CLINICAL NOTE

Death After Acute Withdrawal of Intrathecal Baclofen: Case Report and Literature Review

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A 21-year-old man with C1 sensory-incomplete ventilator-dependent quadriplegia, treated with good results with an intrathecal baclofen pump for intractable spasticity since age 17, developed increasing spasticity and fevers when his pump began to malfunction. He became unresponsive and developed hypotension, severe hyperthermia, and ventricular tachycardia that required chemical and electrical cardioversion. Although he was receiving oral baclofen when his pump failed, and he was given an intrathecal bolus of baclofen, he subsequently developed rhabdomyolysis, hepatic enzyme elevations, and a consumptive coagulopathy. Cerebral ischemia then occurred, causing brain death. The literature about intrathecal baclofen withdrawal is reviewed to illustrate that it can be a life-threatening event.

PATIENTS WHO HAVE HAD spinal cord injuries or who have other diseases affecting the spinal cord often have severe spasticity. The increased muscle tone and spasms can make hygiene and other activities of daily living difficult and can be very painful, leading to loss of sleep and emotional distress. Intrathecal baclofen has emerged as a very effective treatment for spinal spasticity which is often refractory to oral medications. We describe a patient who was treated with intrathecal baclofen with good results, but is the first reported patient with spinal spasticity to have died of complications related to baclofen withdrawal when his pump stopped working.

CASE REPORT

The patient was a 21-year-old man. In 1986, at 11 years of age, he had been hit by an automobile while he was a pedestrian. He sustained a C1/C2 dislocation with C1 sensory-incomplete ventilator-dependent quadriplegia. He also sustained cerebral contusions, and a ventriculo-peritoneal shunt was placed for hydrocephalus. After the accident, he had severe spasticity that was partially controlled with oral medications, including baclofen.

In 1989, he was admitted to the rehabilitation service after an above-elbow amputation for an arteriovenous malformation that caused pain and congestive heart failure. During that hospital stay, an attempt was made to wean the patient off oral baclofen.[1] Approximately 24 hours after the second decrease in dosage, he experienced hyperthermia with temperatures to 41.7°C rectally. He was treated with cooling blankets and intravenous diazepam, and his baclofen dosage was increased, resulting in resolution of the hyperthermia. Results of a complete workup for sepsis were negative; thermoregulatory dysfunction secondary to high spinal cord lesion, as well as environmental causes for hyperthermia, was thought to be unlikely because of the temporal relationship of the hyperthermia to the baclofen dosage changes. Several months after this incident, weaning from baclofen was attempted at an outside hospital, with similar results.

The patient was maintained on oral baclofen but because his spasticity was only partially controlled, an intrathecal baclofen pump[a] was placed in 1993. He was begun on intrathecal baclofen at a concentration of 2,000μg/mL, delivering 300μg/d via the simple continuous mode. His dose was subsequently increased to 390μg/d. He had an excellent response to the pump, with significantly decreased lower extremity muscle tone and many fewer and less severe spasms. However, he still had upper extremity spasticity, so he was maintained on oral baclofen 40mg and diazepam 5mg, each administered four times daily in addition to the intrathecal baclofen. Other medications included oxybutynin 5mg administered four times daily, nitrofurantoin 100mg daily, Entex LA twice daily, and bisacodyl 10mg daily per gastrostomy tube and 10mg daily per rectum.

There were no complications with the pump until December 1996 when the low battery alarm sounded. A pump replacement procedure was scheduled but was postponed when the alarm could not be heard during the preoperative evaluation. Alarm malfunctions had happened before with patients at our institution, hence the decision to postpone the surgery until the low battery alarm sounded again. The pump was refilled on June 16, 1997, and telemetry was performed on June 18, 1997. At his telemetry appointment the low battery alarm was sounding. He was scheduled for pump replacement on June 27, 1997.

On June 24, 1997, the patient experienced increased muscle tone and spasticity as well as low-grade fevers. In the early morning of June 26, he was febrile, with a pulse rate of 180 beats/min and a blood pressure of 60/40mmHg. He was unresponsive at that time, although at his baseline he was oriented and able to communicate by blinking his eyes. Emergency Medical Services was called and found him febrile with a temperature of 41.1°C, hypotensive with a systolic blood pressure of 60mmHg, and tachycardic with a pulse rate of 180 to 190 beats/min. He was on his ventilator at its normal settings of assist control rate of 10 breaths/min and tidal volume of 700cc, but was requiring increasing amounts of oxygen to keep his saturation above 93%. In the emergency department of a different hospital, he did not respond to verbal commands or painful stimuli. His pupils were midposition and reactive. His vital signs were temperature of 43°C, pulse rate of 188 beats/min, respiratory rate of 10 breaths/min on the ventilator, and systolic blood pressure of 60mmHg. An ECG showed

