European Review for Medical and Pharmacological Sciences 2018; 22: 5371-5376

Delirium tremens in an AUD patient after an intrathecal baclofen pump induced total alcohol abstinence

M.E. CALVO[1], T. GUNNARSSON[2], L. SMITH[3], M. HAO[4]

[1]Department of Anesthesia, Anesthesia and Chronic Pain, McMaster University, Hamilton, Ontario, Canada
[2]Department of Neurosurgery, McMaster University, Hamilton, Ontario, Canada
[3]St. Joseph's Hospital, Hamilton, Ontario, Canada
[4]Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

Abstract. – OBJECTIVE: Delirium Tremens (DT) is the most severe complication of alcohol withdrawal syndrome (AWS), and has a mortality rate of 1-5%. Baclofen is recommended for spasticity treatment, but it has recently been used for alcohol withdrawal symptoms reduction and alcohol abstinence.

CASE REPORT: A cervical spinal cord injury patient was treated for two years with oral baclofen 80 mg/day for spasticity. He is alcohol-dependent and a cannabis user and required an intrathecal baclofen (ITB) pump implant. A week after the implant, he stopped drinking, as "he didn't felt the urge anymore". The AWS appeared five days after the last alcohol intake and DT at 7 days. Diazepam 20 mg was used up to three times per day, but didn't seem to improve or reduce the anxiety, agitation, visual or auditory hallucinations. Two years later the patient remains alcohol abstinent and still on intrathecal baclofen.

CONCLUSIONS: Alcohol-dependent patients can abruptly stop their alcohol intake, while in continuous infusion of intrathecal baclofen. Baclofen can be useful in the acute treatment of AWS as it seems to reduce diazepam requirements and in long-term alcohol abstinence. In the presence of AWS, while on chronic baclofen, no dose reduction should be attempted, as it can worsen the AWS or trigger baclofen withdrawal.

Key Words
Delirium tremens, Baclofen, Alcohol withdrawal syndrome, Alcohol abstinence, Alcohol dependence.

Abbreviations

DT: Delirium Tremens, AWS: Alcohol Withdrawal Syndrome, GABA: Gamma Aminobutyric Acid, CIWA: Clinical Institute withdrawal assessment for alcohol, NMDA: N-methyl-D-aspartate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, CT: Computerized Tomography, ITB: Intrathecal baclofen, T: Temperature, BP: Blood pressure, bpm: beats per minute.

Introduction

Chronic central nervous system exposure to alcohol produces adaptive changes developing tolerance to the effects of acute alcohol intake. These results showed down-regulation of the GABA A receptors to GABA and up-regulation of NMDA and AMPA receptors for glutamate[1,2]. Reduction or cessation of alcohol intake produces an acute imbalance and the development of alcohol withdrawal symptoms[1,2].

The most severe manifestation of alcohol withdrawal syndrome (AWS) (Table I) is delirium tremens (DT) (Table II). It usually appears 48-72 h after the last drink, but can present up to 10 days later[2,3]. Delirium, psychosis, hallucinations, hyperthermia, malignant hypertension, seizures and coma are common manifestations of DT. The mortality rate is 1-5%[2,3]. Recently, scholars[1,3,4] have reported the use of drugs that act on the Gamma Aminobutyric Acid (GABA) pathways in the treatment of AWS and long-term alcohol abstinence.

Baclofen, a synthetic derivative of GABA, acts as a GABA B receptor and has been approved for spasticity treatment, because of its effects at the spinal/thalamic level. It restricts the calcium conductance and increases potassium conductance into the pre-synaptic nerve terminal, hyperpolarizing it, reducing the release of transmitters and the production of post-synaptic excitatory potentials along Alfa motor neurons. This, in return, relaxes the spastic muscles[5].

Oral baclofen doesn't cross the blood brain barrier effectively. Therefore, when the limiting factors for spasticity treatment are the side effects from high oral doses, an intrathecal baclofen (ITB) pump is indicated.

Corresponding Author: Maria E. Calvo, MD; e-mail: marucalvo822@yahoo.com

Table I. Symptoms of Alcohol Withdrawal Syndrome.

Headache
Diaphoresis
Insomnia
Palpitations
Tremor
Anxiety
Hallucinations (tactile, visual or auditory)
Seizures (tonic – clonic)
Delirium
Symptoms generally appear 6 to 12 hours after reduced or last alcohol intake.

Table III. Calculations of grams of alcohol per drink.

