signed rank test})\). Figure 1B shows the average lower extremity spasm score at each time period after both treatment and placebo administration. Although no trend was observed after placebo administration, a highly significant reduction in average lower extremity reflex score was observed over time with the active drug administration, with the maximum effect occurring 6 hours after treatment. There were significant differences noted in the average lower extremity reflex score between the active drug and placebo at 4 hours \((P<0.0001)\) and 6 hours \((P<0.0001, \text{both Wilcoxon signed rank test})\) after administration.

**Upper Extremities**

Upper extremity treatment responses were similar to lower extremity responses, although of slightly lesser magnitude because the upper extremity baseline scores were less than those in the involved lower extremities (Figure 2).

The average \((\pm \text{SD})\) upper extremity Ashworth score decreased 1.1 points, from \(2.8 \pm 1.1\) before treatment to \(1.8 \pm 0.8\) 6 hours after treatment \((P<0.0001, \text{Friedman test})\). Despite the fact that most of these patients had minimal spasms, there was a trend noted with the active drug on the spasm frequency. The average upper extremity spasm score decreased 0.5 points, from \(0.7 \pm 1.0\) before treatment to \(0.2 \pm 0.4\) 6 hours after treatment \((P=0.1544)\). The biceps reflex score decreased 0.9 points, from \(2.1 \pm 0.9\) to \(1.2 \pm 0.9\), over the same time frame \((P=0.0004)\). No trend was observed with placebo administration for upper extremity muscle tone, spasm, or reflex scores \((P>0.05, \text{Friedman test for all})\).

There were no statistically significant differences in baseline upper extremity tone, spasm and biceps reflex scores between the active drug and placebo before administration \((P>0.05, \text{Wilcoxon signed rank test})\). Conversely, there were statistically significant and clinically meaningful differences between the active drug and placebo at 6 hours after administration for upper extremity muscle tone \((P<0.0001)\), spasm frequency \((P=0.0117)\), and reflex scores \((P=0.0006, \text{Wilcoxon signed rank test for all})\).

**Continuous Infusion of ITB for Up to 1 Year**

Seventeen adult CVA patients (average age 50 years, range 16 to 86 years) are reported. All patients were >6 months from the onset of their stroke (mean 41 months, range 10 to 107 months) before ITB pump placement. Four were followed up for 6 months after implantation, and 13 were followed up for 1 year (Table 2). Eleven of the 17 patients who received implants were right CVA patients with left-sided hemiparesis, 4 were left CVA patients with right-sided hemiparesis, and 2 were brain stem stroke patients with quadriparesis. Of the 22 patients admitted to the study, 19 were implanted. Two implanted patients (subjects 18 and 19)
were dropped from data analysis in the continuous infusion trial. One patient had developed a chronic hepatitis C infection, and the other was a pediatric patient. They were dropped from the study because of potential confounding physiological changes: from peripheral neuropathy and from developmentally related neurological changes due to maturation, respectively. Both had a dramatic and sustained drop in their spastic hypertonia as a result of ITB pump placement. Ten males and 7 females underwent pump placement.

Lower Extremities

After continuous ITB treatment for up to 1 year, the average \((\pm SD)\) lower extremity Ashworth score decreased 1.9 points, from 3.7\(\pm 1.0\) before treatment to 1.8\(\pm 1.1\) after treatment \((P<0.0001,\) Friedman test; Figure 3A). The average lower extremity spasm score decreased 0.6 points, from 1.2\(\pm 1.3\) to 0.6\(\pm 1.0\) after treatment but was not statistically significant \((P=0.4282,\) Friedman test; panel B). The average reflex score for the affected lower extremities decreased 1.4 points, from 2.4\(\pm 1.3\) before treatment to 1.0\(\pm 1.3\) after treatment \((P<0.0001,\) Friedman test; panel C).

Upper Extremities

Upper extremity treatment responses were similar to lower extremity responses, although of slightly lesser magnitude because the initial upper extremity baseline scores were lower than those of the lower extremities (Figure 4).

