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PRACTICAL PEARL

Dexmedetomidine for Acute Baclofen Withdrawal

Simon Morr · Christopher M. Heard · Veetai Li · Renée M. Reynolds

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Abstract
Background Intrathecal baclofen is widely accepted as a treatment option for severe spasticity through its γ-Aminobutyric acid-B ($GABA_B$) agonist properties. Abrupt cessation can lead to severe and life-threatening withdrawal characterized by altered mental status, autonomic dysreflexia, rigidity, and seizures. This symptomatic presentation is similar to alcohol withdrawal, which is mediated by modification of $GABA_A$ expression. Use of the α2-adrenergic agonist dexmedetomidine for the treatment of ethanol withdrawal has been widely reported, raising the question of its potential role in baclofen withdrawal. We present a case of the successful treatment of acute severe baclofen withdrawal with a dexmedetomidine infusion.
Methods A 15-year-old patient with spastic quadriparesis and cerebral palsy underwent unexpected removal of his baclofen pump due to an infection that was encountered during a planned pump revision. Following removal, he was placed on high dose enteral baclofen every 6 h. Despite further benzodiazepine supplementation, he had progressive hemodynamic instability, severe rebound spasticity, and intermittent spontaneous clonus consistent with baclofen withdrawal. A dexmedetomidine infusion was titrated to a peak dose of 16 mcg per hour with successful treatment of withdrawal symptoms.
Results The patient became normotensive without tachycardia. Tone and agitation improved.
Conclusion Dexmedetomidine is to our knowledge a previously unreported option for treatment of acute severe baclofen withdrawal. We report a case of safe and efficacious use in a patient with spastic quadriparesis on chronic intrathecal baclofen. Scientifically rigorous comparison with other options remains to be performed.

Keywords Acute baclofen withdrawal · Adrenergic alpha-2 receptor agonist · Dexmedetomidine · Intrathecal baclofen · Cerebral palsy treatment

Abbreviations

GABA	γ-Aminobutyric acid
ICU	Intensive care unit
mcg	Micrograms
NMDA	*N*-methyl-D-aspartate

Introduction

Dexmedetomidine is a selective α-2 adrenergic agonist and sedative utilized in the management of critically ill patients that causes far less respiratory depression and prolonged ventilator dependency than benzodiazepines. It has been effectively used in controlling autonomic dysreflexia,

S. Morr · V. Li · R. M. Reynolds
Department of Neurosurgery, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, New York, USA

S. Morr · V. Li · R. M. Reynolds (✉)
Department of Neurosurgery, Women & Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222, USA
e-mail: rreynolds@ubns.com

C. M. Heard
Department of Anesthesiology, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, New York, USA

C. M. Heard
Division of Pediatric Clinical Care, Women & Children's Hospital of Buffalo, Buffalo, NY, USA

altered mental status, and seizures in acute ethanol withdrawal [1–12] as well as sympathetic over-activity, clonus, and hyperreflexia in serotonin syndrome [13].

Intrathecal administration of baclofen, a γ-Aminobutyric acid-B ($GABA_B$) agonist, is a well-established therapy in cases of intractable spasticity where oral baclofen is inadequate or produces unacceptable side effects [14–17]. Acute withdrawal in physiologically accustomed patients resembles acute ethanol withdrawal and is characterized by reflex spasticity, dysautonomia, hyperthermia, and depressed sensorium. Withdrawal mimicking sepsis and hypotension has also been reported [18]. Severe cases may present with rhabdomyolysis, multiorgan dysfunction, and death [19–21].

Acute ethanol intoxication and chronic dependence are associated with enhanced and globally diminished γ-Aminobutyric acid-A ($GABA_A$) function, respectively [22, 23]. Indeed, this clinical and biopharmacological kinship between alcohol and baclofen has led to the use of baclofen as a treatment for alcohol dependence and withdrawal [24–26]. This raises the question of the potential effectiveness of dexmedetomidine as an alternative or adjunct to benzodiazepines in acute baclofen withdrawal [26]. We report a case of acute baclofen withdrawal successfully managed with dexmedetomidine.