Vol. of beverage in cc X percentage of alcohol by volume X ethanol density.
Ethanol density = 0.789 g/cm^3
Example:
Beer: 500 cc of 5% alcohol by volume
500 cc X 0.05 X 0.789 g/cm^3 = 19.7 g of Alcohol
Wine: 150 cc of 12.5% alcohol by volume
150cc X 0.125 X 0.789g/cm^3 = 14.8 g of Alcohol
Liquor: 50 cc of 40% alcohol volume
50cc X 0.4 X 0.789 g/cm^3 = 15.8 g of Alcohol

Preliminary data suggest that baclofen is a promising drug for the treatment of cravings in alcohol-dependent patients, reducing intake and enhancing abstinence[4]. Its efficacy has also been compared with the "gold standard" of diazepam in the treatment of AWS in cirrhotic patients[3]. We report a case of an alcohol-dependent patient, on chronic oral baclofen treatment that after a change in the route of administration, suddenly stopped his alcohol consumption and developed a delayed and subtle presentation of delirium tremens.

Case report

A 46 year-old male had a cervical spinal cord injury two years prior, and since then he was treated with oral baclofen 80 mg/day for spasticity with adequate adherence to the treatment. He is alcohol-dependent, drinking 6 to 8 beers per day, approximately 20 gr of alcohol per beer (Table III) and a cannabis user. He required an intrathecal baclofen (ITB) pump implant, as increases in the oral baclofen dose to treat his spasticity, were not tolerated.

Table II. DSM-5 criteria for withdrawal delirium (Delirium Tremens).

Criteria for delirium
A. Disturbance in attention and awareness.
B. The disturbance develops over a short period of time, represents and acute change from baseline attention and awareness and fluctuates.
C. Disturbance in cognition (memory, orientation, language, visuospatial ability or perception)
D. A and C not better explained by and established neurocognitive disorder, reduced level of arousal or coma.
E. Evidence from the history, physical examination or laboratory findings that this represents another medical condition, substance intoxication or withdrawal, toxin exposure or due to multiple etiologies.

DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) American Psychiatric Association.

The surgical procedure was uneventful and the baclofen intrathecal pump was set at 115 mcg/day and the oral dose reduced to 45 mg/day with a tapering schedule. A week later, the patient stopped drinking, as "he didn't felt the urge anymore."

Five days after his last alcohol intake, he was admitted for persistent somnolence and anorexia. He was afebrile, alert and oriented, the heart rate (HR) and blood pressure (BP) were within normal limits, the blood work (complete blood count, electrolytes and glucose) was normal and the urinalysis was negative for leukocytes.

The initial suspicion was probable baclofen overdose and a decision was made to stop the oral baclofen 45 mg/day and keep the intrathecal dose the same, to avoid baclofen withdrawal.

Other Medications

For generalized neuropathic pain: hydromorphone 2 mg q6h PRN, hydromorph Contin 12 mg q8h PO, Cymbalta 30 mg/day PO and Gabapentin 1600 mg/day.

On the second day of his admission, he was disoriented and experiencing hallucinations and the CIWA-ar score (Clinical Institute withdrawal assessment for alcohol score)(Table IV) was 11 and the protocol for acute alcohol withdrawal was initiated (Table V). Thiamine 100 mg TID PO started and hydromorph Contin was reduced from 12 mg PO q8h to q12h to prevent the additive effect on respiratory depression with the benzodiazepines.

Tests

CBC and extended electrolyte panel (Ca 2+, B12) were normal, except for a low K+ of 3.3 mmol/L, glucose of 6 mmol/L, urinalysis was negative for nitrites, but positive 3+ for ketones, liver function tests, total bilirubin, head CT was also normal.

Table IV. Management of acute alcohol withdrawal.

1. Replace electrolytes, glucose as needed
2. Administer IV fluids as needed
3. Benzodiazepines (see below)
4. Thiamine 300mg PO or 100mg IM

