Effects of intrathecal baclofen on voluntary motor control in spastic paresis

MARK L. LATASH, PH.D., RICHARD D. PENN, M.D., DANIEL M. CORCOS, PH.D., AND GERALD L. GOTTLIEB, PH.D.

Departments of Neurosurgery and Physiology, Rush Medical College, and Department of Physical Education, University of Illinois at Chicago, Chicago, Illinois

Intrathecal baclofen injections were given to six patients with long-standing spastic paresis resistant to any nondestructive treatment, including oral baclofen. Attempts by the patients at voluntary muscle activation before intrathecal administration of baclofen led to considerable uncontrolled coactivation of antagonist and distant muscles. After the injection, dramatic suppression of the spastic signs was accompanied by more selective voluntary muscle activation. Tonic coactivation of the antagonists and distant muscle groups during voluntary contractions was decreased while the agonist level on electromyography (EMG) was not affected (three cases) or only slightly reduced (three cases). Furthermore, in one patient with sufficient residual motor control function, there was a considerable increase in the speed of fast isotonic movements, accompanied by the emergence of the ability to generate phasic muscle bursts on EMG that were characteristic of normal motor patterns. The results suggest that baclofen exerts different effects upon reflex pathways and descending motor pathways. This therapy appears to be a promising way for improving residual motor control in patients with increased muscle tone and/or reflexes.

Key Words • Baclofen • Spasticity • Paresis • Intrathecal Drug Infusion • Infusion Pump

Deterioration of motor neuron function due to upper motor neuron damage is associated with a velocity-dependent increase in stretch reflexes and increased muscle tone. The precise relationship between these signs of spasticity and motor function has been an issue of debate for many years. Hughlings Jackson considered the positive signs of spasticity to be a release phenomenon and the motor disability to be a negative symptom reflecting motor neuron damage. In his view, the two are linked causally, but eliminating the signs of spasticity would not be expected to help motor function. Landau has restated this position and forcefully argued that motor function cannot be improved with medications, nerve blocks, electrical stimulation, or destructive neurosurgical procedures which might reduce spasticity. He has warned that such expectations will not be met because they do not deal with the primary problem of diminished neural input to segmental control of the final common path. Landau's view has been challenged by a number of studies in which hyperactive reflexes and co-contraction of antagonist muscles appear to interfere with proper motor function. In particular, Corcos and his colleagues demonstrated that the hyperactive soleus reflex in spastic patients could interrupt voluntary dorsiflexion. In this case, it seems that more normal movement might occur if the hyperactive reflex were suppressed.

A previous study has shown that intrathecal baclofen can cause complete suppression of hyperactive mono- and polysynaptic reflexes in severely spastic patients. Thus, intrathecal baclofen provides a tool with which to study impaired voluntary motor control in the same patients with and without signs of spasticity. This approach has demonstrated that, in spite of severe upper motor neuron deficits, the elimination of spasticity allows the emergence of improved patterns of muscle activation and, in some cases, improved voluntary movements.

Materials and Methods

Patient Population

Six patients with long-standing spasticity and impaired voluntary motor control were studied before and after lumbar administration of intrathecal baclofen (Table 1). Their spasticity originated from multiple sclerosis (Cases 1 to 4), cervical spinal cord trauma (Case 5), and posttraumatic supraspinal pathology (Case 6). In Case 6, computerized tomography and magnetic resonance
Intrathecal baclofen and voluntary motor control