Case Report

Patient Profile

A 40-kg 15-year-old male born at 27 weeks of gestational age with a Papile grade III intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy, severe developmental delay, and spastic quadriparesis initially underwent placement of a Synchromed IIB intrathecal baclofen pump (Medtronic, Minneapolis, MN) 7 years prior to the current planned surgical revision. The patient was receiving 220 micrograms (mcg) of baclofen daily. One month prior to the procedure, a round area of skin irritation was noted on the lower part of the abdomen overlying the pump edge. Local wound care with bacitracin and additional padding did not improve the lesion.

Preoperative physical examination revealed a well nourished, severely developmentally delayed, non-verbal male with spastic quadriparesis (modified Ashworth Scale scores of 3 in the extremities). Abdominal and lumbar incisions were well healed without induration or breakdown. A 1.0 cm × 1.0 cm area of erythema could be visualized inferomedial to the abdominal incision with a palpable pump edge under the region. Given that the pump end-of-life was approaching, the decision was made to electively re-implant a fresh pump while revising the subcutaneous pocket to alleviate the pressure on the lower abdominal wall.

Operative Intervention

The patient was intubated after standard anesthetic induction. After positioning the patient in the lateral decubitus position with the right side up, the lumbar and abdominal sites were exposed, sterilized, and draped in the usual fashion. The abdominal incision was infiltrated with lidocaine and opened. Upon opening the capsule around the pump, a slimy, fibrinous, and slightly purulent exudate was encountered. The pump was explanted, and cultures were obtained for microbiologic review. The lumbar incision was opened, and the intrathecally bound catheter was clamped, and cut; 3 mL of cloudy-appearing cerebrospinal fluid was collected for microbiological analysis. Due to the significant concern for infection, the decision was made to remove the pump system. A suture was placed at the fascial exit site to prevent a cerebrospinal fluid leak. Intraoperative fluoroscopy was used to verify complete removal of the pump-catheter system. The wounds were closed in a multilayer fashion after copious irrigation. A Jackson-Pratt drain was left within the abdominal pocket.

Postoperative Course

Following removal of the pump-catheter system, the patient was transferred while intubated and receiving propofol to the pediatric intensive care unit (ICU) for close monitoring in light of his high risk of developing baclofen withdrawal. The multidisciplinary pediatric subspecialty team caring for the patient included critical care medicine, anesthesiology, physiatry, and infectious disease. The patient was placed on enteral baclofen (30 mg, every 6 h) via gastrostomy tube and scheduled intravenous lorazepam (0.25 mg, every 6 h) with supplemental lorazepam (0.5 mg doses, every 2 h) as needed. Despite these measures, the patient continued to have tachycardia up to 140 beats per minutes, systolic hypertension up to 160 mmHg with diastolic pressures up to 90 mmHg, severe rebound spasticity with Ashworth Scale scores of 4 and 5, and frequent intermittent episodes of spontaneous clonus in the lower extremities. He was successfully extubated approximately 36 h postoperatively but was noted to be in significant discomfort. Further escalation of benzodiazepine use was not utilized because of the real danger of respiratory depression. Given the continued concern for baclofen withdrawal as a source of the symptomatology and the lack of improvement with standard therapies, including up to hourly administration of 0.5–1 mg of lorazepam, a dexmedetomidine infusion was commenced on postoperative day 2 at a rate of 6 mcg per hour (0.15 mcg/kg/hr) and

titrated for control of autonomic instability and tone to a peak dose of 16 mcg per hour (0.40 mcg/kg/hr). The peak dose was reached over approximately 20 h from commencement of infusion. This dose was maintained for 3 days, after which the infusion was weaned over 36 h. The patient became normotensive without tachycardia, and tone improved to Ashworth scores of 2 and 3 within approximately 6 h of reaching the peak dose. Signs of pain and agitation also improved.

