

# **Intrathecal baclofen withdrawal syndrome- a life-threatening complication of baclofen pump: A case report**

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## **Abstract**

**Background:** Intrathecal baclofen pump has been used effectively with increasing frequency in patients with severe spasticity, particularly for those patients who are unresponsive to conservative pharmacotherapy or intolerable side effects at therapeutic doses. Drowsiness, nausea, headache, muscle weakness, light-headedness and return of pre-treatment spasticity can stem from the intrathecal pump delivering an incorrect dose of baclofen. Intrathecal baclofen withdrawal syndrome is a very rare, potentially life-threatening complication of baclofen pump, which is caused by abrupt cessation of intrathecal baclofen.

**Case presentation:** A 24-year-old man with past medical history of cerebral palsy and spastic quadriparesis who developed hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure and multisystem organ failure, a full-blown intrathecal baclofen withdrawal syndrome. Intrathecal baclofen pump analysis revealed that it was stopped due to programming error. He was treated effectively with early restoration of baclofen pump and proper intensive care management.

**Conclusion:** Episodes of intrathecal baclofen withdrawal syndrome are mostly caused by preventable human errors or pump malfunction. Education of patients and their caregivers about the syndrome, and regular check up of baclofen pump may decrease the incidence of intrathecal baclofen withdrawal syndrome. Oral baclofen replacement may not be an effective method to treat intrathecal baclofen withdrawal syndrome. Management includes early recognition of syndrome, proper intensive care management, and prompt analysis of intrathecal pump with reinstatement of baclofen at a previously prescribed dose.

## **Background**

Baclofen is a gamma-aminobutyric acid (GABA) analog that has inhibitory effects on spinal cord reflexes and brain. Intrathecal baclofen (ITB) therapy consists of long-term delivery of baclofen to the intrathecal space. Intrathecal baclofen has been used to treat spasticity due to cerebral palsy, brain or spinal cord injury, multiple sclerosis, dystonia, stroke and stiff-man syndrome, particularly for those patients who are unresponsive to conservative pharmacotherapy or intolerable side effects at therapeutic doses of oral baclofen [1]. There are various side effects like drowsiness, nausea, headache, muscle weakness and light-headedness that can stem from the pump delivering an incorrect dose of baclofen. Sudden cessation of ITB administration can cause mild symptoms like reappearance of baseline level of spasticity associated with pruritis, anxiety and disorientation [2]. These mild symptoms represent “loss of drug effect”, and experienced in all patients where ITB is discontinued. However, abrupt cessation of ITB could result in a rare life-threatening withdrawal syndrome in a small (but unknown) proportion of patients. We report a case of ITB withdrawal syndrome developing hyperthermia, severe spasticity, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure and multisystem organ failure.

## **Case presentation**

A 24-year-old man admitted to our intensive care unit (ICU) with a possible diagnosis of seizure disorder and sepsis. He had a past medical history of cerebral palsy and spastic quadriparesis. Three years ago, he had an ITB pump implanted for spasticity refractory to high doses oral baclofen. Patient had significant improvement in spasticity, social, and functional capacity in the last three years. One day, he developed some

disorientation and increased spasticity. He was taken to some local physician, who prescribed oral baclofen (120 mg daily in four divided doses) for increased spasticity and advised to have an immediate check up of his ITB pump. Next day, his spasticity increased even after taking oral baclofen during this time period. He developed multiple seizures and respiratory distress in the next 24 hours. Subsequently, he was admitted in a local hospital where he got intubated and later transferred to our ICU for aggressive management.