The average \((\pm SD)\) upper extremity Ashworth scores decreased 1.4 points, from 3.2\(\pm 1.1\) before treatment to 1.8\(\pm 0.9\) after treatment \((P<0.0001).\) The average upper extremity spasm score decreased 0.4 points, from 0.7\(\pm 1.0\) before treatment to 0.3\(\pm 0.8\) after treatment, but this decrease was not significant \((P=0.8685).\) The biceps reflex score in the affected extremities decreased 1.1 points, from 2.4\(\pm 0.8\) to 1.5\(\pm 1.2\), also not statistically significant \((P=0.3337,\) Friedman test for all).

**ITB Effects on Normal Extremities**

Fifteen of the 17 reported subjects were hemiparetic with normal motor strength, motor tone, no spasms, and normal reflexes in one upper and one lower extremity on the same side. It is well known that therapeutic dosages of ITB over a short period of time appear to affect the “normal side” reflexes.\(^9\) To assess the affects of ITB on the normal side and to determine whether the normal side might accommodate long-term continuous ITB, we evaluated the deep tendon reflexes for these extremities separately. The average lower extremity reflex score decreased on the normal side by 1.6 points, from 1.9\(\pm 0.8\) before treatment to 0.3\(\pm 1.2\) after several months to 1 year of continuous ITB treatment (Figure 5A). The average upper extremity reflex score decreased and approached statistical significance as it dropped 1.2 points, from 1.9\(\pm 0.7\) before treatment to 0.7\(\pm 0.9\) \((P=0.0858,\) Friedman test) after continuous infusion of ITB (Figure 5B). While the reflexes on the normal side are affected, it is not as significant as that seen in the extremities affected by the stroke. There was no noted motor weakness on the normal side throughout the study utilizing the standard 1 to 5 motor strength testing for the same joints as utilized for the Ashworth score. No patient or

### Table 2. Average Extremity Tone in Patients Before and After ITB Pump Placement

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Before Treatment</th>
<th>After 12 mo</th>
<th>Before Treatment</th>
<th>After 12 mo</th>
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<tr>
<td>1</td>
<td>40</td>
<td>F</td>
<td>4.0</td>
<td>1.0</td>
<td>3.8</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>M</td>
<td>4.0</td>
<td>4.0</td>
<td>3.5</td>
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</tr>
<tr>
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<td>66</td>
<td>F</td>
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<td>3.0</td>
</tr>
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<td>4</td>
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<td>M</td>
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<td>1.8</td>
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<td>M</td>
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<td>1.0</td>
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<td>6</td>
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<td>F</td>
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<td>2.5</td>
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<tr>
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<td>F</td>
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<td>18</td>
<td>M</td>
<td>2.2</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Figure 2.** The average upper extremity muscle tone (A), reflex (B), and spasm frequency (C) for patients before treatment (admit) and at 1 hour, 2 hours, 4 hours, and 6 hours after a 50-\(\mu g\) bolus of 50 \(\mu g\) of ITB (bold line) or placebo (thin line).
family member perceived any change in motor strength in the “involved” limbs or the “normal” limbs.

**Dosage**

The average dosage of ITB to achieve this reduction was $268 \pm 175 \text{ mg/d}$ (range 50 to $660 \text{ mg/d}$). There was no statistically significant change in the muscle tone and spasm frequency at 6-month follow-up versus 1-year follow-up ($P < 0.05$, Wilcoxon signed rank test) (Figure 6), and the dosage to maintain this reduction in tone increased only 47 mg.

**Other Issues**

Three patients went from wheelchair dependence to independent ambulation with assistive devices. All dependent patients were more comfortable and were easier to manage at home with regard to hygiene, ADL, and assisted transfers.

Five patients had changes in urinary voiding patterns with initial pump placements, all related to urinary retention. With a reduction in ITB dosage, this resolved and did not return despite later dosage increases. Postoperative headaches with nausea were transient in several patients. The headaches were treated conservatively by keeping the patient supine for a day and with administration of intravenous fluids. The headaches were felt to be due to a CSF leak associated with catheter placement.

No patient developed seizures after pump placement, nor was there a history of seizures in any of these patients prior to pump placement. There were no infections or meningeal as a result of pump and catheter placement. Detailed functional improvements were not evaluated in this study, because several of the patients had to go through profound stretching and dynamic splinting to regain functional range of motion before going on to therapy to improve motor function and reduce disability. These studies are ongoing.