The drain was removed on postoperative day 2. The cerebrospinal fluid cultures grew coagulase-negative staphylococcus aureus for which the patient underwent a 2-week course of intravenous antibiotics with ceftriaxone. The patient was transferred to the floor on postoperative day 12 and discharged home on postoperative day 14 with scheduled enteral baclofen, 25 mg, and lorazepam, 0.5 mg, every 6 h each. The clonazepam dosage that was initiated years previously as an antiepileptic agent was maintained at 0.25 mg twice daily throughout his hospitalization and after discharge. Six weeks postoperatively, the patient was awake and interactive with reactive pupils, a symmetric face, in no distress, and occasionally producing a smile. Upper- and lower-extremity Ashworth scores were 3 and 4, respectively, with three beats of clonus in the lower extremities. Incisions were clean, dry, and intact with near resolution of the previously discolored area of skin where friction and pressure were concentrated. The patient had been weaned to 30 mg of baclofen and 0.25 mg of clonazepam administered enterally three times daily. His family is currently contemplating pump reimplantation versus continuing oral baclofen therapy.

Discussion

Baclofen withdrawal is a life-threatening condition that may be associated with reflex spasticity, dysautonomia, hyperthermia, depressed sensorium, fever, rhabdomyolysis, multiorgan dysfunction, disseminated intravascular coagulopathy, and death [19–21, 27, 28]. Benzodiazepines and enteral baclofen are the mainstay of treatment for acute baclofen withdrawal. Previously published cases of acute intrathecal baclofen withdrawal have reported requirements of 30 to >120 mg per day of enteral baclofen divided over several doses for symptom control; the reported lower doses were often supplemented with other medications, such as benzodiazepines and barbiturates [29]. Dantrolene [30] and cyproheptadine [31, 32] are other reported adjunct therapies. Nevertheless, oral daily doses of 240 mg of baclofen may fail to mitigate symptomatic withdrawal of intrathecal baclofen and have significant untoward side effects [33].

Use of an externalized intrathecal catheter for baclofen infusion has also been reported [34, 35]. This may be less desirable in cases where infection is suspected or documented, as in our case, or if spinal access is difficult. Additionally, continuous intrathecal infusion via an external pump requires specialized equipment, resources, and training, yet such therapy is an option for a decompensating patient.

Clonidine and tizanidine are oral α-2 adrenergic agonists that have been studied as alternatives to baclofen for controlling a variety of conditions and symptoms [36–40]. To our knowledge, dexmedetomidine, an α-2 adrenergic agonist more suited for critical care use, is a previously unreported option for the treatment of acute severe baclofen withdrawal. The recommended adult dose in the ICU setting for sedation is 0.3–0.7 mcg/kg/hour for up to 24 h following an initial loading dose of 0.5–1 mcg/kg over 10 min [41]. Although this drug does not have Food & Drug Administration approval for pediatric use, a significant body of evidence exists to support its safe and efficacious use for both short-term procedural sedation as well as longer ICU sedation. The pharmacokinetics in infants and children are similar to those for adults, with a terminal elimination half life of approximately 2–3 h. A slower loading infusion, rather than a bolus dose, is necessary for initial quick use due to the risk of severe bradycardia or heart block if given by a bolus dose [42]. Loading doses of up to 6 mcg/kg/hour have been safely used in pediatric patients in clinical pharmacokinetic studies [43].

We report a case of safe and efficacious use of dexmedetomidine in a patient with spastic quadriparesis experiencing sudden cessation of chronic intrathecal baclofen therapy. Advantages over enteral benzodiazepines and baclofen, as well as parenteral benzodiazepines, are its superior safety profile in avoiding respiratory depression and decreased sensorium. Though not utilized in our case, dexmedetomidine has been studied in the anesthesia setting in intranasal and intramuscular formulations when immediate intravenous access was not available [44, 45]. Additionally, it does not require specialized externalized catheter access to the subarachnoid space, thereby diminishing risk of infection and minimizing strain on resources and personnel.

Scientifically rigorous comparison with other options remains to be performed. Weight-based dose titration needs to be established on pharmacological grounds and confirmed with experimental multi-subject evidence. The mechanism of action for dexmedetomidine in the specific case of baclofen needs further elucidation, as does the relationship between $GABA_A$ and $GABA_B$ active substances in the setting of chronic use, dependence, and withdrawal.

Conflict of interest Simon Morr, Christopher Heard, Veetai Li, and Renée Reynolds declare that they have no conflicts of interest.

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