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PRACTICAL PEARL

Acute Intrathecal Baclofen Withdrawal: A Brief Review of Treatment Options

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Abstract
Background Acute baclofen toxicity and withdrawal can present with a constellation of symptoms making differentiation between these two entities and other potential diagnoses challenging. Baclofen withdrawal is associated with numerous complications which may require neurocritical care expertise such as respiratory failure, refractory seizures, delirium, and blood pressure lability.
Methods Case report and literature review.
Results This case report discusses a case of intrathecal baclofen (ITB) withdrawal, focusing on the differential diagnosis for acute baclofen withdrawal and reviews the various options that exist to treat the symptoms of acute baclofen withdrawal such as benzodiazepines, propofol, skeletal muscle relaxants, and tizanidine.
Conclusions Critical care practitioners should be prepared to treat this potentially devastating and often refractory complication of ITB therapy.

Keywords Baclofen · Intrathecal · Withdrawal · Seizure · Tizanidine

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Introduction

Acute baclofen withdrawal and toxicity, either oral or intrathecal, can present with a constellation of symptoms making differentiation between these two entities and other potential diagnoses challenging [1–4]. The differential diagnosis of baclofen withdrawal includes but is not limited to: autonomic dysreflexia, sepsis, serotonergic syndromes, illicit drug abuse, neuroleptic malignant syndrome, and malignant hyperthermia (Table 1) [1, 5–13]. Appropriate diagnosis before treatment initiation is critical as management differs between acute baclofen withdrawal and the other diagnoses. Therapies utilized to manage complications associated with acute baclofen withdrawal may require institution of mechanical ventilation and additional neurocritical care expertise. This case report reviews a representative case of baclofen withdrawal following intrathecal baclofen (ITB) therapy and discusses the recognition and treatment of life-threatening baclofen withdrawal and differentiating it from other potential causes that require neurocritical care [9]. This report highlights the unique features related to the rapid withdrawal that can occur following interruption of intrathecal administration of baclofen via an implanted programmable pump.

Table 1 Differential diagnoses of intrathecal baclofen withdrawal

Diagnosis	Intrathecal baclofen withdrawal	Intrathecal baclofen overdose	Sepsis	Neuroleptic malignant syndrome	Autonomic dysreflexia	Serotonin syndrome	Malignant hyperthermia
Mechanism	Abrupt reduction $GABA_B$ activity centrally	Abrupt increase $GABA_B$ activity centrally	Systemic hypotension and cytokine release cause decreased cerebral perfusion and altered mentation	Autonomic hyperactivity caused by administration of dopamine-receptor blocking neuroleptic drugs or abrupt withdrawal dopamine agonist drugs	Loss of supraspinal influences above T6 level, spinal cord injury. Response to stimuli below lesion sympathetic and motor overactivity	Acute overload of serotonin transmission. Excessive central serotonin release and/or blocking serotonin reuptake overdose of SSRI's or MDMA	Excessive calcium influx into skeletal muscle, often due to ryanodine receptor mutations and exposure to some anesthetics
Onset	12–24° pump malfunction	Minutes after Pump malfunction	Variable	Variable	Acute onset	Acute onset	Variable
HR	↑	Autonomic instability	↑	↑	↓	↑	↑
BP	Labile	Autonomic instability	↓	↑	↑	Autonomic instability	↑
RR	↑	↓	↑	↑	–	↑	↑
Temp	↓	↑↓-	↑	↑	↑	↑	↑
Neurological mental status	Delirium Hallucinations Agitation Level of consciousness Disorientation	Delirium Drowsiness	Unresponsive	Cognitive changes	Normal level of consciousness	Cognitive changes	Cognitive changes
Muscle activity	↑ Muscle rigidity (lower limbs and trunk) paresthesis	Flaccidity Hyporeflexia		↑ Muscle rigidity (upper trunk/ lower limbs) rigidity	↑ Muscle rigidity (lower limb and trunk)	↑ Myoclonus Hyperreflexia Hypertonicity	↑ Muscle tone (upper/ lower limbs and trunk)
Other features	Multi-organ system failure possible seizures	Seizures	Multiple organ system failure possible	Sweating Rhabdomyolysis Normal WBC	Rhabdomyolysis	Sweating Rhabdomyolysis ↑ WBC (during crisis) Seizures N/V ↑ LFTS	Sweating Rhabdomyolysis Metabolic acidosis