One patient gained 40 lb after pump placement. This was believed to be related to reduced caloric needs as her spasticity decreased. The increased abdominal circumference resulted in the catheter backing out of the intrathecal space approximately 1 year after pump placement. Because she had a multiport catheter, her dosage had to be increased over the previous several weeks. It was felt that the increases in dosage could be accounted for by the reduced delivery of ITB as more of the ports were displaced from the intrathecal space. The system was revised without difficulty. However, because of the higher dose she became very weak and flaccid 24 hours after catheter replacement on $174 \text{ mg/d}$. This was not accompanied by respiratory complications. The dosage was decreased to $100 \text{ mg/d}$, and the patient has done well thereafter.
horn cells. Baclofen is believed to result from hyperpolarization of motor horn cells.

In the brain, baclofen delivered orally has some supraspinal activity, which may contribute to clinical side effects such as drowsiness, confusion, and memory or attention problems at the dosages required to reduce spasticity. Other central effects of the drug have included hallucinations, ataxia, and memory impairments. Sudden withdrawal of orally delivered baclofen may lead to seizures and hallucinations.

The side effects noted with oral baclofen are largely averted via delivery of ITB. The delivery system for ITB therapy consists of a subcutaneously placed pump with a reservoir attached to an intraspinal catheter. This delivery method concentrates the medication within the spinal subarachnoid CSF in the thoracolumbar and sacral spinal regions at a much higher level than that attainable via the oral route.

From there the CSF flows to the arachnoid villi for reabsorption, avoiding a baclofen effect on the cerebral hemispheres. Only low levels of the medication have the potential to reach the brain stem or cerebrum. Several studies have demonstrated the lumbar-to-cistern CSF baclofen concentration gradient is 4.1:1. Muller et al found that continuous intrathecal infusion of 400 μg/d may produce a spinal CSF level of 380 ng/mm. However, in studies concerning the use of orally administered baclofen, Knutsson et al found that the highest measured spinal CSF level in 11 patients was 95 ng/mm. Importantly, the level was <12 ng/mm in most patients. This manner of delivery avoids the cognitive side effects of oral delivery, such as drowsiness and lethargy.

This is the first double-blind randomized crossover study on the use of bolus intrathecal baclofen in stroke patients. In this study we noted no untoward side effects from the bolus trial and found that the medication was well tolerated. The 50-μg bolus dose is quite small and is the same as that used in studies on children with spastic hypertonia from cerebral palsy. Nineteen of the 21 patients dropped their tone scores an average of 2 points in the lower extremities with a 50-μg bolus of ITB. Utilizing the criteria that have been developed for the patients with spastic hypertonia due to other causes, patients who dropped 2 points in either the Ashworth score or the Penn spasm frequency scale generally benefited from long-term treatment with continuous ITB for up to 1 year. The muscle tone scores appear to be the most reliable indicator of effectiveness of intrathecal baclofen in stroke. This is because stroke patients are often so rigid, with such extensive posturing, that it is more difficult to judge spasms and deep tendon reflexes than muscle tone on the Ashworth scale. The Ashworth scale is a reproducible method for measuring muscle tone if averaged over 4 or more joint motions in the same limb.

Deep tendon reflexes were affected bilaterally, although more profoundly in the lower and more affected extremities. This appears to be functionally insignificant, as no patient reported even a subjective change in muscle tone, motor strength, or coordination on the unaffected side. We feel that the deep tendon reflex scores are useful in deciding whether a patient could benefit from an increased dosage of ITB. The deep tendon reflexes are usually absent when the dosage

Figure 5. The average reflexes on the normal side for the hemiparetic patients (15 patients, 11 followed for 1 year) for the lower extremity (A) and upper extremity (B) before treatment (admit) and during 3 months of continuous intrathecal drug administration (with 1-SD bars).

There were no complications related to the short-term discontinuance of coumadin for either the bolus trial or the pump placement. Coumadin was discontinued in patients 1 week before the pump placement and restarted 4 days after placement. Any coumadin discontinuance was on the approval of the treating neurologist.

Discussion

Despite the success reported with the use of continuous ITB for spastic hypertonia from predominately adults with acquired brain injuries, there have been no prospective studies evaluating its use in stroke. Initially, there was some concern that these patients had locked-in patterns of motor movement that would be more difficult to treat. This is the first study to address this neglected population, which is estimated to be quite large.