His vital signs were, temperature 104.6°F (40.3°C), heart rate 127-beats per minute, and blood pressure was 85/45 mm/Hg. He was orally intubated on assist-control mode with respiratory rate of 15 breaths per minute, FiO<sub>2</sub> 60%, tidal volume 5.5 mL/kg and positive end expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O, saturating 100% of oxygen. In the local hospital, he was documented to have high fever of 107°F (41.6°C) and he received intravenous lorazepam, phenytoin, pantoprazole, piperacillin/tazobactam and dopamine. On physical examination, neurologically he was unconscious with decerebrate posturing and his Glasgow coma scale was 6. He had absent corneal and gag reflexes but he was moving all four limbs in response to noxious stimuli. He was also noted to have extreme spasticity in all four limbs. Lung examination revealed decreased breath sounds in left lower bases of lungs. Cardiac examination was unremarkable. He had a palpable baclofen pump on abdominal wall and bowel sounds were heard. His initial differential diagnoses were septic shock, meningitis, neuroleptic malignant syndrome and malignant hyperthermia.

Initial laboratory results were creatinine phosphokinase (CPK) 5250 U/L (Normal, 52 to 336 U/L) and MB fraction 12.1 ng/ml. Serum chemistry revealed sodium

142 mmol/L, potassium 5.1 mmol/L, chloride 120 mmol/L, bicarbonate 13 mmol/L, and creatinine 2.1 mg/dl. Hemogram showed white cell counts 12.2 K/UL, hemoglobin 16.5 g/dl and platelet counts of 9 K/UL (Normal, 150-450 K/UL). Liver function tests showed aspartate aminotransferase (ALT) 1128 U/L, alanine aminotransferase (AST) 1140 U/L, alkaline phosphatase 90 U/L, total bilirubin 1.2 mg/dl (conjugated fraction 0.7 mg/dl), prothrombin time 20.2 seconds (Normal, 11-13.5 seconds), and INR was 2.0 (Normal <1). Blood and urine cultures were obtained. Chest radiograph was normal but computed tomography (CT) scan of chest revealed left basal atelectasis. His CT scan of head did not show any acute infarct or bleeding. His initial management included intravenous fluids, norepinephrine, platelet transfusion, phenytoin, propofol and broad-spectrum antibiotics (vancomycin, ceftriaxone) for suspected meningitis and septic shock. He received intravenous lorazepam (4-8 mg every four hours) for his spasticity. Next day, his spasticity improved, and an ITB specialist analyzed his baclofen pump. His baclofen pump analysis revealed that it was stopped due to programming error, which was restarted at a previously prescribed baclofen rate (260 µg/day).

On third hospital day, his serum CPK was 15,878 U/L, AST was 2566 U/L, ALT was 2993 U/L, while MB fraction came down to 3.4 ng/ml. His urine output decreased (<400 ml/ day) and serum creatinine increased in the range of 5-6 mg/dl. He was hemodialyzed few times during the course of his hospitalization due to acute renal failure. His echocardiogram showed left ventricular ejection fraction of 20-25% and severe global hypokinesis, while electroencephalogram did not reveal any epileptogenic activity. He developed full-blown multisystem organ failure with evidence of shock liver, renal failure, respiratory failure, disseminated intravascular coagulation, and myocardial

depression. His nutrition was started on nasogastric tube feedings, and proper ventilator care was taken through a tracheostomy tube. His serum baclofen obtained at the time of admission was less than 0.02 µg/ml (expected values, 0.08-0.4 µg/ml). After a 3-week course of aggressive management in ICU, he was weaned off from the ventilator and his multiple organ shock resolved. At a six-month follow up, he was observed in a nursing home with his baseline functional, social, and family activities.