Diazepam	10-20 mg PO q 1-2 H for CIWA-Ar ≥ 10 or SHOT ≥ 2. If patient cannot take diazepam orally, give diazepam 10-20 mg IV q 1-2H. If history of withdrawal seizures, diazepam 20 mg PO q 1-2 H x 3, regardless of CIWA-Ar or SHOT score.
Lorazepam	2-4 mg PO, SL, IM, IV q 1-2 H for CIWA-Ar ≥ 10 or SHOT ≥ 2. If history of withdrawal seizures, lorazepam 4 mg PO q 1-2 H x3, regardless of CIWA-Ar or SHOT score.
Precaution	Avoid diazepam and use small doses (e.g., 0.5-2 mg) of lorazepam if: • Intoxication (estimated BAC > 30-40 mmol/l) • Liver dysfunction and failure • Low serum albumin • Elderly • On opioids or methadone • Pneumonia or COPD
Indications for admission	• Marked tremor, sweating worsening/not improving despite after 80 mg diazepam 16 mg lorazepam • Two or more seizures • QT interval > 500 msec, not resolving • Repeated vomiting, dehydration, electrolyte imbalance • Impending or early DTs: confusion, disorientation, delusions, agitation • Suspected Wernicke's encephalopathy: opthalmoplegia, ataxia, confusion • Serious concurrent medical or psychiatric illness (e.g., pneumonia)

Taken from the Protocol for acute alcohol withdrawal management from the Women's College Hospital, Toronto, Ontario, Version date: May 29, 2017.

Vital signs

The patient remains afebrile (36.9-37.1°C), BP range from 140/95 to 160/89 mmHg, HR100-112 bpm, SAT: 94-100%.

The delirium tremens diagnosis was established on the 7th day of alcohol abstinence. He presented with fluctuating attention, visual and auditory hallucinations. No seizures, malignant hypertension, hyperthermia, asterixis, stigmata of chronic cirrhosis were observed nor were increases in spasticity.

Two to three doses of diazepam 20 mg PO were used for 3 days to treat the anxiety, agitation, visual and auditory hallucinations with no noticeable effect.

The patient was discharged home on his eight day of hospitalization, after clearing the CIWA-ar protocol. Twelve days after his last drink and 5 days after he developed DT.

One month post-discharge, his ITB infusion was increased by 10% to 130 mcg/day for spasticity control as per protocol. Two years later the patient was still alcohol abstinent with a well functioning ITBP and at the same dose.

Discussion

The sudden alcohol suspension and sustained abstinence that was observed in this patient was not expected, this patient was not seeking treatment for alcohol dependence and the physicians involved in his care where neuromodulation specialists with no experience in the use of baclofen for alcohol abstinence.

Table V. CIWA-Ar Score for Alcohol Withdrawal

Alcohol Withdrawal Assessment Scoring Guidelines (CIWA - Ar)

Nausea/Vomiting - Rate on scale 0 - 7

0 - None
1 - Mild nausea with no vomiting
2
3
4 - Intermittent nausea
5
6
7 - Constant nausea and frequent dry heaves and vomiting

Tremors - have patient extend arms & spread fingers. Rate on scale 0 - 7.
0 - No tremor
1 - Not visible, but can be felt fingertip to fingertip
2
3
4 - Moderate, with patient's arms extended
5
6
7 - severe, even w/ arms not extended

Anxiety - Rate on scale 0 - 7
0 - no anxiety, patient at ease
1 - mildly anxious
2
3
4 - moderately anxious or guarded, so anxiety is inferred
5
6
7 - equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions.

Agitation - Rate on scale 0 - 7
0 - normal activity
1 - somewhat normal activity
2
3
4 - moderately fidgety and restless
5
6
7 - paces back and forth, or constantly thrashes about

Paroxysmal Sweats - Rate on Scale 0 - 7.
0 - no sweats
1- barely perceptible sweating, palms moist
2
3
4 - beads of sweat obvious on forehead
5
6
7 - drenching sweats

Orientation and clouding of sensorium - Ask, "What day is this? Where are you? Who am I?" Rate scale 0 - 4
0 - Oriented
1 – cannot do serial additions or is uncertain about date

2 - disoriented to date by no more than 2 calendar days

3 - disoriented to date by more than 2 calendar days
4 - Disoriented to place and / or person

Tactile disturbances - Ask, "Have you experienced any itching, pins & needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?"
0 - none
1 - very mild itching, pins & needles, burning, or numbness
2 - mild itching, pins & needles, burning, or numbness
3 - moderate itching, pins & needles, burning, or numbness
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Auditory Disturbances - Ask, "Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn't there?"
0 - not present
1 - Very mild harshness or ability to startle
2 - mild harshness or ability to startle
3 - moderate harshness or ability to startle
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Visual disturbances - Ask, "Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you or that you know isn't there?"
0 - not present
1 - very mild sensitivity
2 - mild sensitivity
3 - moderate sensitivity
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Headache - Ask, "Does your head feel different than usual? Does it feel like there is a band around your head?" Do not rate dizziness or lightheadedness.

