Prolonged intrathecal baclofen withdrawal syndrome

Case report and discussion of current therapeutic management

ANDREA F. DOUGLAS, M.D., HOWARD L. WEINER, M.D., AND DAVID R. SCHWARTZ, M.D.

Department of Neurological Surgery, Division of Pediatric Neurosurgery, and Department of Medicine, New York University Medical Center, New York, New York

The authors describe a patient who experienced a prolonged course of intrathecal baclofen withdrawal syndrome after removal of an implantable baclofen pump for treatment of pump infection and meningitis. The current literature outlines management options for the acute management of this syndrome. In this report the authors discuss the long-term presentation of this syndrome and suggest a treatment strategy for management of the syndrome.

A 37-year-old man who presented with a baclofen pump infection and meningitis experienced acute onset of intrathecal baclofen withdrawal syndrome 12 hours after the pump had been surgically removed. The patient’s symptoms evolved into a severe, treatment-refractory withdrawal syndrome lasting longer than 1 month.

Oral baclofen replacement with adjunctive administration of parenteral γ-aminobutyric acid agonists only served to stabilize the patient’s critical condition throughout his hospital course. Replacement of the baclofen pump and restoration of intrathecal delivery of the medication was necessary to trigger the patient’s dramatic recovery and complete reversal of the withdrawal syndrome within approximately 48 hours.

These findings indicate that a more direct method of treating infected baclofen pumps than immediate surgical removal is necessary to prevent the onset of intrathecal baclofen withdrawal syndrome. Various options for preventing the onset of the syndrome while simultaneously treating the infection are discussed.

**Key Words** • intrathecal baclofen withdrawal • baclofen pump infection • baclofen • spasticity

INTRATHECAL baclofen infusion with the aid of an implantable pump system has been approved for use in children and adults in the US for many years. In patients with traumatic brain injury, anoxic encephalopathy, cerebral palsy, multiple sclerosis, spinal cord injury, and other syndromes producing unremitting progressive spasticity, intrathecal delivery of baclofen improves quality of life by reducing spasticity, contractures, and pain while making daily activities more manageable. 1,2,4,12,13,16,25

For patients dependent on intrathecal baclofen for the control of spasticity, abrupt discontinuation of medication delivery may be associated with a well-described withdrawal syndrome. 1,3,8,10,17,21,22,24 The syndrome of intrathecal baclofen withdrawal may be characterized by spasticity greater than that initially present, hyperthermia, autonomic dysregulation, seizures, CNS depression, rhabdomyolysis, disseminated intravascular coagulation, and multisystem organ failure. 1,3,8,10,17,21,22,24 Despite early diagnosis and therapy, intrathecal baclofen withdrawal may lead to significant incidences of morbidity and mortality. The syndrome may be refractory to replacement oral baclofen and other GABAergic drugs and may be quite prolonged. 1,3,8,20

We present the case of a patient with a spinal cord injury in whom an infected baclofen pump led to methicillin-resistant *Staphylococcus aureus* meningitis. Surgical removal of the device precipitated a severe, treatment-refractory withdrawal syndrome lasting longer than 1 month. The patient’s course in the intensive care unit is detailed, as is his dramatic recovery on reinstitution of steady intrathecal baclofen. We discuss the syndrome, its differential diagnosis, and classic therapy. In addition, we suggest alternatives to surgical pump removal that might have preempted our patient’s difficult course.

**Case Report**

**History and Examination.** This patient is a 37-year-old man who has been paraplegic since he suffered a T4–6 injury during a motor vehicle accident in 1996. The patient underwent a subfascial implantation of a SynchroMed baclofen pump (Medtronic, Minneapolis, MN) for control of his spasticity approximately 4 years prior to admission after an attempt at medical treatment had failed. He had experienced recent good control of his symptoms on a daily regimen of 180 μg of intrathecal baclofen.

