

# **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 inappropriate dosage 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 intrathecal baclofen withdrawal syndrome consists of hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure and multiple organ dysfunctions. Intrathecal baclofen pump analysis revealed that it was stopped due to programming error. He was treated effectively with early restoration of baclofen pump and appropriate intensive care management.

**Conclusion:** Most episodes of intrathecal baclofen withdrawal syndrome are caused by preventable human errors or pump malfunction. Education of patients and their caregivers about early signs and symptoms of 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 supportive care, and prompt analyses of intrathecal pump with reinstatement of baclofen at appropriate 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 inappropriate dosage of baclofen. Some ITB withdrawals are limited and may cause only a return of patient's pre-treatment spasticity, which is easily recognized and treated more effectively [2]. Abrupt withdrawal from ITB can result in a rare life threatening withdrawal syndrome. We report a case of ITB withdrawal syndrome developing hyperthermia, severe spasticity, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure and multiple organ dysfunctions.

## **Case report**

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 quadriplegia. 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 disorientation and some spasticity and was taken to some local physician, who advised him to take oral baclofen (30 mg four times daily) for increased spasticity and immediate

check up of his ITB pump. Next day, his spasticity was increasing even after taking oral baclofen during this time period. He developed multiple seizures and respiratory distress in the next 24 hours and admitted in some 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 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 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), MB fraction was 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. White cell counts 12.2 K/UL, hemoglobin 16.5 g/dl and platelet count 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 / INR were 20.2 seconds (Normal, 11-13.5 seconds) and 2.0 (Normal<1) respectively. 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 until the next day ITB specialist analyzes his baclofen pump. His baclofen pump analysis revealed that it was stopped due to programming error, which was restarted at his previous baclofen rate of 260 µg/day.

On third hospital day, his serum CPK was 15878 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 multiple organ dysfunctions 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 successful conservative management in ICU, he was weaned off from the ventilator and his multiple organ shock resolved. Three month later, he was observed in 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]. Absence of substantial therapeutic benefit from oral baclofen can result from an inadequate penetration of the blood-brain barrier by the drug. Since central nervous system (CNS) side effects often occur on high doses of oral baclofen, therapeutic effect usually cannot be improved by increasing the dose. 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 100 times lower the doses of baclofen and with 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  $\mu\text{g}/\text{day}$  in titration with clinical effects. ITB is also equipped with an alarm that signals low volume, low battery, or malfunction. Unfortunately, approximately 40 % of patients with ITB pumps have some kind of catheter or pump malfunction that leads to overdose or withdrawal [5].

The precise mechanism of action of baclofen as a muscle relaxant and antispasticity 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 [7] (directly or via inhibiting substance P). 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. It has no effect on tendon reflexes, muscle force or ankle clonus.

Long term ITB infusion causes down regulation of GABA<sub>B</sub> receptors sensitivity and thus increases 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 withdrawal of ITB causes a spectrum of clinical symptoms that might initially remain unnoticed. Initially patient may suffer pruritis, spasticity and disorientation, which may become more severe like hallucinations, hyperthermia, myoclonus, seizures and coma [9-12]. Rhabdomyolysis, disseminated intravascular coagulation, fever up to 109.4°F (43°C) [9, 11], multisystem organ failure[10], cardiac arrest and death [9, 12, 13] have been well reported in association with this syndrome. Food and drug administration (FDA) of USA has also included 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 has been

reported due to empty pump reservoir, catheter leaks or displacement, pump malfunction, programming error and refill of pump with improper drug concentration [1, 14]. ITB withdrawal syndrome has been fatal in many cases, 6 patients died out of 27 cases reported to FDA [13]. Although most reported episodes of ITB withdrawal were caused by preventable human errors or oversights, 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], thus 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 oral baclofen may not be adequate to overcome ITB withdrawal because those patients's spasticity is already refractory to oral baclofen. 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, comparable to patients who had effective spasticity control with ITB pump [17]. Although our patient received oral baclofen (30 mg four times daily) initially but these doses may be low enough or it may need very high or near toxic doses of oral baclofen to prevent ITB withdrawal syndrome. Failure of high dose oral baclofen suggests that prompt restoration of baclofen pump, spasticity control with intravenous

benzodiazepines and proper supportive care might be the best strategy to treat severe ITB withdrawal syndrome.

Intrathecal baclofen bolus is appropriate but due to the risk of inadvertent overdose, an experienced physician should immediately perform reinstatement of ITB pump. High dose dantrolene (a direct muscle relaxant 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 muscle contractions but it is unlikely that dantrolene may have any GABA agonist effects. 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. Furthermore our patient had a successful recovery in response to early restoration of baclofen pump in addition to adequate supportive care. Moreover, education about the early signs of baclofen withdrawal in the patient, their caregivers, and medical personnel should facilitate prevention, early identification and management of ITB withdrawal syndrome.