Case Report

The patient is a 45-year-old female with a history of paraplegia and severe lower extremity spasticity secondary to a mid-thoracic spinal cord injury caused by a self-inflicted gunshot wound in 1995. Spasticity was being treated with an ITB pump delivering 550 mcg/day. Initially, she presented to her physiatrist's office complaining of night sweats and emesis and was noted to have significant akathisia with an unchanged neurological function and baseline spasticity. She had missed a scheduled ITB pump check 4 days previously, though no low alarm had sounded. The ITB pump (SynchroMed II, Medtronic, Inc., Minneapolis, MN) had a 37.4 ml reservoir filled with baclofen (2000 mcg/ml) with adequate doses of baclofen remaining for approximately 60 days of therapy. The ITB pump was noted on abdominal radiograph to be located above the ileum with appropriate catheter tip placement, and compared to previous studies, the pump was reported as being "flipped." She had not responded to oral baclofen nor intramuscular lorazepam (2 mg) administered by the physiatrist. She was referred to the emergency department for further evaluation where she had moderate lower extremity spasticity and was afebrile without meningeal signs. The ITB pump catheter was noted to be protruding through the skin of her back. Her white blood cell count was 11,200. The patient was admitted, cultures (blood and urine) were sent, and the ITB pump was removed intraoperatively with cultures obtained. Cerebrospinal fluid (CSF) revealed 62 white and 4,700 red blood cells, a glucose of 46 mg/dl (serum 110 mg/dl) and a gram stain without bacteria.

Postoperatively, the patient was alert and oriented with oral baclofen (20 mg every 6 h) begun that afternoon. However, she became progressively confused with agitation on postoperative day 2. Oral baclofen was increased (40 mg po every 6 h) and lorazepam (2 mg po every 4 h) was begun. Antibiotics were initiated due to the possibility of sepsis. An abdominal CT showed no abscess or fluid collections and a non-contrast head CT demonstrated no acute changes. An echocardiogram revealed no wall motion abnormalities, valvular disease, or vegetations. ITB pump hardware cultures grew methicillin-sensitive *Staphylococcus aureus* with no growth from other cultures (CSF, blood, urine). Arterial blood gas on FiO2 0.21 had a pH 7.43, pCO2 38, pO2 101 with oxygen saturation of 98%.

After myoclonic-like movements, an electroencephalogram (EEG) was performed, which showed intermittent epileptiform discharges over the bilateral frontal regions with moderate generalized and bihemispheric slow-wave activity greater over the frontotemporal regions suggestive of moderate diffuse cerebral dysfunction greater over the frontotemporal region. The patient was initiated on phenytoin for this seizure-like activity and continuous EEG with video monitoring. Her lower extremity spasticity had increased, and the patient became delirious. Concerned with baclofen withdrawal, her baclofen and lorazepam doses were increased, and tizanidine was also added. A loading dose of 4 mg tizanidine was given due to her increased spasticity, followed by a maintenance dose of 2 mg every 8 h. Her continuous EEG following phenytoin showed epileptiform discharges over the frontal electrodes suggestive of potential epileptogenicity in the right frontal region; however, no clinical seizures or ictal discharges were noted, and there was improvement in the overall background activity during this time period. The patient slowly improved on the combination of lorazepam, oral/enteral baclofen, tizanidine, and phenytoin and progressively demonstrated improved mental status and lower extremity spasticity. Her ITB pump was not replaced. By postoperative day 5, she was beginning to following commands. By postoperative day 7, she was alert and oriented and able to follow commands. She was discharged to home without the need for oral therapy for spasticity (her spasticity was at a tolerable level upon discharge and the benzodiazepine/baclofen combination was causing sedation which blunted her neurological examination). She was also discharged on phenytoin, linezolid, and metoprolol.