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wide-complex ventricular tachycardia with a rate of 190 beats/min. Cardioversion was attempted at 100J, with no change in rhythm. At that point, initial electrolyte values were as follows: sodium, 123mmol/L; potassium, 7.2mmol/L; chloride, 89mmol/L; and bicarbonate, 28mmol/L. The ventricular tachycardia was believed to be secondary to the elevated potassium level, so glucose, insulin, and bicarbonate were given. Immediately, the complexes narrowed, the blood pressure increased, and the pulse rate decreased. He was admitted to the medical intensive care unit (ICU) at the other hospital.

On arrival in the ICU, his temperature was 43°C and cooling measures were provided. His temperature normalized to 37°C. He was on the ventilator at his usual settings and was receiving 100% oxygen, which was subsequently weaned to 40%. He was unresponsive, his pupils were 2mm and sluggishly reactive, and he had a positive oculocephalic reflex. A chest X-ray showed an opacity of his left lung base, possibly consistent with an elevated left hemidiaphragm. His urinalysis was unremarkable. Cerebrospinal fluid analysis showed a white blood cell count (WBC) of 75/cc (59% neutrophils, 34% lymphocytes, 7% monocytes), red blood cell count of 8,325/cc, and a glucose level of 102mg/dL. Electrolyte values improved: sodium, 133mmol/L; potassium, 3.0mmol/L; chloride, 99mmol/L; and bicarbonate 17mmol/L. Other abnormal laboratory values included creatinine kinase (CK), 2,941 U/L; lactate dehydrogenase (LDH), 527U/L; aspartate aminotransferase (AST), 192U/L; WBC, 26,900/μL; platelet count, 91,000/μL; prothrombin time (PT), 17.5sec; partial thromboplastin time (PTT), 33.0sec; and international normalized ratio (INR), 2.1. Urine, tracheal, cerebrospinal fluid, and blood cultures were taken, and intravenous gentamicin and ceftriaxone were given empirically. However, it was believed that the hyperthermia was most likely secondary to the failure of his baclofen pump. The patient was given 100μg of baclofen intrathecally under fluoroscopic guidance, with marked improvement in his hyperrigidity. He was hydrated for possible rhabdomyolysis. He was transferred in guarded condition to our institution the day after admission.

On admission to our medical ICU, the patient was unresponsive, with pupils fixed at 4mm. There was a positive oculocephalic reflex, and negative corneal and gag reflexes. Abnormal laboratory values on admission included AST, 646U/L; alanine aminotransferase (ALT), 453U/L; LDH, 1,145U/L; total bilirubin, 127g/dL; platelet count, 34,000/μL; CK, 10,891U/L (MB fraction, 0.7%); troponin, >15,000ng/mL; fibrin split products (FSP) 10-40μg/mL; D-dimer, 1-2μg/mL; and INR, 2.5. An emergent head computed tomography (CT) scan at admission showed diffusely effaced cisterns with evidence of a diffuse cerebral vascular accident. He was empirically started on vancomycin, in addition to the gentamicin and ceftriaxone that he was already being given, to cover for meningitis and aspiration pneumonia, and he was hydrated for his rhabdomyolysis. The culture results from the other hospital were negative. Twenty-four hours after admission, his right pupil was fixed and dilated. He was started on mannitol and was hyperventilated. A neurosurgical consultation ruled out any neurosurgical options. A cerebral blood flow study obtained on the fourth hospital day was consistent with brain death, as was a neurologic examination. The patient was removed from the ventilator and died that day; no autopsy was performed.

DISCUSSION

Baclofen is a β-chlorophenyl derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). It is a GABA agonist, binding specifically to the bicuculline-insensitive $GABA_B$ receptors.[2] These receptors are widely distributed throughout the central nervous system, including the dorsal horn of the spinal cord.[3] Baclofen has an inhibitory effect on monosynaptic and polysynaptic spinal reflexes, thus reducing excessive tone.[4] This inhibition is probably accomplished by a decrease in presynaptic transmitter release as well as by an inhibition of postsynaptic neuronal excitation.[5] Oral baclofen has become the drug of choice for treating spasticity of spinal origin because it has no known harmful side effects on the heart, liver, or kidneys. Reported central side effects include drowsiness, ataxia, confusion, and decreased concentration, but these are usually only noted when excessive doses are used.[6] Baclofen does not readily cross the blood-brain barrier, so high oral doses are required before clinical benefits occur.[7] Oral doses distribute evenly to the supraspinal and spinal levels of the central nervous system, which leads to unwanted central side effects, especially sedation.[8]