0 - not present
1 - very mild
2 - mild
3 - moderate
4 - moderately severe
5 - severe
6 - very severe
7 - extremely severe

The CIWA-Ar is not copyrighted and may be used freely. The maximum score is 67. Patients scoring less than 10 do no usually need additional medication for withdrawal.

Which prompted a further revision of the pharmacokinetics of baclofen, as this patient was alcohol-dependent before and after his cervical injury and during the 2 years of treatment with oral baclofen (80 mg/day) for spasticity. We know that oral baclofen is not effective crossing the blood brain barrier, therefore when the route of administration changed to intrathecal, the patient stop his alcohol consumption spontaneously. A determination of the dose required at the site of action in the CNS is rather difficult, because the pharmacokinetic of baclofen in the CNS have marked inter-individual variations[6,7]. The transport mechanism and pharmacology that governs the intrathecal drug dispersion within the CSF and CNS are still poorly understood[8].

The cisternal CSF concentration of baclofen is considerable lower, 1/3 to 1/7 than the CSF of lumbar levels[7] and this doesn't accurately reflect the concentration at the site of action[6,7,9]. There are no correlations between either ITB dosages or catheter tip placement and CSF concentration of baclofen.

An intrathecal dose of baclofen is 100-1000 times smaller than the oral daily dose[10]. Therefore, exact calculations based in oral dose – CSF equivalence are very inaccurate, for example: 80 mg/day of oral baclofen could translate into 80-to 800 mcg intrathecally.

Adjustments in ITB for spasticity treatment are based on clinical response rather than expected CSF concentration, but initiation of a therapy has best practice suggestions:

– The starting daily dose should be twice the effective bolus dose found during the ITB screening test;
– Taper the oral baclofen after ITB therapy, no abrupt discontinuation;
– Drug labeling recommends daily dose increase of 10-30% increase once every 24 hours for spasticity of spinal origin, during in patient titration[11]. Our patients screen test dose was 50 mcg, improvement of the ashworth score pre and post injection, deemed him suitable for ITB and an increase of 15% within the first 24 hours of implant was done, the total dose was 115 mcg. The rationale for baclofen use in alcohol dependence is the possible role of mesolimbic dopamine neurons in the mediation of alcohol intake and reinforcement. The GABA B receptors are located in the ventral tegmental area, where the mesolimbic dopamine neurons originate, and baclofen might exert inhibitory action on the dopamine neurons which may suppress the alcohol stimulated dopamine release[1,3].

Baclofen has shown some efficacy in the reduction of the main components of alcohol cravings, alcohol intake, relieving AWS and maintenance of abstinence[3].

The oral dose that required to stop alcohol cravings has been described as 30 mg/d, the length of time varies from 27 days to 12 weeks[3]. Other RCTs have used higher doses for up to 6 months, mean of 180 mg/day with more side effects and less results in maintenance of abstinence, but tendency towards a reduction in alcohol consumption and a significantly decreased craving[12,13].

When investigating the disparity in the dosing of baclofen for alcohol cessation, it has to be remembered that the propose site of action is the ventral tegmental area, the pharmacokinetics of baclofen in the CSF have inter-individual variation, and baclofen itself is moderately hydrophilic, which makes the response to an oral dose difficult to predict, as it happens with spasticity treatment, where the dose is determine by the clinical response and patient tolerance. However, with an intrathecal administration, a higher CSF concentration would be achieved; for our patient the issue of being a chronic oral baclofen user was not as compelling as the fact that the CSF concentration of baclofen at the site of action was not enough to stop the alcohol cravings, until the route of administration changed, and even then it took 7 days with a continuous infusion.

Open label trials reported that baclofen rapidly reduced the symptoms of severe AWS[1]. A possible hypothesis is that baclofen regulates the release of excitatory amino acids presynaptically (e.g. glutamate) attenuating the AWS[12]. Another hypothesis is that baclofen can block the expression and sensitization of anxiety-like behavior in animals, because the receptors that are involved are GABA A and B[1,14,15].

Our patient's original complaint was somnolence and anorexia; the presentation of the AWS, 5 days after the last drink, is not typical. It is possible that the baclofen may have delayed and lessened the intensity of the AWS, but did not stop its progression to DT. The presentation was not as severe as expected on a patient with a spinal cord injury; no autonomic hyperreflexia, seizures or increased in spasticity were reported. Patients with spinal cord injuries present with worsen spastic tone with pathology as common as urinary track infections.

