

## Development of an Acute Withdrawal Syndrome Following the Cessation of Intrathecal Baclofen in a Patient with Spasticity

RICHARD N. SIEGFRIED, M.D.,\* LOUIS JACOBSON, M.D., CH.B.,† CHARLES CHABAL, M.D.‡

Baclofen (B-4 chlorophenyl- $\alpha$ -amino butyric acid), a GABA receptor agonist, is used intrathecally in the treatment of severe spasticity.<sup>1</sup> Baclofen is a viable alternative to destructive operative neurosurgical procedures and chemical neurolysis. Increased spasticity and neuropsychiatric symptoms have been associated with the sudden withdrawal of oral baclofen.<sup>2,3</sup> This report describes a case of withdrawal following the sudden inadvertent cessation of intrathecal baclofen.

## CASE REPORT

A 35-yr-old man who was quadriplegic as a result of a C<sub>4</sub> spinal cord injury suffered during a motor vehicle accident in 1985, was evaluated November 1989 by the authors' institution pain service for the management of spasticity refractory to conventional oral medications. The patient's spasticity had been controlled initially with oral baclofen and diazepam, but he soon became refractory to 80 mg/day and 35 mg/day, respectively. Therefore it was felt that he was a candidate for long-term intrathecal baclofen administration in an attempt to control his spasticity.

An initial diagnostic single intrathecal injection of 50  $\mu$ g baclofen resulted in excessive muscle relaxation. A subsequent dose of 25  $\mu$ g baclofen produced more satisfactory relief of spasticity. Intrathecal administration of a placebo (sterile preservative-free water) did not alter the muscle tone. Consequently, the implantation of a Medtronic Synchromed<sup>TM</sup> infusion system for the intrathecal delivery of baclofen was recommended.

The pump was implanted, and the dose of baclofen delivered by continuous infusion was progressively increased from a starting dose of 50  $\mu$ g/day. Over a period of 20 months, the dose was incrementally increased as clinically indicated. At the preceding pump refill visit, the dose had been increased from 30  $\mu$ g/h (720  $\mu$ g/day) to 35  $\mu$ g/h (840  $\mu$ g/day). The volume alarm limit (0.5 ml) in the pump was not changed, and the patient was scheduled for a return visit at the customary 6-week interval. A constant infusion was used. Bolus infusions of baclofen were not programmed into the pump, and the patient had no access to any baclofen boluses. Clinical assessment of rigidity, quantitation of observed spasms, and patient comfort were used as a guide. The patient returned for evaluation, testing of pump function, reprogramming,

and pump refilling every 6 weeks. Forty-one days after refilling the pump reservoir with approximately 18 ml baclofen in a concentration of 2,000  $\mu$ g/ml and increasing the daily dose to 840  $\mu$ g, the patient began experiencing paresthesias, severe headache, disorientation, sleeplessness, and increased spasticity. The calculated volume of baclofen administered to the patient, on admission 41 days and 4 h after refill, was 17.29 ml.

The symptoms and the lower extremity spasms worsened over the ensuing 36 h. The patient displayed increasing disorientation, which progressed to intermittent loss of consciousness and seizures. He was brought to the hospital. On arrival, his vital signs were: blood pressure, 135/92 mmHg; heart rate, 120 bpm; respiratory rate, 24 breaths/min; and oral temperature, 100° F. He was awake but disoriented to person, place, and time. Physical examination revealed a confused, agitated, and diaphoretic patient with markedly increased lower extremity tone as well as frequent lower extremity spasms.

Computed telemetry of the implanted pump revealed a calculated residual volume of 0.3 ml. Attempted aspiration of the pump reservoir contents revealed that the reservoir was empty. The pump reservoir was filled immediately with 18 ml baclofen (2,000  $\mu$ g/ml). The pump was restarted at one-half its initial rate. Though the patient's symptoms appeared to be related to the empty reservoir, other possible causes were considered. These included infection, metabolic disturbance, and mechanical disruption of the pump. The patient was admitted to the hospital for observation, evaluation, and special investigations.

Immediately upon admission, an initial dose of 30 mg oral baclofen was given. Oral baclofen (10 mg four times daily) was prescribed. During the first day of hospitalization, his sensorium rapidly cleared. His blood pressure and heart rate, however, remained extremely labile, ranging from 160/110 to 84/58 mmHg and 179 to 82 bpm, respectively. Oral temperature ranged from 102.7° to 98.4° F. The lower extremity spasms progressively decreased over a period of 24 h. Muscle tone returned to baseline with an increase in the intrathecal baclofen rate to 840  $\mu$ g/day on the second hospital day. Results of the complete blood count, cerebrospinal fluid analysis, electrolyte panel, and blood cultures performed at the time of admission all were within normal limits. An x-ray of the chest and abdomen demonstrated that the patient's intrathecal catheter was intact. Approximately 48 h after his initial presentation to the medical center, the patient was discharged having returned to baseline function.

## DISCUSSION

One aspect of the maturation of the human nervous system involves the refinement of motor skills. This is accomplished through the inhibition and enhancement of primitive motor reflexes by the brain stem and motor cortex. In the case of spinal cord injury, brain stem control is impaired resulting in the release of flexor and extensor reflexes. Spasticity, therefore, may be considered the result of the plastic reorganization of spinal cord reflexes partially or completely separated from the control by

\* Acting Instructor of Anesthesiology.

† Associate Professor of Anesthesiology.