Although oral baclofen does not produce many side effects, there have been many reported complications resulting from its withdrawal. These include seizures,[9-12] auditory and visual hallucinations,[9,10,13-18] paranoid delusions,[10,13,18,19] grandiose delusions,[14,20] diplopia,[10] dyskinesia,[14,18] rebound or increased spasms,[1,6,15] and hyperthermia.[1] Withdrawal symptoms begin 1 to 3 days after baclofen dosage is decreased or stopped and disappear approximately 24 to 72 hours after baclofen is restarted. There are no known reports of any long-term consequences or deaths directly related to oral baclofen withdrawal, and withdrawal can usually be prevented by slow tapering of the dosage.[10,12,20]

Although oral baclofen is often effective in reducing the increased tone caused by spinal cord lesions, approximately 25% of adults with spinal cord injury are unresponsive to oral baclofen or have intolerable side effects from the high dosages required to control the spasticity.[21] In 1984, treatment with continuous intrathecal infusion of baclofen was first reported to significantly reduce spasticity among patients with spasticity of spinal origin.[22] In an early study of seven patients with spasticity caused by multiple sclerosis or spinal cord injury, the lower extremity muscle rigidity was reduced to normal in all the patients, and the spasms in the six patients who were symptomatic were greatly reduced.[23] Later, a balanced, randomized, double-blind, crossover study was done with 20 patients with spasticity resulting from multiple sclerosis or spinal cord injury.[24] Each patient underwent one trial of baclofen and another of saline placebo. In this study, the period of baclofen administration could be distinguished from the period of saline infusion by the improvement in muscle tone and spasm frequency. Each of the 20 patients subsequently had the pump implanted, and muscle tone was brought into the normal range in all patients, with spasms becoming clinically negligible. In both studies by Penn and colleagues, the patients were much more comfortable and easier to care for after implantation of the pump. Many subsequent reports confirm that intrathecal baclofen is extremely useful in reducing spasticity of spinal origin.[21,25-34]

Intrathecal baclofen probably has such a profound effect on spasticity for several reasons. Intrathecal administration produces at least four times higher cerebrospinal fluid levels with only 1% of the systemic dose.[24] Also, infusion into the lumbar area concentrates the baclofen at specific sites in the spinal cord where the $GABA_B$ receptors are located.[3] By the time baclofen reaches the brain, it is in much lower concentrations, and so the central side effects that occur in patients taking oral baclofen are much less likely.[24]

In many of the case series that have been reported, complications have been noted that have caused an interruption or decrease in intrathecal drug delivery.[21,23,24,27-35] These complica-

tions include pump malfunction, infections necessitating pump removal, and catheter kinks, holes, and dislodgments. In 1995, Penn and coworkers[36] summarized the incidence of catheter-related problems in 102 patients implanted with the SynchroMed pump at Rush-Presbyterian-St. Lukes Medical Center in Chicago since the first clinical trials were started 10 years previously. Sixty of these patients had no catheter-related problems, whereas the remaining 42 had from one to five complications, the most common being a kink with or without a hole or break in the catheter. Catheter dislodgment, disconnection, pump disconnection, and fibrosis were other reported complications, with the cause of disrupted drug delivery not known in about 19% of cases.

Withdrawal from intrathecal baclofen appears to be a much more serious problem than withdrawal from oral baclofen. Several cases have been reported in recent literature (table 1). These cases are all similar and generally involve increased spasticity, severe hyperthermia, rhabdomyolysis, and hypotension along with other organ system failures. Thus, withdrawal of intrathecal baclofen appears to cause serious systemic effects rather than the psychiatric and neurologic effects resulting from the withdrawal of oral baclofen. The symptoms reported above are similar to those of neuroleptic malignant syndrome (NMS), and the possibility that baclofen withdrawal may cause neurotransmitter changes in the brain similar to those involved in NMS has been suggested.[41] It has also been suggested that the hypermetabolic state caused by the increased spasticity is responsible for the symptoms noted above.[1]

