Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity

JOE I. ORDIA, M.D., EDWARD FISCHER, M.D., ELLEN ADAMSKI, R.N., AND EDWARD L. SPATZ, M.D.

Department of Neurosurgery, Boston University Medical Center Hospital, and Boston University School of Medicine, Boston, Massachusetts

The aim of this study was to determine the efficacy, safety, and cost-effectiveness of intrathecal baclofen delivered by a programmable pump for the chronic treatment of severe spasticity. Sixty-six patients with severe spasticity of spinal cord origin that was refractory to oral baclofen or who experienced intolerable side effects with this form of the drug were screened. The first nine participated in a double-blinded, randomized, placebo (normal saline)-controlled trial to determine response to a bolus dose of intrathecal baclofen. Subsequent patients were enrolled in an open-label treatment protocol without a placebo trial. All passed the screening, and the pump was implanted in 59 patients. Spasticity scores and medical costs before and after surgery were analyzed.

In all patients, the mean Ashworth score for rigidity decreased from 4.3 preoperatively to 1.4 (p < 0.0005) with use of intrathecal baclofen. The spasm frequency score decreased from a mean of 3.6 to 0.5 (p < 0.0005). Activities of daily living, sleep, and skin integrity improved, and pain was eradicated in some. Constipation occurred in six patients. A reduction in dosage was necessitated by muscular hypotonia in three ambulatory patients, areflexic bladder and urinary retention in three others, and nausea, dizziness, and drowsiness in one. Catheter-related problems occurred 19 times in 15 patients. One pump was explanted because of infection in the pump pocket, and one was removed after it eroded through the skin. There were no pump failures. The use of intrathecal baclofen resulted in a decrease in the average length of subsequent hospitalizations. It is concluded that intrathecal baclofen delivered by an implanted programmable pump is a safe, effective, and cost-efficient method for treatment of severe intractable spinal spasticity.

Key Words • baclofen • spasticity • programmable pump • spinal cord injury • multiple sclerosis

Pasticity is a motor disorder characterized by a velocity-dependent increase in muscle tone (rigidity) and uncontrolled repetitive involuntary contractions of skeletal muscles (spasms). Next to the loss of voluntary control, spasticity is often the most troublesome problem in patients with upper motor neuron lesions. Baclofen, an agonist of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), is the most widely used antispasmodic drug. Oral administration often results in tolerance, and as higher doses become ineffective they produce central nervous system (CNS) side effects such as confusion and drowsiness. Ablative procedures have a high failure rate. Animal studies and human trials have demonstrated that infusion of small doses of baclofen into the subarachnoid space can dramatically control spasticity.

Clinical Material and Methods

Study Population

Sixty-six patients with intractable spasticity of spinal cord origin were enrolled in the study between February 1989 and February 1992. Medical treatment had failed in all of these patients. Fifty-nine underwent implantation of a programmable pump (SynchroMed Infusion System; Medtronic Inc., Minneapolis, MN). Of these, 27 had spinal cord injury (SCI), whereas 26 suffered from multiple sclerosis (MS). Others had familial spastic paraparesis (two patients), spinal cord tumor, cervical spondylotic myelopathy, transverse myelitis, and amyotrophic lateral sclerosis (one patient each). Severe spasticity was defined as an Ashworth score of 3 or higher or a spasm score of 2 or higher. The mean duration of symptoms was 12 years (range 5 months–34 years). The ages of the patients ranged from 16 to 73 years (mean 42 years). There were 35 males and 24 females. The mean follow-up period was 42 months (range 23–70 months). Informed consent was obtained. The study protocols were approved by the Institutional Review Board for Human Research at Boston University Medical Center.

Prescreening Clinical Evaluation

A prescreening assessment included a medical history, physical, and neurological examinations. Spasticity was
Intrathecal baclofen

**TABLE 1**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>rigidity (Ashworth scale)</td>
<td></td>
</tr>
<tr>
<td>no increase in tone</td>
<td>1</td>
</tr>
<tr>
<td>slight increase in tone giving a &quot;catch&quot; when affected</td>
<td>2</td>
</tr>
<tr>
<td>part(s) move in flexion or extension</td>
<td>2</td>
</tr>
<tr>
<td>more marked increase in tone but affected part(s) easily flexed</td>
<td>3</td>
</tr>
<tr>
<td>considerable increase in tone; passive movement difficult</td>
<td>4</td>
</tr>
<tr>
<td>affected part(s) rigid in flexion or extension</td>
<td>5</td>
</tr>
<tr>
<td>spasm frequency*</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>no spontaneous spasms; vigorous sensory &amp; motor stimulation results in spasms</td>
<td>1</td>
</tr>
<tr>
<td>occasional spontaneous spasms &amp; easily induced spasms</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 but &lt;10 spontaneous spasms/hr</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 spontaneous spasms/hr</td>
<td>4</td>
</tr>
</tbody>
</table>

* Spasms are measured by the number of spontaneous flexor and extensor muscle spasms over a 1-hour period.

measured by the degree of rigidity in the lower limbs (Ashworth score) and by the spasm frequency score (Table 1). Pregnant women or those with childbearing potential who were not using birth control were excluded. Allergy to baclofen and impaired renal or hepatic function were also grounds for exclusion. A radiographic study, computerized tomography scan, or magnetic resonance image of the spine was obtained in patients with spinal deformity.