Baclofen is structurally similar to GABA and binds to presynaptic GABA-B receptors within the brain stem, dorsal horn of the spinal cord, and other CNS sites. On the basis of electrophysiology and preclinical studies, the mechanism of the antispasticity effects associated with intrathecal baclofen is believed to result from hyperpolarization of motor horn cells.
reaches maximal therapeutic response levels on the Ashworth scale.

Clearly, the lower extremities responded more to the double-blind bolus trial of baclofen than did the upper extremities with regard to muscle tone, spasms, and reflexes. This has been reported in patients with traumatic brain injury but has never been systematically studied in the stroke population. This may be due to a number of issues. First, patients were screened for admission to the study primarily because of disabling lower extremity spastic hypertonia, and the upper extremity involvement was often less profound. Also, spastic hypertonia can vary from day to day, as was noted by the difference in the admission upper extremity tone scores between the placebo group and the active drug group. However, it is likely that the greatest potential benefit of ITB therapy may be in the patients with significant spastic hypertonia in the lower extremities, since this is where the medication is concentrated. This is most likely due to the fact that studies have demonstrated that the lumbar-to-cisternal drug concentration in the CSF is 4.1:1.24

Because intrathecally delivered baclofen crosses to the spinal cord quite quickly, it makes sense to move the delivery catheter more cephalad in patients with spasticity/dystonia involvement of the upper extremities. In patients with considerable spasticity and/or dystonia in the upper extremities, we have experienced considerable success placing the catheter tip up to the midthoracic area. Still, the effect of ITB in the upper extremities was not as dramatic as in the lower extremities. This in part is accounted for by patient selection, because the patients were selected for their predominately lower extremity spastic hypertonia. However, it appears that the drug effect does decrease as one moves cephalad with continuous delivery. While moving the catheter more cephalad may help, it appears that the effect is still always more profound in the lower extremities.

During the first months of continuous therapy, many patients required frequent dose adjustments as they adapted to changes in lifestyle and improved functional status with reduced spasticity. Many patients must learn to adapt to mobility, transfer, and self-care techniques after a reduction of their spasticity. Patients typically required a period of intensive inpatient rehabilitation to benefit functionally from the decreased motor tone and/or increased voluntary motor control they experienced with the administration of ITB. Patients were generally scheduled for follow-up 10 days after pump placement and then as frequently as necessary, beyond the scheduled data collection times, to obtain optimal dosing.

Dose adjustments, determined by the caregivers and researchers with the most basic goal of decreasing the tone or spasm frequency 2 points in the affected limbs, were limited to an increase of 20% of the current dose or 50 μg, whichever was less. The goal was to reduce the tone or spasm frequency to normal as closely as possible. Only when there was a perceived functional detriment with transfers, mobility, activities of daily living, or posture, or there was no change in the tone or spasm frequency levels with the last increase, was there consideration of not increasing the ITB dose. These dose adjustments can be performed as early as 24 hours after the previous dose adjustment. In this study, the effects of ITB on spasm frequency were not as profound, probably because these patients were predominately “dystonic” rather than “spastic.” From a physiological standpoint, spasticity is defined as a motor disorder characterized by a velocity-exaggerated increase in tonic stretch reflexes (muscle tone), with exaggerated reflex responses, resulting from hyperactivity of the stretch reflex. The dystonia acquired as a result of a stroke often presents as a persistent attitude or posture of the extremities, such as an overextension or overflexion of the hand, inversion of the foot, or torsion of the spine associated with twisting, lateral bending, or torsion of the back. Another description of dystonia is a “syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures.” While dystonia is the second most common movement disorder, only 25% to 33% of the cases can be considered to be secondarily acquired due to an injury or illness to the CNS. Indeed hemidystonia, in contrast to focal dystonia, almost always results from injury or illness involving the CNS. Spastic hypertonia from stroke encompasses a variety of conditions, including dystonia, rigidity, myoclonus, muscle spasm, posturing, and/or spasticity. All of these conditions may contribute to increased tone or involuntary movement and may not be easily distinguishable from one another in the severely afflicted individual.