Six weeks before hospital admission, the patient underwent a scheduled pump generator change at our institution without any complication. He later presented to another hospital with complaints of severe abdominal pain lasting 8 days and headache and fever lasting 4 days. He was noted to have a postoperative wound infection. Lumbar puncture revealed CSF with a glucose level of 31 mg/dl, a protein
level of 178 mg/dl, a white blood cell count of $2 \times 10^{10}/\text{mm}^3$, and a red blood cell count of 3750/$\text{mm}^3$. Laboratory cultures grew methicillin-resistant 
*S. aureus*, and the patient was placed on a course of intravenous vancomycin. Within 48 hours, the patient’s symptoms resolved and he defervesced.

**Preoperative Care.** The patient was transferred to our institution for further management of meningitis thought to be caused by a baclofen pump infection. On arrival at our institution, oral baclofen therapy was started at a dose of 20 mg every 4 hours in anticipation of removal of the baclofen pump. Intravenous rifampin was added for staphylococcal synergy. Approximately 12 hours after the start of the oral baclofen therapy, the patient was transferred to the operating room for pump removal.

**Operation and Early Postoperative Course.** At surgery a portion of CSF and the pump and all catheters were sent to the laboratory where each grew methicillin-resistant 
*S. aureus* in culture. Postoperatively, the patient was placed in a monitored setting and observed for signs of baclofen withdrawal. Approximately 12 hours after surgery, he began to experience increasing spasticity in his lower extremities as well as rising body temperature, diaphoresis, and marked lability of his heart rate and blood pressure.

**Initial Treatment.** The patient was transferred to the intensive care unit. The dosage of oral baclofen was increased to 40 mg every 4 hours, and oral tizanidine (4 mg every 8 hours) and intravenous lorazepam (1 mg every 6 hours) were added to the patient’s regimen as needed in an attempt to prevent progression of the suspected withdrawal syndrome. The patient continued to display labile vital signs, with marked oscillation of blood pressure, heart rate, and temperature. At one point his temperature rose from 99 to 107˚F over a period of 4 hours. He had mild rhabdomyolysis and an altered mental status characterized by agitation and delirium progressing to obtundation. A continuous intravenous infusion of Diprivan (up to 120 $\mu$g/kg/min) and an intermittent intravenous infusion of lorazepam were titrated to decrease CNS excitation and muscle activity. An intermittent intravenous infusion of neosynephrine was titrated to treat hypotension. Within 72 hours after surgery, the patient’s spasticity, mental status, and autonomic lability worsened. A CT scan of the head, which was performed at that time, appeared unremarkable and a urine toxicology screen yielded nondiagnostic findings. Hyperthermia, leukocytosis, and transient decreases in blood pressure prompted initiation of broad-spectrum antibiotic coverage and a search for sources of infection. A lumbar puncture was performed to assess the adequacy of the treatment for meningitis, and was also used to administer 50 $\mu$g of intrathecal baclofen.

**Later Postoperative Course and Continued Treatment.** The withdrawal syndrome continued unabated. The CSF profile, now 7 days after removal of the baclofen pump, appeared completely normal as did a new CT scan of the head. All cultures (CSF, blood, urine, and sputum) remained nondiagnostic. Eight to 10 days after removal of the baclofen pump, the patient’s spasticity and mental status began to improve. On Day 12 of his hospital stay, however, he began to experience aspiration pneumonia requiring initiation of appropriate antibiotics and a short course of mechanical ventilation. This episode was associated with a decline in mental status, blood pressure, and heart rate lability, as well as severe hyperthermia and worsening spasticity. A course of treatment was also begun for diarrhea associated with *Clostridium difficile* infection.

On hospital Day 23, all antibiotics were discontinued and a full fever workup was initiated including magnetic resonance imaging of the brain and spine; CT scanning of the chest, abdomen, and pelvis; and a gallium scan. All studies were unrevealing. On that day, another 50 $\mu$g of intrathecal baclofen was administered. During the next week the patient slowly defervesced, his mental status improved significantly, and his spasms became well controlled.