**Screening Procedure**

The first nine patients received a double-blinded, randomized, placebo-controlled trial. Placebo (saline) and 50 μg of baclofen were randomly administered intrathecally on Days 1 and 2; the code was then broken. If there was no response to the 50 μg dose, placebo or 75 μg of baclofen were randomly administered on Days 3 and 4. The code was again broken. Patients showing no response were then randomized to placebo or 100 μg of baclofen on Days 5 and 6. Each dose was separated by at least 24 hours.

A positive response consisted of a reduction in the mean Ashworth score or the mean spasm frequency score of two or more points for at least 4 hours. The trial was stopped when a positive response was obtained. Those who responded to placebo or did not respond to the 100-μg bolus were not eligible for pump implantation.

The remaining 57 patients were enrolled into an open-label treatment protocol without placebo. A 50-μg dose of baclofen was administered initially. If there was no positive response the trial was continued in a stepwise fashion with dose increases in 25-μg increments every 24 hours to a maximum of 100 μg. An interval of at least 1 week was allowed between the screening and the implantation of the pump. All implantations were performed by the same surgeon (J.I.O.).

**Implantation Procedure**

Implantation of the infusion pump was performed with the patient receiving local or general anesthesia. The patients were placed in the lateral decubitus position to provide access to the back and abdomen. A lumbar puncture was performed with a Tuohy needle through a small incision in the lumbar area. A radiopaque silicon rubber catheter was fluoroscopically guided toward the conus medullaris. The pump was placed in a subcutaneous pocket in the lower quadrant of the abdomen and connected to the catheter. The initial daily dose of baclofen was double the effective screening dose. Patients remained hospitalized for a few days for dose titration. During this phase the dose was increased or decreased by 10% to 40% once a day until the response was satisfactory. The initial follow-up review was performed 2 to 4 weeks postsurgery and subsequently every 2 to 3 months for pump refill.

**Cost Study**

The first 10 eligible patients to give consent were studied. Patients who had received acute rehabilitation less than 1 year before surgery were excluded. Records of all hospitalizations and other healthcare-related costs from 1 year before the implantation of the pump through the end of the 1st year postsurgery were collected. Medical costs 1 year before and 1 year after surgery were compared.

**Statistical Analysis**

The primary statistical outcome variables were changes in the Ashworth and spasm frequency scores and were analyzed by the Wilcoxon rank-sum test.14

**Results**

**Clinical Response to Intrathecal Baclofen**

All 66 patients responded positively to the bolus dose of intrathecal baclofen. Sixty-one (92%) responded to 50 μg, three required 75 μg, and two required 100 μg. None responded to placebo. The mean Ashworth score for rigidity decreased from 4.3 preoperatively to 1.4 (p < 0.0005) at the last follow-up review, at which time patients were receiving chronically infused intrathecal baclofen. The spasm score decreased from a mean of 3.6 to 0.5 (p < 0.0005) in the same period. Several patients found that activities of daily living such as transferring from wheelchair to bed were easier to accomplish. Muscle aches and pain, sleeplessness, and the overall misery associated with uncontrolled spasms were considerably improved. One college student’s grades sharply improved because he was more alert after discontinuing large doses of oral antispasmodic medications.

Several females found that maintaining personal hygiene was more satisfactory when they no longer had adductor spasticity and scissoring at the hips. Four reported that they were able to have sexual intercourse. Some male patients also found sexual intercourse easier. Four ambulatory patients were able to walk with less effort, whereas one patient who had previously been wheelchair bound became ambulatory. Voice was clearer in four patients, a finding confirmed by family members. The mechanism involved appears to be relief of intercostal and oropharyngeal spasms.

A number of patients who had previously felt embarrassed by their severe spasms in public were able to...
resume their social lives. Two previously unemployed patients became gainfully employed, one as a taxi driver. With spasms eliminated, a number of patients took fewer sick days off from work.