‡ Assistant Professor of Anesthesiology.

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Address reprint requests to Dr. Jacobson: Anesthesiology Services (112-A), Veterans Affairs Medical Center, 1660 South Columbian Way, Seattle, Washington 98108.

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higher centers.<sup>4</sup> The muscle spasms and increased muscle tone that result can cause significant pain and suffering.

GABA-ergic inhibitory information channels play an important role in the balance of excitation and inhibition pertaining to motor function. Consequently, GABA receptor agonists such as baclofen have been used to enhance GABA-ergic inhibitory activity.<sup>5</sup> It has proved effective for the inhibition of spasticity caused by a variety of central nervous system disorders. Unfortunately, patients requiring baclofen therapy may become refractory to the drug when administered orally. Intrathecally administered baclofen has been shown to have a profound relaxant effect, which is believed to result from higher cerebrospinal levels of the drug than can be achieved by other known routes.<sup>5,6</sup> Since baclofen is effective in patients with complete spinal cord transections, its primary site of action appears to be in the spinal cord.<sup>7</sup> Presynaptic GABA-B receptors, capable of inhibiting release of a variety of neurotransmitters, have been found in many areas of the central nervous system. In the spinal cord, they appear to be concentrated in laminae 1 to 4 of the dorsal horn.<sup>8</sup> Intrathecal administration is believed to be more effective in delivering baclofen to the desired receptor sites in the lumbar region of the spinal cord.

The abrupt withdrawal of oral baclofen therapy has been associated with the development of withdrawal symptoms.<sup>2,3</sup> The symptoms associated with withdrawal have included: sleeplessness, agitation, confusion, hallucinations, paranoia, buccolingual dyskinesia, tonic/clonic movements, seizures, and hypersexuality. These symptoms usually develop 12–72 h after the discontinuation of baclofen and have resolved 24–72 h after the reinstitution of the oral drug. This case of presumptive sudden withdrawal of intrathecal baclofen manifested many similar features.

If the intrathecal pump was correctly filled at the last clinic visit and the pump was delivering baclofen at the programmed rate, then the pump reservoir should have contained some residual baclofen (0.71 ml) at the time the patient presented to the hospital. The dose at the preceding pump refill visit was 30  $\mu\text{g}/\text{h}$ , or 720  $\mu\text{g}/\text{day}$ , which is equivalent to 15.12 ml over 42 days. Therefore, the patient had approximately 3 ml left in the pump at the pump check and refill 6 weeks previously. At that time, however, the infusion rate was increased to 35  $\mu\text{g}/\text{h}$  (840  $\mu\text{g}/\text{day}$  or 17.64 ml volume infused over 42 days), and this produced the problem encountered and described in the case report. Interruption in the delivery of baclofen probably occurred because the pump reservoir was filled with insufficient baclofen and the low volume alarm limit was set too low. The pump was filled with baclofen *via* a crudely calibrated disposable plastic 20-ml syringe. The normal margin of error involved in filling the syringe with 18 ml could have resulted in less than

18 ml being instilled. The volume alarm was set at 0.5 ml. If less than 17.5 ml had been instilled, the alarm would not have been actuated before the pump was empty. At the time of presentation, although the calculated reservoir volume by telemetry was 0.3 ml, the pump reservoir was probably empty. We would not necessarily expect to precisely aspirate small volumes of 0.3–0.5 ml from the reservoir. However, had the reservoir contained this volume of baclofen, we would have expected that the infusion of baclofen would be ongoing and that the patient would not have manifested symptoms and signs of acute baclofen withdrawal.

Unfortunately, implantable pumps for the intrathecal administration of drugs are unable to detect the absolute amount of drug in the reservoir. The pumps rely on the programmer to enter the volume of drug placed into the reservoir at each refill. An internal calculation is carried out to determine the amount of drug remaining in the reservoir based upon the rate of infusion and the starting volume as entered by the programmer. If the reservoir is filled with a volume of drug that is less than that entered by the programmer, it is possible for the pump's low volume alarm to remain silent even with an empty reservoir. It is critically important that the low volume alarm be set at an adequate level. In the case presented in this report, the low volume alarm was set at 0.5 ml. The error involved in filling a crudely marked syringe with 18 ml of solution could easily result in an error of 0.5 ml or more. Consequently, an alarm volume of 1–2 ml would be more appropriate.

This case serves to highlight several important points with regard to the intrathecal administration of baclofen. Withdrawal symptoms similar to those resulting from the discontinuation of oral baclofen can develop following sudden cessation of intrathecal baclofen. The symptoms of baclofen withdrawal may mimic those of meningitis. It is therefore important that meningitis be included in the differential diagnosis. A thorough neurologic examination with particular attention to signs of meningeal irritation must be performed. Laboratory examinations including cerebrospinal fluid analysis and a complete blood count should be obtained when indicated. The patency and integrity of the intrathecal catheter must be confirmed radiographically. In addition to computed telemetry, mechanical pump function can be evaluated by serially sampling the reservoir volume and comparing it to the volume calculated by the pump. Accurate measurement of drug volume when refilling the pump reservoir is important. Pump telemetry and refill visits with patients should be made at intervals where there is no possibility that the reservoir will empty before the follow-up visit. Possibly, in the future, a "smart" pump with the capability to sense the amount of drug in its reservoir will become available. Meanwhile, this therapy for spasticity must be imple-

mented with precautions adequate to prevent the interruption of drug delivery.

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