## **Discussion**

Intrathecal baclofen provides effective improvement in spasticity of patients whose conditions are not sufficiently managed by oral baclofen and other oral medications [1]. Regardless of the cause of spasticity (cerebral or spinal), anti-spastic effects of baclofen occur at spinal level. Poor response of oral baclofen in many patients can be explained by the fact that spinal cord represents only about 2% the mass of the brain, and receives proportionately lower blood flow as a fraction of cardiac output. Therefore, cerebral side effects often occur before therapeutic anti-spastic effects of oral baclofen are observed. ITB pump provides direct, pattern-controlled delivery of baclofen to the spinal cord via an implanted programmable pump. Precise delivery by the ITB pump yields better spasticity reduction at 1000 times lower the doses of baclofen, and minimum adverse effects as compared with oral baclofen. ITB provides reduced tone, spasms and pain, increased mobility, improves speech, sleep quality and bladder control, with a response rate up to 97% in adults and children [3, 4]. ITB pump is approximately 3 inches wide and 1 inch thick, surgically implanted in subcutaneous tissue of anterior abdominal wall. Baclofen is delivered via a silicone rubber catheter into lumbar subarachnoid space, approximately 100-900 µg/day in titration with clinical effects. ITB

is also equipped with an alarm that signals low volume, low battery, or malfunction. Nine years ago, catheter or pump-related malfunction that leads to an overdose or withdrawal has been reported in 40 % of patients with ITB pumps [5]. Catheter system, operative techniques and programming of the pump have now been improved significantly to reduce the incidence of an overdose or withdrawal.

The precise mechanism of action of baclofen as a muscle relaxant and anti-spasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal cord level [6], possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen also causes enhancement of vagal tone and inhibition of mesolimbic and nigrostriatal dopamine neurons (directly or via inhibiting substance P) [7]. Baclofen is a structural analog of the inhibitory neurotransmitter GABA, and may exert its effects by stimulation of the GABA<sub>B</sub> receptor to cause muscle relaxation. Baclofen reduces increased muscle tone and Babinski sign, tendon reflexes ankle clonus, and sometimes decreases muscle force.

Long term ITB infusion causes down-regulation of GABA<sub>B</sub> receptors and thus down-regulation probably accounts for decreased sensitivity to baclofen over time. Although GABA<sub>B</sub> receptors are down-regulated, it is the baclofen itself that causes increased inhibitory tone in CNS and spinal cord [8]. Therefore, abrupt ITB withdrawal results in a predominance of excitatory effects and simulates other conditions that are associated with CNS hyperexcitability and severe spasticity. Sudden cessation of ITB administration can cause mild symptoms like reappearance of baseline level of spasticity associated with pruritis, anxiety and disorientation. These mild symptoms represent “loss

of drug effect”, and experienced in all patients where ITB is discontinued. However, more severe symptoms like hyperthermia (109.4°F), myoclonus, seizures [9-12], rhabdomyolysis, disseminated intravascular coagulation, multisystem organ failure [10], cardiac arrest, coma, and death [9, 12, 13] have been well reported, and represent a full-blown, life-threatening ITB withdrawal syndrome. Food and drug administration (FDA) of USA has also included a drug label warning for baclofen withdrawal syndrome in April 2002 [1, 13]. Differential diagnosis includes malignant hyperthermia, neuroleptic-malignant syndrome, autonomic dysreflexia, sepsis and meningitis. ITB withdrawal syndrome has been fatal in some cases, 6 patients died out of 27 cases reported to FDA [13]. Most reported episodes of ITB withdrawal were caused by preventable human errors or oversights. However, catheter dislodgement, catheter migration and kinks, and other catheter-related issues might be more common than pump-related malfunctions [1, 14]. Close attention to pump refill and programming procedures may reduce the incidence of ITB withdrawal syndrome.