A few patients had increased urinary bladder capacity and reduction in the number of daily catheterizations. Some converted from an indwelling catheter to intermittent drainage. We retrospectively identified six patients who had undergone routine urodynamic studies prior to and after pump implantation. Four of these patients were quadriplegic from SCI, whereas two had MS. Five of the six had detrusor hyperreflexia and bladder–sphincter dyssynergy prior to surgery, and one SCI patient had a hypotonic bladder. With intrathecal baclofen treatment, hyperreflexia decreased in one patient with SCI, and one developed a hypotonic bladder. Hyperreflexia was unchanged in one patient, and the one with a hypotonic bladder preoperatively remained unchanged. Of the two MS patients, one had persistent hyperreflexia, whereas the other had a decrease in contractility.

Prior to implantation of the pump, the average daily dose of oral baclofen was 99 mg. The average initial effective dose of intrathecal baclofen was 126 µg daily (range 14–280 µg). There was no correlation between the oral dose and the effective intrathecal dose. There was no significant difference between dosages in SCI (118 µg/day) and MS patients (140 µg/day) (p = 0.14). The average dose was higher for nonambulatory (131 µg/day) than for ambulatory patients (93 µg/day) (p = 0.03). Quadriplegic patients averaged 130 µg per day versus 110 µg per day for paraplegic patients (p = 0.17).

During the course of therapy, many patients demonstrated a steady escalation of the effective dose, with most achieving a stable dose after 6 months. The dose increased from an average of 126 µg daily (range 14–280 µg) initially, to 256 µg at 6 months, and 272 µg at 12 months. The daily dose later remained stable at an average of 276 µg at 24 months and 275 µg at 48 months, with a range of 42 to 700 µg (Fig. 1).

Patients with MS showed a greater variability in dosage than those with SCI, which was probably a reflection of the fluctuations found in the course of MS (Fig. 2).

Drug Tolerance

Pharmacological tolerance was identified in one patient with MS 21 months after the pump was implanted. The dose of intrathecal baclofen administered in this patient increased from 520 to 800 µg daily over a 2-month period. Radiographic and radionuclide studies showed the system to be patent. He was given a 1-month drug holiday from intrathecal baclofen, during which he received 2 mg of intrathecal morphine daily. When intrathecal baclofen was resumed, he had an excellent response to 100 µg daily.

Treatment Complications

Six patients with preexisting constipation were more symptomatic postsurgery. All responded to a vigorous bowel regimen consisting of enemas and suppositories. Muscular hypotonia in three ambulatory patients, urinary retention in three others, and nausea, dizziness, and drowsiness in one patient responded to a decrease in dosage. There was no respiratory depression and no coma. Problems with the intrathecal catheter occurred 19 times in 15 patients. These consisted of seven breaks in five patients, nine occlusions, two punctures, and one dislodgement. Two pumps were explanted, one because of infection in the pump pocket and the other because of skin erosion. One cerebrospinal fluid (CSF) leak was treated with laminectomy and repair of the dura. There were no pump failures. Our current use of a thicker-walled catheter has resulted in a decrease in catheter-related problems.

One patient died from progression of severe MS 2 years after the pump was implanted. Another patient with advanced MS died of urosepsis 18 months after she received the pump. Neither patient experienced complications from intrathecal baclofen therapy.
Cost–Benefit Analysis

There was a reduction in the average length of hospitalizations, but no change in the overall utilization of outpatient resources during the 1st year after the pump was implanted. The gross cost savings for all hospitalizations were calculated, rather than just those related to spasticity, as in a recent study in Canada.\textsuperscript{21} For the year prior to implantation, excluding days spent in screening, the 10 patients had 12 hospitalizations with an average length of stay of 7.9 days, for a total of 95 days. For the 1st year postimplantation, excluding the implant itself, they had 12 hospitalizations, with an average length of stay of 5.7 days, for a total of 68 days. The net reduction in hospital days was 27, for an average reduction of 2.7 hospital days per patient. This represented an annual savings of $6750 per patient when we applied an average charge of $2500 per day, based on costs at our institution.

To determine the overall impact of this therapy on hospitalizations, the 58 days (average of 5.8 days per patient) spent in screening and implanting were analyzed. Assuming that the reduction in hospital days continues beyond the 1st year, the cost of implanting the system is paid back in less than 2 1/2 years on average.

Discussion

Spasticity can be debilitating for patients with disorders of the upper motor neuron. Failure of the descending inhibitory signals from brain centers to reach the motor neuron allows the exaggeration of the excitatory afferent impulses from proprioceptive pathways. The rigidity and spasms are most noticeable in the antigravity muscles (flexors of the arms and extensors of the legs). Although some use the rigidity to stand or pivot, for most individuals spasticity is painful and is an impediment to rehabilitation, self-care, and sleep. Violent spasms can result in decubitus ulcers, fractures and dislocations, and may propel the patient out of the wheelchair.