Treatment and Monitoring of Acute Baclofen Withdrawal

The cornerstones of treating baclofen withdrawal are focused on diminishing acute exacerbations in muscle spasticity, treating blood pressure lability, and prevention and treatment of central nervous system complications such as seizures and delirium. Central to these treatments are considerations for the receptors affected by chronic baclofen use. Downregulation of GABA type b receptors occurs with prolonged baclofen GABA agonism, which may lead to tolerance [14]. When baclofen concentrations within the intrathecal space are substantially reduced, the result is a hyperactivity of afferent nerve impulses and associated severe sequelae such as seizures, muscle spasticity, and agitation [1]. Owing to the higher CSF concentrations following intrathecal administration, abrupt cessation of ITB administration (e.g., pump malfunction, infected hardware, etc.) can result in a rapid onset of acute baclofen withdrawal as a medical emergency pertinent to neurocritical care. Currently, there is not a definitive, effective approach to treating acute baclofen withdrawal. Numerous agents have varying degrees of success in the prevention and treatment of baclofen withdrawal symptoms including oral and ITB, benzodiazepines, propofol, cyproheptadine, and dantrolene.

Oral and ITB replacement have been the most widely used methods for treating withdrawal [1]. Oral baclofen alone is not adequate replacement for large intrathecal doses, although it is still commonly given to patients experiencing withdrawal [8, 15]. Large oral doses of >120 mg/day (divided in 6–8 doses) are recommended by some authors [1]. However, oral baclofen is often not effective in the early stages of acute baclofen withdrawal, due to its slow onset of action (3–4 days) and time to peak effect (5–10 days). This is especially pertinent with acute withdrawal following ITB, as the onset of withdrawal may occur rapidly (most typically within 12–24 h). In addition, oral baclofen may be inconsistently absorbed in critically ill patients with gastrointestinal processes or those not tolerating enteral nutrition. Patients may have withdrawal symptoms within this acute timeframe (<24 h) unless baclofen is supplemented intrathecally or other alternative agents are used to treat the withdrawal symptomatology.

Perhaps more significantly, oral baclofen doses result in markedly lower CSF concentrations than intrathecal doses. One study demonstrated a 100-fold decrease in CSF concentrations when comparing a 50 mcg ITB bolus and a 30 mg oral baclofen dose [15, 16]. If possible, it is prudent to use an external intrathecal catheter to provide bolus doses or an infusion until the implanted pump can be repaired or replaced [17]. The patient should ideally be restarted on the same dose and rate that was provided by the implanted pump [1]. Bolus doses may also be given through the access port on the pump with an intact catheter or by lumbar puncture after assessing opening pressure during cases of meningitis [8, 18]. A commonly used intrathecal bolus dose is 50 mcg, with maintenance infusion doses ranging from 12 to 2003 mcg/day [1, 8, 16]. In our case, a decision was made to avoid intrathecal administration due to concern about possible other infectious etiologies including sepsis, meningitis, and potential pump infection.

The most common adjuvant therapy for baclofen withdrawal is benzodiazepines [1, 8, 10, 15, 19, 20]. Benzodiazepines activate pre-sympathetic GABA type a receptors, thereby circumventing the problem of down-regulation in GABA type b receptors seen in patients with a long history of baclofen use. Benzodiazepines used to treat baclofen withdrawal include lorazepam, diazepam, and midazolam. Benzodiazepine doses should be increased in the treatment of baclofen withdrawal until muscle relaxation, normothermia, stabilization of blood pressure, and cessation of seizures occurs. Although specific dosing recommendations are lacking, rapid titration of benzodiazepines require the ability to provide airway and circulatory support in a neurocritical care unit if high doses are required. Initiation of intravenous benzodiazepine therapy with diazepam or midazolam might be preferable due to quick onset of action. Transition to lorazepam may be advisable for patients who will require benzodiazepine therapy long-term to avoid tachyphylaxis or excessive drug accumulation.