TABLE 1
Characteristics of the patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Type of Spasm*</th>
<th>Duration of Spastic Symptoms (yrs)</th>
<th>Ashworth Index†</th>
<th>Babinski Sign‡</th>
<th>H-Reflex§</th>
<th>Ankle Clonus‖</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>multiple sclerosis</td>
<td>F/E</td>
<td>1</td>
<td>2.8</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>multiple sclerosis</td>
<td>F/E</td>
<td>1</td>
<td>4.8</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>multiple sclerosis</td>
<td>F/E</td>
<td>1.5</td>
<td>4.6</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>multiple sclerosis</td>
<td>F</td>
<td>1</td>
<td>5.0</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>spinal cord trauma</td>
<td>F/E</td>
<td>1</td>
<td>2.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>supraspinal trauma</td>
<td>F/E</td>
<td>7</td>
<td>4.0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* F/E = symmetrical flexor-extensor spasms; F = predominance of flexor spasms. In the multiple sclerosis patients the duration of the disease was much longer (from 4 to 24 years).
† Average values of Ashworth Index\(^7\) for the ankle, knee, and hip joints of both legs for the first five patients and for the right leg only for Case 6.
‡ Presence (+) or absence (−) of the Hoffmann (H)-reflex in the right soleus muscle group.
§ Presence (+) or absence (−) of the Hoffmann (H)-reflex in the calf muscle group of these five patients by electrical stimulation of the tibial nerve.
‖ Ankle clonus longer than 3 seconds; − = absence of ankle clonus.

imaging of the brain demonstrated mild generalized atrophy and a decrease in size of the left peduncle. All of the patients demonstrated typical spastic signs, including Babinski's sign, vigorous tonic muscle contractions in response to passive joint movements (reflected by the Ashworth Index\(^7\) in Table 1), and uncoordinated and inappropriate activation of antagonist and distant muscles during attempts at voluntary muscle activation. Five patients demonstrated ankle clonus; it was also possible to induce the Hoffman (H)-reflex in the calf muscle group of these five patients by electrical stimulation of the tibial nerve.

The patients were part of a group of 20 patients in whom the effects of chronic intrathecal baclofen were evaluated. All of these patients had failed to respond to oral medications, including baclofen, and destructive procedures were being considered to reduce their spasticity. The study was approved by the Rush Human Investigation Committee and the Food and Drug Administration (new drug and device investigations). Prior to testing, each patient signed an informed consent form after being familiarized with the experimental apparatus.

Apparatus

In Cases 1 to 5, electromyograms (EMG's) of the primary flexor and extensor muscles of the right leg (soleus, tibialis anterior, quadriceps, and hamstring muscles) were recorded and processed by a digital computer. In the patient with a supraspinal disorder (Case 6), EMG's of the primary flexor and extensor muscles of the right arm (biceps, brachioradialis, and long and lateral heads of triceps muscles) were recorded simultaneously with angle and acceleration at the right elbow joint.

The EMG's were recorded using surface electrodes* with built-in field effect transistor preamplifiers and filters with an optimal bandpass of 40 to 500 Hz. Elbow angle was measured with a potentiometer mounted on the manipulandum shaft; acceleration was measured with an accelerometer mounted on the distal end of the manipulandum. Each signal was sampled at a rate of 1000/sec with 12-bit resolution. The EMG's were digitally rectified and all signals were low-pass filtered (average 25 msec moving window).

Trial Procedure

In Cases 1 to 5, severe spasms made external fixation devices dangerous. Therefore, the only indices of voluntary muscle activation were EMG's of the muscles. The patients were either sitting in a wheelchair (Cases 3, 4, and 5) or lying supine on a bed (Cases 1 and 2). They were asked to perform a movement of the right ankle or knee joint as strongly as they could. Three trials were recorded for each movement. All of these patients had only a weak residual motor function, and attempts at the movements did not lead to visible limb displacement either before or after baclofen administration. The best single trials, indicated by the highest agonist level on EMG and the lowest coactivation of other muscles, both before and after baclofen administration, were plotted and compared.

Motor function was preserved much better in the patient with a supraspinal disorder (Case 6). This patient was asked to perform elbow flexion and extension movements as fast as possible from a starting position of 65° or 135° in the elbow joint (full flexion corresponds to 180°) to a target specified on a monitor screen. Accuracy requirements were not stressed. The amplitude of the movements was 54°; the target width was 9°. Six trials were recorded for both flexion and extension before and after baclofen injection. For the purpose of averaging, the trials were aligned with respect to the beginning of the first agonist burst from the biceps or lateral head of the triceps muscle. Averaged results before and after baclofen injection were plotted and compared.