The treatment of spasticity follows a stepladder approach beginning with physical therapy and stretching exercises and progressing to invasive measures. Oral baclofen was approved by the Food and Drug Administration (FDA) in 1977 and is still the most widely used antispasmodic medication. Approximately one-third of the patients treated with oral baclofen become refractory or have intolerable side effects at effective doses. Intrathecal baclofen is a safe and effective alternative to ablative procedures, which are often ineffective.

The addition of a chlorophenyl group to GABA (Fig. 3) produces the more lipophilic baclofen. By itself, GABA has no therapeutic application because it is impermeable across the blood-brain barrier (BBB), which excludes molecular weights of more than 500. The BBB is even more repellent to hydrophilic substances such as GABA, blocking molecular weights greater than 150. Baclofen has a molecular weight of 213.67 but is partly lipophilic and has greater access to the CNS. The BBB can be bypassed by direct introduction of the drug into the CSF.

The infusion system used in this study consists of a pump, an intrathecal catheter, and an external computer programmer. The pump is made of titanium, has a diameter of 3 in, a thickness of 1 in, and is powered by a lithium battery that has a life span of 3 to 5 years. The device should not be implanted in the presence of cutaneous or systemic infection. Because telemetry may interfere with other electronic devices, the appropriate manufacturers should be consulted before implanting the pump in a patient who has another electronic device.

Phases of Therapy

There are four phases in the therapy, as follows: 1) patient selection according to the criteria described above; 2) screening trial to determine response to intrathecal baclofen before pump implantation; 3) implantation of an intrathecal catheter that is placed with the tip between T-10 and L-2; it is tunneled to the pump, which is placed in a subcutaneous pocket in the abdominal wall; and 4) maintenance therapy, establishing the minimum dose for each patient that relieves troublesome spasticity, preserves any residual voluntary movement, and is free of side effects. Patients are weaned from oral baclofen over 2 to 4 weeks because abrupt cessation of baclofen may result in withdrawal symptoms, delirium, hallucinations, and seizures.
Refill intervals are usually 2 to 3 months. Baclofen is stable in the pump for up to 90 days. The effective dose tends to increase with time.6,10,26,28 When tolerance develops, patients become refractory to increasing doses of medication. Efficacy can be reestablished at a lower dose after a drug holiday. Intrathecal morphine9,10 has been successfully used during this holiday. Others have reported success with intrathecal fentanyl,5 but this drug is not approved by the FDA presently for intrathecal use. Progression of disease, decubitus ulcers, urinary tract or systemic infection, or a system malfunction can also result in loss of efficacy. An abrupt loss of efficacy is likely to be due to a system failure. The device may be evaluated by telemetry, radiographic, and radioisotope studies.29

Benefits of Baclofen Therapy

The primary benefit is the relief of severe spasms and rigidity. Patients become more independent with increased self-care and mobility. Voluntary muscle control previously masked by spasms might even reemerge.17 Improved sleep, increased independence, and in some the ability to have sexual intercourse enhances the quality of life. Urinary function may improve following reduction of detrusor hyperreflexia and uninhibited bladder contractions.4,10,22,25,30 The muscle pain that frequently accompanies the spasms may also be helped. Baclofen is an antagonist of substance P and has analgesic properties that can suppress central pain.11,31

Risks of Baclofen Therapy

The most frequent drug related side effects include drowsiness, dizziness, constipation, and muscular hypotonia.4,30 Seizures can occur in patients with a preexisting brain lesion,13 or if baclofen is abruptly withdrawn. Drug overdose may produce respiratory depression, hypotension, bradycardia, and coma. In case of an overdose, ventilatory support, intravenous fluids, and vasopressors should be available for resuscitation. The pump should be stopped and emptied. Some CSF may be removed via lumbar puncture. Baclofen has no direct antidote, but drowsiness and respiratory depression might be reversed by 1 to 2 mg of intravenous physostigmine given over 5 to 10 minutes.20 Physostigmine should be used with caution to avoid seizures, bradycardia, and disturbances of cardiac conduction.8

Conclusions

Long-term intrathecal baclofen administered by an implanted programmable pump is a safe, clinically effective, and cost-effective method for treatment of severe intractable spasticity of spinal origin.1,4,17,21,23,25,28

Acknowledgment

We wish to thank Mr. Richard O’Brien for his help in scheduling patients and for his overall assistance with this study.

References
Intrathecal baclofen


Manuscript received July 18, 1995.
Accepted in final form April 15, 1996.
This work was supported in part by a research grant from Medtronic Inc., Minneapolis, Minnesota.
Address reprint requests to: Joe I. Ordia, M.D., Department of Neurosurgery, Boston University Medical Center Hospital, 720 Harrison Avenue, Boston, Massachusetts 02118.