There has been no reduction of voluntary motor function noted in this patient population treated with continuously delivered intrathecal baclofen and this is consistent with results from other studies. In patients who rely on reflex spastic hypertonia to assist them with functional activities, a reduction in their baseline spastic hypertonia is of concern. This can be assessed in the bolus trial. An excessive loss of tone, which occurs during the baclofen screening trial, is not a direct contraindication for pump placement. One should perform detailed motor strength testing and assess for changes in transfers and mobility at 1, 2, 4, and 6 hours after the bolus if a significant loss of motor strength or tone is relevant to the functional status of the patient. Because the pump can be used to modulate the spastic hypertonia via computer programmable titration of baclofen delivery, patients who rely on some reflex tone for functional activities can have the dose adjusted precisely to fit their needs. For this reason, frequent patient evaluations over time during the baclofen screening trial are particularly valuable in the cerebral disorder patient population.

The majority of our patients continue to undergo therapy to reduce soft- and dense-tissue contractures and further improve functional mobility. For the patients with arthrogenic contractures, it is unlikely that any treatment, other than surgery, will correct the problem. This process takes many months. Once contractures are reduced as far as possible by splinting and range-of-motion exercises, selected patients may go on to tendon lengthening procedures. It is expected that these surgeries will not need to be repeated now that the spastic hypertonia is adequately controlled. Until now, it has not been possible to predict the amount of remaining motor function or coordination the patient may possess without a reduction in the motor tone. Although the bolus trial can provide some insight, many patients will not be...
able to be fully assessed until after several months of continuous ITB combined with physical and occupational therapy. These patients have never learned how to coordinate their movements with a reduced level of motor tone. Retraining this coordination to develop new motor engrams requires considerable therapy. Among patients with spastic hypertonia with residual functional motor strength, it is rare that a decrease in motor strength occurs with therapeutic doses of intrathecal baclofen.\textsuperscript{1,8} Often, an increase in functional strength has been reported.\textsuperscript{7–10} The increase in functional strength is thought to result from a reduction in motor tone, which often is so high before treatment that it effectively reduces the voluntary motor capacities of the hypertonic extremities. Two of our patients have entered the constraint-induced therapy program at our institution\textsuperscript{35,36} after >6 months of continuous treatment with ITB.

**Conclusion**

Continuous intrathecal infusion of baclofen can maintain a reduction in spastic hypertonia in the upper and lower extremities associated with stroke. This reduction in tone will allow more freedom of movement and the potential for improved function when combined with a therapy program after ITB pump placement. The next step in research with regard to pharmaceuticals that reduce spastic hypertonia is to define the types of therapy and doses of therapy that need to be combined with a particular pharmaceutical intervention. This will allow one to better select the combinations that may most benefit the particular presentation of a spastic hypertonic patient.

**References**

In the last decade, there has been a lot of excitement in the field of stroke rehabilitation with the introduction of 3 new therapies for spastic hypertonia: tizanidine, botulinum toxin, and intrathecal baclofen (ITB). These new modalities have offered clinicians more treatment options and sparked a renewed interest in better understanding spastic hypertonia and its contribution to disabilities in stroke. Tizanidine is viewed as superior to baclofen because of reports of more benign adverse-event profile,1 but while effective in certain situations, its use in stroke survivors is limited by side effects such as sedation and drowsiness.2 Botulinum toxin therapy is effective in focal spasticity3,4 but is limited by severity of spastic hypertonia and the maximum dose that can be injected every 3 to 4 months.5 Thus, a niche for ITB therapy has been carved out for stroke survivors who have severe, functionally limiting, multijoint spastic hypertonia with predominant involvement of the lower limbs, and who cannot either tolerate the effects of oral drugs or respond to adequate doses of other therapies.

A small, but well-designed, trial of ITB in unilateral spastic hypertonia reported that tone, spasms, and reflexes improved after continuous ITB infusion in stroke survivors with unilateral spastic hemiplegia.6 Moreover, the unaffected limbs maintained strength. Yet many clinicians appeared reluctant to use ITB in stroke, because of concerns that intrathecally administered baclofen may not only affect the spastic limbs but also cause weakness in the uninvolved side. The preceding study by Meythaler and colleagues lessens this concern. In addition, it notes—albeit informally—functional improvement in some of the subjects. Using a randomized, double-blind, placebo-controlled method during the screening phase and an open-label design for the long-term follow-up period, the investigators showed that continuous ITB infusion resulted in maintained improvement in muscle tone (measured by the Ashworth scale) and spasm frequency and reflex scores, particularly in the affected lower limbs. This does not come as a surprise, because many studies have proven the efficacy of ITB in managing spastic hypertonia in patients with cerebral disease or trauma. However, in reality stroke survivors do not care about improvements in Ashworth scores or degrees of joint range of motion. What really matters to them cannot be expressed by numerical scales. Rather, they ask: “Will I be able to walk again?” “Will I be able to feed myself again?” “Will these painful spasms ever stop so that I can have restful sleep?” Thus, the important question for clinicians should be: In addition to improving muscle tone and spasms, can ITB therapy also unleash the potential for motor recovery?