Another alternative treatment agent for baclofen withdrawal is propofol. It has been successfully utilized in conjunction with other drugs and as a sole agent in one case report [8, 21, 22]. While propofol's mechanisms are numerous and not fully understood, propofol has presynaptic activity at GABA type a receptors, which may help circumvent the problem of down-regulation [23]. Although dose recommendations for propofol in baclofen withdrawal are lacking, one case report titrated propofol in the range of 5–150 mg/h representing relatively low doses compared to typical requirements for ICU sedation. Propofol's short half-life and quick onset of action enable clinicians' rapid and precise titratability to symptom resolution. Propofol necessitates the neurocritical care environment because of its potential respiratory and hemodynamic effects.

Cyproheptadine has been used as an adjuvant to baclofen replacement in several case reports [1, 9, 10, 18, 24]. The surge of excitatory nerve activity that occurs during baclofen withdrawal is speculated to result in an excess of serotonergic activity. Many of the symptoms of ITB withdrawal are similar to serotonergic syndromes [9]. Cyproheptadine, a potent serotonin antagonist, can reduce many of the withdrawal symptoms. Reported dosing ranges from 4 mg every 8 h to 8 mg every 6 h. Given its reported success as an adjunct therapy, cyproheptadine may be useful in patients already receiving baclofen replacement and benzodiazepines.

Dantrolene has also been used with acute baclofen withdrawal because of treatment efficacy of spasticity similar to spasticity associated with neuroleptic malignant syndrome and malignant hyperthermia [1, 11, 22, 23]. Dantrolene blocks calcium release from the sarcoplasmic reticulum, which decreases excitation–contraction of skeletal muscles. Dantrolene may be considered as an adjunct in patients with extreme muscle spasticity refractory to other therapies.

Tizanidine is an alpha$_2$-adrenergic agonist that acts at the level of the spinal cord to decrease excitatory input to alpha motor neurons. It is indicated for the management of spasticity and has been reported by a few authors to be an effect adjunct to baclofen or benzodiazepines for baclofen withdrawal [1, 8, 17]. Doses ranged from 8 to 12 mg/day in 3–4 divided doses. Tizanidine represents an intriguing option for the acute management of spasticity in this setting because the mechanism of action circumvents GABA receptor down-regulation. In addition, the alpha-blockade may also aid in mitigating the agitation and hyperactivity often seen in baclofen withdrawal. Similar to cyproheptadine and dantrolene, tizanidine should only be used as an adjunct to other treatments. In our patient reported above, tizanidine played a pivotal role in allaying the acute increase in spasticity and tone due to baclofen withdrawal.

The treatment of delirium in acute baclofen withdrawal is a difficult issue. The primary agent used in most intensive care units for acute delirium is haloperidol. However, in acute baclofen withdrawal, practitioners should consider some of the adverse effects typical of haloperidol. Haloperidol and other butyrophenones may cause hypotension upon administration. In patients already with blood pressure lability, caution should be exercised to ensure no rapid alterations in blood pressure occur. In addition, haloperidol may lower the seizure threshold, which may be problematic in patients already at risk of seizure [25]. Use of neuroleptic medications is often necessary to treat severe delirium, but dosing should be judicious and monitoring should be frequent to avoid complications of this therapy. The role of sedatives that have been suggested to decrease the risk of delirium, such as propofol and dexmedetomidine, remain ill-defined at this point [26].

Summary

In cases of acute baclofen withdrawal following interruption of ITB administration because of pump-related issues, treatment should focus on repairing or replacing the malfunctioning intrathecal pump with the goal of resuming baclofen delivery to the intrathecal space as promptly as possible. In cases of acute infection where this may not be possible, acute treatment of baclofen withdrawal may necessitate medications other than baclofen to prevent the deleterious effects of withdrawal. Benzodiazepines represent a reasonable option based on the clinical experiences and reports currently available. High-dose or continuous infusion benzodiazepines or propofol may be necessary for those with severe withdrawal requiring neurocritical care. Specific symptoms may require different adjunct therapies. Cyproheptadine may be helpful for symptoms involving serotonergic syndromes while dantrolene may be helpful with excessive spasticity. Tizanidine may represent a viable option for patients with spasticity and blood pressure lability (particularly hypertension). Oral baclofen does not achieve concentrations remotely near the range resulting from directly infused ITB and, as a consequence, is not particularly effective for acute baclofen withdrawal.

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