Approximately 35 days after admission to the hospital and removal of the infected baclofen pump, the patient was stable hemodynamically and did not demonstrate any evidence of systemic infection. His mental status was ‘lighter’ despite the continued regimen of oral baclofen and intravenous propofol and lorazepam. The baclofen pump was replaced and restarted at the previous intrathecal daily dose of 180 $\mu$g. The oral regimen of baclofen and tizanidine was immediately discontinued and the use of intravenous medications was tapered over 24 to 48 hours. Within 48 hours after replacement of the pump, the patient’s mental status returned to his normal baseline, and he demonstrated no residual spasticity. Nine days after pump replacement and 44 days after its original removal, the patient was stable and ready for transfer to a rehabilitation facility.

**Discussion**

Spasticity is a known manifestation of upper motor neuron injury that is thought to be produced by an absence or reduction in the normal descending inhibition of alpha motor neurons. Baclofen is a GABA agonist whose precise mechanism of action in the CNS for the reduction of spasticity is not completely understood. It is known, however, that the drug binds to the GABA$_B$ receptor on the presynaptic terminal of Ib muscle spindle afferents, activating a G-protein–linked cascade. This causes synaptic inhibition by increasing potassium ion conductance while decreasing calcium ion conductance in the presynaptic terminal, hyperpolarizing the cell and decreasing the amplitude of excitatory postsynaptic potentials of the alpha-motor neuron. The result is a counteraction to the loss of tonic inhibition. Long-term intrathecal baclofen administration is thought to decrease GABA$_B$ receptor sensitivity, and withdrawal of the drug is associated with a rebound excitability of the entire CNS that is not easily reversed by small doses of either oral or intrathecal baclofen or other GABA agonists.

Removal of baclofen from a patient with long-term dependence on intrathecal delivery is known to be associated with a potentially fatal syndrome evolving over a 1- to 3-day period. This syndrome is characterized by rebound spasticity, hemodynamic lability, severe hyperthermia, and altered mental status. The literature outlining the recognition, diagnosis, and management of intrathecal baclofen withdrawal syndrome often offers descriptions of patients with routine pump malfunction secondary to catheter kinking or programming errors, which lead to inappropriate delivery and dosing of intrathecal baclofen.
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nosed, simply changing the hardware or refilling or reprogramming the pump is sufficient to treat these patients.\(^{1,8}\) In contrast, development of a systematic multidisciplinary approach to the treatment of intrathecal baclofen withdrawal is necessary in situations in which immediate reinitiation of intrathecal baclofen is more difficult.

Despite awareness of intrathecal baclofen withdrawal syndrome, early detection and treatment still poses a challenge for medical caregivers of this patient population. In the patient with a cervical or high thoracic spinal cord injury the syndrome may be initially confused with autonomic dysreflexia. Indeed, the combination of symptoms may exaggerate the autonomic dysregulation inherent to each.\(^{2,3,13}\) Typical baclofen withdrawal can be easily distinguished from other syndromes with overlapping presentations such as neuroleptic malignant syndrome, malignant hyperthermia, and serotoninergic syndromes by interpretation of the patient’s history, physical examination, and clinical presentation.\(^{10,11,12,24}\) As in the present case, septic shock is often included in the differential diagnosis, and multisystem organ failure is the common pathway to death in all these entities.\(^{7,10,17}\)