The Cochrane Review reported that baclofen seems to be well tolerated and has comparable efficacy to diazepam. It potentially reduces the need for benzodiazepines in the treatment of AWS[1].

In our case, the acute withdrawal protocol was followed and diazepam was given, but no significant improvement was observed from it, when evaluating the CIWA-ar score, related to agitation, visual or auditory disturbances.

Conclusions

We should be mindful of the fact that alcohol-dependent patients can abruptly stop their alcohol intake, when treated with intrathecal baclofen, putting them at risk of AWS and DT.

Baclofen in this case seems to have lessened and maybe delayed the presentation of AWS and DT. It could reduce the requirements of diazepam, but there is not enough evidence to suggest changes in the acute withdrawal protocol.

In the presence of AWS in a baclofen user, no changes on the baclofen dose should be made, as it can worsen the original condition or trigger baclofen withdrawal.

Consent

This case report does not have any patient identifying information. Our Ethics Board (Hamilton Integrated Research Ethics Board) exempts it from REB approval as per TCPS (Chapter 2, Article 2.1/2.2) guidelines.

Conflict of Interests

The authors declare they have no conflict or financial interests.

References

1) Liu J, Wang LN. Baclofen for alcohol withdrawal. Cochrane Database for Syst Rev 2015; 4: 1-9.
2) Mirijello A, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, Caputo F, Leggio L, Gasbarrini A, Addolorato G. Identification and management of alcohol withdrawal syndrome. Drugs 2015; 75: 353-365.
3) Addolorato G, Leggio L, Abenavoli L, Agabio R, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. Am J Med 2006; 119: 276.e13-18.
4) Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomized, double blind controlled study. Lancet 2007; 370: 1915-1922.
5) Watve SV, Sivan M, Raza WA, Jamil FF. Management of acute overdose or withdrawal state in intrathecal baclofen therapy. Spinal Cord 2012; 50: 107-111.
6) Albright AL, Thompson K, Signe C, Minnigh MB. Cerebrospinal fluid baclofen concentrations in patients undergoing continuous intrathecal baclofen therapy. Dev Med Child Neurol 2007; 49: 423-425.
7) Saval A, Chiodo AE. Effects of intrathecal baclofen concentration of spasticity control: case series. J Spinal Cord Med 2008; 31: 394-398.
8) Hettiarachchi HD, Hsu Y, Harris TJ Jr., Linninger AA. The effect of pulsatile flow on intrathecal drug delivery in the spinal canal. Ann Biomed Eng 2011; 39: 2592-2602.
9) Brennan PM, Whittle IR. Intrathecal baclofen therapy for neurological disorders: a sound knowledge base, but many challenges remain. Br J Neurosurg 2008; 22: 508-519.
10) Ertzgaard P, Campo C, Calabrese A. Efficacy and safety of oral baclofen in the management of spasticity: a rationale for intrathecal baclofen. J Rehabil Med 2017; 49: 193-203.
11) Boster AL, Adair RL, Gooch JL, Nelson ME, Toomer A, Urquidez J, Saulino M. Best practices for intrathecal baclofen therapy: dosing and long-term management. Neuromodulation 2016; 19: 623-631.
12) Beraha EM, Salemink E, Goudriaan AE, Bakker A, de Jong D, Smits N, Zwart JW, Geest DV, Bodewits P, Schiphof T, Defourny H, Van Tricht M, Van der Brink W, Wiers RW. Efficaty and safety on hight dose baclofen for the treatment of alcohol dependence: a multicenter randomized double blind control trial. Eur Neuropsychopharmacol 2016; 26: 1950-1959.
13) Reynaud M, Aubin HJ, Trinquet F, Zakine B, Dano C, Dematteis M, Trojak B, Paille F, Detilleux M. A randomized, placebo-controlled study of high-dose baclofen in alcohol-dependent patients-the ALPADIR study. Alcohol 2017; 52: 439-446.
14) Colombo G, Agabio R, Carai MAM, Lobina C, Pani M, Reali R, Addolorato G, Gessa GL. Ability of baclofen in reducing alcohol intake and withdrawal severity: I-preclinical evidence. Alcohol Clin Exp Res 2000; 24: 58-66.
15) Knapp DJ, Overstreet DH, Breese GR. Baclofen blocks expression and sensitization of anxiety-like behavior in an animal model of repeated stress and ethanol withdrawal. Alcohol Clin Exp Res 2007; 31: 582-595..