* Boston Elbow Myoelectrodes manufactured by Liberty Mutual, Hopkinton, Massachusetts.
FIG. 1. Single electromyographic (EMG) trials during voluntary dorsiflexion (activation of tibialis anterior (TA)) in a patient with multiple sclerosis (Case 1) before (A) and after (B) intrathecal baclofen administration. There is significant activation of an antagonist (soleus (SOL)) muscle leading to ankle clonus and coactivation of distant muscles (quadriceps (QUAD) and hamstrings (HAM)) before baclofen injection. Baclofen administration caused suppression of this activity without suppressing the agonist tracing to a comparable extent (compare TA in A and B). The EMG scales are in μV; total time scale is 3000 msec, and time scale bin is 50 msec.

**Baclofen Injection**

A bolus intrathecal baclofen injection (50 to 75 μg of baclofen in 25 μg/cc saline) was given at the lumbar level over 1 minute. Baclofen was obtained in powder form and was reconstituted by the pharmacy at Rush Medical Center according to protocol approved by the Food and Drug Administration. A permanent subcutaneous drug pump was later implanted to provide programmed intrathecal delivery of baclofen.

**Results**

Attempts at voluntary muscle activation before baclofen administration led to levels of coactivation of antagonist and distant muscle groups comparable to the agonist activation level in all patients (Figs. 1A, 2A, and 3). This muscle activity produced slow, awkward changes in the joint position. Attempts at voluntary movement provoked ankle clonus in three patients. Illustrative recordings from Case 1 are presented in Fig. 1.

In all patients, intrathecal baclofen administration led to a dramatic suppression of both mono- and poly-synaptic responses. Babinski signs, calf muscle H-reflexes, ankle clonus, and muscle reactions to passive joint movements practically disappeared over a period of 30 to 60 minutes. While the signs of spasticity were suppressed, residual voluntary motor control became more selective; concomitant activation of antagonist and distant muscles was virtually eliminated (Figs. 1B and 2B). The maximum agonist level on EMG's obtained during attempts at voluntary activation was not reduced in three cases. In three other cases, the agonist level was reduced on the EMG, although not as much as the accompanying antagonist contractions.

The most dramatic changes were seen in the patient with supraspinal pathology (Case 6) for whom it was possible to record kinematic variables during attempts at voluntary movements in standardized experimental conditions. This patient was unable to relax the muscles in his right arm in the initial resting position and demonstrated pronounced coactivation of antagonist muscles which slowed his movements. The EMG's and mechanical variables were recorded during attempts at voluntary elbow flexion movements both before and after the injection (Fig. 3). After baclofen administration, this patient became able to relax his muscles in the initial position (Fig. 3). The peak velocity increased twofold. The EMG's became more like those seen in normal subjects with distinct phasic bursts in both agonist and antagonist muscle groups. The long-lasting antagonist EMG component practically disappeared. There were no visible changes in the EMG peak levels.

† Subcutaneous drug pump manufactured by Medtronic Inc., Minneapolis, Minnesota.
Intrathecal baclofen and voluntary motor control

**Discussion**

All six patients in this series had markedly reduced voluntary motor function and signs of upper motor neuron lesions, including hyperactive tonic and phasic stretch reflexes. Attempts to move provoked inappropriate co-contraction of agonist and antagonist muscle groups at the joint of the intended movement and often caused discharges in other, more distant muscle groups. After lumbar intrathecal baclofen administration, the signs of spasticity were eliminated and more selective and appropriate patterns of muscle activation occurred. This unmasking of voluntary motor control demonstrates that hyperexcitable spinal circuits significantly interfered with descending motor commands. While the functional gains in most of our patients were minimal, the point is clear that for these individuals spasticity actively interfered with motor control and was not simply a sign of neural damage.