Acute management of patients with intrathecal baclofen withdrawal syndrome has depended on replacement baclofen by an oral route with the addition of other GABA agonists. Benzodiazepines are thought to be excellent alternate or adjuncts to oral baclofen in this setting because they activate GABA\(_{A}\) receptors in the CNS and because their antagonism of spasticity and CNS excitation bypasses the downregulated GABA\(_{A}\) receptor pathways.\(^{2,3}\) Propofol, another GABA\(_{A}\) receptor agonist with a short plasma half-life, has also been used to good effect, with a continuous intravenous infusion titrated to the withdrawal symptoms including spasticity and hyperthermia. In one recent case series, prompted by postulated similarities of this syndrome with serotoninergic syndrome, Meythaler, et al.,\(^{17}\) used the antiserotonergic drug cyproheptadine with good result. The authors proposed that intrathecal baclofen withdrawal might lead to excessive serotonin activity, which occurs when GABA\(_{A}\) receptor-directed presynaptic inhibition of serotonin is lost. Dantrolene, a nonspecific skeletal muscle relaxant that inhibits calcium release from the sarcoplasmic reticulum, was not used in this case. Although the drug of choice is anesthetic agent–associated malignant hyperthermia, it is modestly effective at reducing muscle rigidity and hyperthermia resistant to GABA agonists in the baclofen withdrawal syndrome.\(^{11}\)

As in our case, infections of intrathecal baclofen pumps with associated meningitis present a scenario in which a caregiver should consider the possibility of managing a prolonged withdrawal syndrome. Because it is not considered safe to replace intrathecal hardware in a patient with an active infection, these patients face a potentially much longer period of time during which the intrathecal delivery of the drug and reversal of the syndrome may not be possible. In the case discussed, a constant regimen of oral baclofen and tizanidine with intravenous propofol and lorazepam were modestly useful in controlling the patient’s spasticity, agitation, and hyperthermia. Episodes of hospital-associated infection seemed to exacerbate the underlying state of CNS excitation and autonomic instability, promoting a vicious cycle that prolonged the patient’s hospital course. Although both sepsis and autonomic dysreflexia may have contributed to our patient’s prolonged presentation, we believe that his prompt and complete recovery following the reinitiation of full-dose intrathecal baclofen support the notion of an ongoing withdrawal. Although the patient required large doses of intravenous neosynephrine to maintain adequate arterial blood pressure and a brief period of mechanical ventilation, we were successful in avoiding the onset of multisystem organ failure.

The presentation and treatment of this patient raises the question of whether an attempt should be made to treat an infected pump in situ and later remove and replace the entire system simultaneously once the infection has been treated. A few authors have outlined a plan for simultaneous delivery of intrathecal antibiotics and baclofen by using the already implanted pump delivery system; in a number of patients this successfully treated pump infections.\(^{6,20,23}\) These authors first performed in vitro testing of the compatibility of baclofen with the prescribed antibiotic and then filled the baclofen pump reservoirs with both drugs to allow their coadministration.\(^{20,23}\) Another alternative suggestion is to remove the pump, leaving in place a lumbar drain that can be used for continuous delivery of baclofen as well as for intrathecal delivery of the appropriate antibiotic.\(^{6,20,23}\) Having constant access to the CSF would allow for frequent checks of the CSF profile and cultures, similar to the technique one may use in treating a ventriculoperitoneal shunt infection. These approaches would allow for safe removal and treatment of the infected source while simultaneously preventing the onset of intrathecal baclofen withdrawal. We were reluctant to place a lumbar drain for delivery of intrathecal baclofen in this case because during the period of prolonged baclofen withdrawal, although the meningitis was already effectively treated with intravenous antibiotics, the patient’s course was complicated by the presence of other systemic infections.

In our case, replacement of the implantable baclofen pump was performed almost 40 days after the patient presented with his infection, and only after all other sources of infection had been detected and completely treated. Almost immediately after reinitiation of continuous intrathecal baclofen, all manifestations of withdrawal were reversed. A more effective and direct management tactic, such as that described earlier to salvage the original pump, might have greatly benefited this patient. Larger studies are needed to evaluate the risks versus benefits of this approach. If a consistent microbiological cure can be achieved without hardware removal, the reductions in morbidity, mortality, and costs would be substantial.

References


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A. F. Douglas, H. L. Weiner, and D. R. Schwartz

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