## **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 leads to ITB withdrawal syndrome. Regular check up of the ITB pump by specialist, education about the early symptoms and signs of 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, prompt analyses of intrathecal pump with reinstatement of baclofen and proper supportive care is the mainstay of management in 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.

### **Acknowledgements**

Written consent was obtained from the patient's mother for publication of this case report.

### **References**

1. Coffey RJ, Edgar TS, Francisco GE, Graziani V, Meythaler JM, Ridgely PM, Sadiq SA, Turner MS: **Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life-threatening syndrome.** *Arch Phys Med Rehabil* 2002, **83**(6):735-741.

2. Coffey JR, Cahill D, Steers W, Park TS, Ordia J, Meythaler J, Herman R, Shetter AG, Levy R, Gill B *et al*: **Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study.** *J Neurosurg* 1993, **78**(2):226-232.
3. Penn RD: **Intrathecal baclofen for spasticity of spinal origin: seven years of experience.** *J Neurosurg* 1992, **77**(2):236-240.
4. Van Schaeybroeck P, Nuttin B, Lagae L, Schrijvers E, Borghgraef C, Feys P: **Intrathecal baclofen for intractable cerebral spasticity: a prospective placebo-controlled, double-blind study.** *Neurosurgery* 2000, **46**(3):603-609; discussion 609-612.
5. Penn RD, York MM, Paice JA: **Catheter systems for intrathecal drug delivery.** *J Neurosurg* 1995, **83**(2):215-217.
6. Allerton CA, Boden PR, Hill RG: **Actions of the GABAB agonist, (-)-baclofen, on neurones in deep dorsal horn of the rat spinal cord in vitro.** *Br J Pharmacol* 1989, **96**(1):29-38.
7. Peng CT, Ger J, Yang CC, Tsai WJ, Deng JF, Bullard MJ: **Prolonged severe withdrawal symptoms after acute-on-chronic baclofen overdose.** *J Toxicol Clin Toxicol* 1998, **36**(4):359-363.
8. Kroin JS, Bianchi GD, Penn RD: **Intrathecal baclofen down-regulates GABAB receptors in the rat substantia gelatinosa.** *J Neurosurg* 1993, **79**(4):544-549.
9. Green LB, Nelson VS: **Death after acute withdrawal of intrathecal baclofen: case report and literature review.** *Arch Phys Med Rehabil* 1999, **80**(12):1600-1604.
10. Sampathkumar P, Scanlon PD, Plevak DJ: **Baclofen withdrawal presenting as multiorgan system failure.** *Anesth Analg* 1998, **87**(3):562-563.
11. Reeves RK, Stolp-Smith KA, Christopherson MW: **Hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation associated with baclofen pump catheter failure.** *Arch Phys Med Rehabil* 1998, **79**(3):353-356.
12. Meinck HM, Tronnier V, Rieke K, Wirtz CR, Flugel D, Schwab S: **Intrathecal baclofen treatment for stiff-man syndrome: pump failure may be fatal.** *Neurology* 1994, **44**(11):2209-2210.
13. **MedWatch 2002 Safety Alert - Lioresal (baclofen injection)**  
[\[http://www.fda.gov/medwatch/safety/2002/baclofen.htm\]](http://www.fda.gov/medwatch/safety/2002/baclofen.htm)
14. Kao LW, Amin Y, Kirk MA, Turner MS: **Intrathecal baclofen withdrawal mimicking sepsis.** *J Emerg Med* 2003, **24**(4):423-427.
15. Siegfried RN, Jacobson L, Chabal C: **Development of an acute withdrawal syndrome following the cessation of intrathecal baclofen in a patient with spasticity.** *Anesthesiology* 1992, **77**(5):1048-1050.
16. Al-Khodairy AT, Vuagnat H, Uebelhart D: **Symptoms of recurrent intrathecal baclofen withdrawal resulting from drug delivery failure: a case report.** *Am J Phys Med Rehabil* 1999, **78**(3):272-277.
17. Greenberg MI, Hendrickson RG: **Baclofen withdrawal following removal of an intrathecal baclofen pump despite oral baclofen replacement.** *J Toxicol Clin Toxicol* 2003, **41**(1):83-85.
18. Khorasani A, Peruzzi WT: **Dantrolene treatment for abrupt intrathecal baclofen withdrawal.** *Anesth Analg* 1995, **80**(5):1054-1056.

19. Meythaler JM, Roper JF, Brunner RC: **Cyproheptadine for intrathecal baclofen withdrawal.** *Arch Phys Med Rehabil* 2003, **84**(5):638-642.