Currently, the only effective treatment for intrathecal baclofen withdrawal appears to be supportive care and resumption of intrathecal baclofen, if possible. Dantrolene was effective in one case reviewed[39] and may have contributed to patient stabilization in others.[40,41] Diazepam also may have contributed to patient stabilization in two of the patients described.[41,42] Diazepam, like baclofen, works as a GABA agonist and has the same inhibitory effect on spinal reflexes to reduce muscle tone. The half-life of diazepam is longer than that of baclofen, and it can be given intraveneously more quickly than baclofen can be given intrathecally. Thus, diazepam may be a better choice in the treatment of intrathecal baclofen withdrawal. The dose of GABA agonist, however it is given, would need to be high to saturate as many receptors as possible. Dantrolene works at the

Table 1: Review of Reported Cases of Intrathecal Baclofen Withdrawal

Ref	Age/Sex of Patient	Diagnosis of Patient	Reason for Withdrawal	Symptoms	Treatment	Resolution
37	35/M	C4 SCI	Reservoir empty	Paresthesias, severe headache, increased spasticity, intermittent loss of consciousness, seizures, labile pulse and BP, febrile to 36.9-39.3°C	Oral baclofen, pump refilling	Complete recovery after 48 hours
38	70/F	Stiff-man syndrome	First time: Pump filled with dilute solution of baclofen. Second time: Pump put on stop.	Spasms, hypotension, tachycardia, tachypnea, cyanosis, acidosis, rhabdomyolysis, intermittent left bundle branch block, fever, leukocytosis, and consumptive coagulopathy	VP, MV, correct filling of pump	First time: Recovered fully Second time: Patient died
39	36/M	C6 SCI	Removal due to pouch infection	Progressive spasms, confusion, agitation, febrile to 42°C, profound respiratory distress, rhabdomyolysis	MV, oral baclofen after pump removal, then dantrolene	Complete resolution after several days, d/c on oral baclofen
40	21/M	Traumatic SCI	Reservoir empty	Hypertonia, febrile to 43.2°C, hypotensive, rhabdomyolysis, hepatic enzyme elevations, coagulopathy	VP, MV, IV dantrolene, pump refilled	Complete resolution after 5 days
	19/M	Same	Same	Same except febrile to 42.1°C	O_2, VP, pump refilled	Same
41	29/M	C6 SCI, severe TBI	Disconnection of intraspinal and extraspinal portions of catheter	Intractable spasticity, febrile to 42.3°C, tachycardia, leukocytosis, hypotension, agitation, rhabdmyolysis, DIC	VP, MV, antibiotics, baclofen per NG, diazepam, dantrolene, repair of pump	Complete recovery after 90-day inpatient stay
42	29/M	C5-6 SCI	Break in spinal catheter	Diffuse spasms, febrile to 42°C, hypotension, agitation, rhabdomyolysis, renal failure, DIC	VP, MV, antibiotics, diazepam, pump repair	Complete recovery 2 days after baclofen restarted

Abbreviations: SCI, spinal cord injury; VP, vasopressors; MV, mechanical ventilation; TBI, traumatic brain injury; DIC, disseminated intravascular coagulopathy; NG, nasogastric.

level of the skeletal muscle by excitation-contraction uncoupling, thus decreasing muscle tone and the hypermetabolic state that excess tone causes.

Although the patient described here was treated with an intrathecal bolus of baclofen at the other hospital, which did improve his spasticity, it is possible that placement of an externalized intrathecal catheter through which continuous baclofen could have been given would have been more beneficial. Because this patient was not initially under our care, it is unclear why neither dantrolene nor diazepam was used in the treatment of his withdrawal symptoms initially. When he was transferred to our institution, it was believed unlikely that he would benefit from either drug or from more intrathecal baclofen; his diffuse cerebral ischemia had already occurred and was probably caused by hypoperfusion that occurred when he was hypotensive and in ventricular tachycardia. It appears that simply giving a patient oral baclofen is not enough to prevent withdrawal symptoms, because the patient described here, as well as a previously described patient,[39] were receiving oral baclofen when withdrawal symptoms developed.

CONCLUSION

The case reported here, and the others reviewed above, illustrate the serious consequences that may result from the interruption or sudden decrease of intrathecal baclofen delivery. In the future, factors that predispose to the development of serious withdrawal symptoms may be found, and patients could then be warned to seek emergent medical treatment at the first sign of pump or catheter failure, which is usually an increase in their spasticity. Until then, interrupted drug delivery in all patients with intrathecal baclofen pumps should be treated as an emergency.

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Supplier

a. SynchroMed Pump, model 8611H, catheter model 8703; Medtronic Neurological, 800 53rd Avenue NE, Minneapolis, MN 55440.