Benzodiazepines are helpful in controlling spasticity and seizures during ITB withdrawal syndrome [1, 10]. Benzodiazepines activate central receptors and GABA<sub>A</sub> receptors of spinal cord by different mechanisms [1]. Therefore, ITB induced down-regulation of GABA receptors do not interfere with benzodiazepine’s mechanism of action. During planned removal of ITB pump due to infection or other causes, premedication with high doses of benzodiazepines and augmented oral baclofen is usually administered in the hospitals to prevent spasticity. Similarly, high dose oral baclofen is also tried in some cases of ITB withdrawal syndrome [15, 16]but failures of high doses oral baclofen (80 mg three times daily) have been reported recently [17]. High

doses of oral baclofen may not be adequate to treat or prevent ITB withdrawal because of down-regulation of central GABA<sub>B</sub> receptors after chronic ITB administration. Moreover, it has been suggested that it may take many hundreds of grams of oral baclofen to achieve a therapeutic baclofen level in cerebrospinal fluid, compared to the patients who had effective spasticity control with an ITB pump [17]. Although, our patient received oral baclofen (120 mg daily in four divided doses) initially but these doses may be low enough to prevent ITB withdrawal syndrome. Failure of high dose oral baclofen suggests that resumption of GABA<sub>B</sub> receptor agonist by prompt restoration of ITB pump, and proper supportive care might be the best treatment. Similarly, high-dose benzodiazepines may be effective because of similar mechanism of action on widespread CNS GABA<sub>A</sub> receptors. High-dose benzodiazepines could be an initial life saving strategy even before analysis and restoration of ITB pump is achieved or in cases where resumption of ITB administration is not as simple as correcting a programming error.

Intrathecal baclofen bolus is appropriate but due to the risk of inadvertent overdose, an experienced physician should immediately perform reinstatement of ITB pump. We had started ITB in our patient at a previously prescribed dose. A much higher doses in ITB pump could have been safely been given to overcome the spasticity since the patient was in an ICU. High dose dantrolene (a direct muscle relaxant that acts on sarcoplasmic reticulum of skeletal muscle) has been tried to reduce spasticity and fever in ITB withdrawal syndrome [18]. Reduction in fever may be due to cessation of repetitive and thermogenic contractions of muscle fibers. It is unlikely that dantrolene has any GABA agonistic effects, and administration of dantrolene may not be accompanied by any correction in anomalies of CNS functions. Therefore, seizures, autonomic instability,

and death may occur in ITB withdrawal syndrome even after controlling spasticity with dantrolene. Cyproheptadine (a non-selective serotonin antagonist) has also been used postulating that ITB withdrawal may be a form of serotonergic syndrome that occurs from loss of GABA<sub>B</sub> receptor-mediated presynaptic inhibition of serotonin [19]. We did not consider dantrolene and cyproheptadine in our patient due to lack of sufficient clinical support in the treatment of ITB withdrawal syndrome. There was a three-day delay in diagnosing and restoration of ITB pump in our patient which lead to deterioration and multisystem organ failure. Early recognition of syndrome and restoration of ITB pump could have prevented this fatal syndrome. However, our patient had a successful recovery in response to restoration of baclofen pump and adequate intensive care management.

## **Conclusion**

Baclofen withdrawal syndrome is a potentially life-threatening complication of intrathecal baclofen pump. Empty pump reservoir, catheter leaks or displacement, pump malfunction, programming error and refill of pump with improper drug concentration are the possible mechanisms, which could lead to ITB withdrawal syndrome. Regular check up of the ITB pump by specialist, education about the withdrawal syndrome in patients and their caregiver may decrease the incidence of ITB withdrawal syndrome. Oral baclofen replacement may not be an effective method to treat ITB withdrawal syndrome. Early recognition of syndrome, high-dose benzodiazepines, prompt analysis of ITB pump with reinstatement of baclofen, and proper intensive care management are the mainstays in the management of ITB withdrawal syndrome.

## **List of abbreviations**

GABA -gamma amino butyric acid, ITB - intrathecal baclofen, CK- creatinine kinase, ALT- aspartate aminotransferase, AST- alanine aminotransferase, CT- computed tomography.

### **Competing interests**

None declared.

### **Authors' contributions**

IM: Direct patient care, article conception and critical, extensive revision of article for important intellectual content. AH: Literature search and review, case review and summary, drafting original article. Both authors read and approved the final manuscript and contributed equally to the manuscript.

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