What should be considered exciting in the study of Meythaler et al are the confirmation of earlier findings that unaffected limbs maintained muscle strength and the observation of functional improvement. The latter is particularly interesting, because many studies in spasticity management use tone reduction as the primary outcome measure and fail to investigate if this reduction of impairment translates to increased function. Understandably, attempts to address functional enhancement as an outcome measure are unsuccessful either because of the insensitivity of established “functional scales” in detecting clinical changes or the inability to reduce functional improvements to a numerical value. Traditional outcome scales may not accurately reflect improvements in pain, life satisfaction, and nursing care, and prevention of complications. Meythaler et al listed functional improvements, such as progression from wheelchair dependence to modified independence in ambulation, increase in comfort, and improvement in ability to transfer. Only one other report specifically addressed functional improvement with ITB therapy use in stroke. In a small observational study (G.E. Francisco, MD, unpublished data, 2001), 8 stroke survivors improved their customary walking speed several months after receiving continuous ITB infusion therapy. Also, a multicenter study currently in progress addresses quality of life and function after ITB treatment.7

It is still unclear why the uninvolved limbs are not affected by ITB, at least clinically. Perhaps ITB has a selective effect on certain spinal cord receptors that also receive supraspinal input modified by cerebral disease. Or maybe the small amount of baclofen in the intrathecal space may not be enough to produce clinically detectable weakness. This is one observation that still needs further investigation to have a better understanding of the mechanism of action of ITB at the cellular level. Conceivably, an animal model may elucidate this matter. There are also concerns, based on animal studies,8 about the potential negative effects of baclofen, an agonist of the inhibitory neurotransmitter GABA, on recovery. Although this has not yet been systematically investigated in humans, the observed clinical improvement in tone and function after ITB therapy makes it unlikely.

If ITB is indeed effective, why is it still not considered a first-line treatment for severe spastic hypertonia in stroke? Perhaps the fact that the ITB pump is surgically placed makes it less attractive than nonsurgical interventions, such as physiotherapy, oral medications, and chemodenervation. In many instances, only when these nonsurgical options fail to adequately relieve spastic hypertonia will clinicians and patients resort to ITB. Thus, the important clinical questions become: “In severe spastic hypertonia, how much time and...
money should be spent on oral medications, nerve blocks, and botulinum toxin before using ITB therapy?” “How long should a stroke survivor experience spasms and discomfort and inability to fully participate in physiotherapy before ITB is considered?” Obviously, this has significant implications, not only in the cost-effectiveness of management strategies but also in rehabilitation efforts and recovery potential. When spastic hypertonia overwhelms the residual motor power, it may prevent rehabilitation therapy from positively influencing recovery and may encourage the phenomenon of “learned non-use” of the affected limbs.

As yet, we are at the early stage of understanding the mechanism of action of ITB in unilateral spastic hypertonia and learning to properly identify in a timely manner which stroke survivors will not adequately respond to therapies other than ITB. We are still faced with the challenge of improving our ability to assess spastic hypertonia and its impact on function, and to measure treatment effects on functional recovery. This pioneering work by Meythaler et al confirms the efficacy of ITB in unilateral spastic hypertonia and how it may help unleash the potential for functional recovery after stroke.

Gerard E. Francisco, MD, Guest Editor
Brain Injury Program
The Institute for Rehabilitation and Research
Department of Physical Medicine and Rehabilitation Alliance
Baylor College of Medicine

and University of Texas Health Sciences Center
Houston, Texas

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Jay M. Meythaler, Sharon Guin-Renfroe, Robert C. Brunner and Mark N. Hadley

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