This finding must be qualified in two ways. Not all of our 20 patients receiving chronic intrathecal baclofen have shown improvement in voluntary motor control. Patients with complete cord transections or severe motor system damage benefit by having their spasms and increased tone reduced by baclofen but obviously cannot perform useful voluntary movements. Furthermore, a patient may achieve control of spasticity and demonstrate improved voluntary muscle activation in the laboratory but the movement may be too weak for useful function. In these cases, Landau and others are correct in contending that the diminished motor input (the negative symptom of the upper motor neuron lesion) is the primary problem. However, patients often make substantial gains in daily living while receiving intrathecal baclofen. Some of these gains have been simply due to the reduction in spasms but others are likely to be due to better motor control unmasked by intrathecal baclofen. The degree of functional gain an individual will achieve is not predictable prior to the administration of intrathecal baclofen. A patient with multiple sclerosis who was bedridden and appeared to have little or no voluntary control in her legs is now ambulatory, but other patients with what appeared to be less severe motor damage have not made such gains. Thus, each patient must be evaluated individually after a period of intrathecal baclofen and after motor retraining before it can be predicted whether elimination of spastic signs can improve voluntary motor function.

The second qualification is that intrathecal baclofen in too high a dose can impair voluntary motor control. A patient may rely on extensor tone for standing or walking. Reduction of muscle tone by baclofen would then be undesirable. In these cases, Burke’s view that spasticity is an adaptive reaction to injury, supplying necessary muscle tone, seems correct. Fortunately for most patients, the level of intrathecal baclofen can be adjusted to their functional needs by means of an implanted programmable pump. No patient in our series or in that of Müller, et al., has had a functional loss once the baclofen has been carefully titrated.

The site of action of baclofen in the spinal cord is not clear. The drug has been shown to be a selective ligand for bicuculline-insensitive gamma-aminobutyric acid (GABA) receptor sites which occur widely throughout the central nervous system. Baclofen-sensitive GABA receptors have also been found on primary afferent terminals. These findings are consistent with observations of pronounced suppression of both mono- and polysynaptic reflexes with intrathecal baclofen in animal models and in man. In spite of this marked suppression of muscle reflexes, the EMG levels accompanying voluntary muscle activation were maintained. The patient with the supraspinal disorder and a hemi-syndrome (Case 6) did not notice any weakness in the unaffected limbs despite a high intrathecal baclofen dose.
This apparent difference in the effects of baclofen upon pathological muscle reflexes and descending motor signals suggests that the action of intrathecal baclofen cannot be regarded as a nonspecific widespread inhibition throughout all spinal structures. Since the site of baclofen action is considered to be mainly pre-synaptic,\textsuperscript{2,26} the observed data can be explained by either a different representation of baclofen-sensitive receptors on descending terminals or a different susceptibility to intrathecal baclofen due to anatomical and pharmacokinetic factors, including diffusion of baclofen throughout spinal cord structures. The lack of apparent changes in intact muscles in the patient with hemi-syndrome (Case 6) suggests that one of the long-term reactions of spinal structures to a spasticity-induced pathology can consist of an increase in the number of GABA-sensitive receptors or sensitization of the existing receptors on pathologically active reflex inputs. This would account for both the strong effects of baclofen on descending and reflex inputs to alpha motoneurons and its lack of effect on intact muscles.

The usefulness of intrathecal baclofen in reducing signs of spasticity is now well documented. The additional finding of improved voluntary motor control in some of the patients was an unexpected benefit. The pessimistic view expressed by Landau\textsuperscript{3} that decreasing signs of spasticity will never help restore motor function clearly needs to be modified. Each patient must be tested individually for residual suppressed voluntary motoneurons and its lack of effect on intact muscles. We acknowledge Mr. Om Paul for the development of the excellent graphic software and Suzanne Savoy, M.N., for her skillful help in handling the patients. The help of Drs. C. Goetz and C. Tanner is also gratefully acknowledged.

Acknowledgments
We acknowledge Mr. Om Paul for the development of the excellent graphic software and Suzanne Savoy, M.N., for her skillful help in handling the patients. The help of Drs. C. Goetz and C. Tanner is also gratefully acknowledged.

References

Manuscript received March 17, 1989.
This work was partially supported by National Institutes of Health (NIH) Grant NS 15630 to Dr. Penn. NIH Grant R-029 NS 23593 to Dr. Corcos, and NIH Grant AR 33189 to Dr. Gottlieb.
Address reprint requests to: Mark L. Latash, Ph.D., Department of Neurosurgery, Rush Medical College, 1753 West Congress Parkway, Chicago, Illinois 60612.