Altered Mental Status at High Altitude

Sydney Ryan, MD,[a,b] Nanette Dudley, MD,[a,b] Michael Green, DO,[b] Charles Pruitt, MD,[a,b] Geoffrey Jackman, MD[c]

Intrathecal baclofen pumps are commonly used in pediatric patients with spastic cerebral palsy. Baclofen binds to γ-aminobutyric acid receptors to inhibit both monosynaptic and polysynaptic reflexes at the spinal cord level. The blockade stops the release of excitatory transmitters and thereby decreases muscle contraction. It is commonly used for lower limb spasticity and has been shown to improve postural ability and functional status. The US Food and Drug Administration has approved baclofen for the treatment of spasticity of cerebral or spinal origin in adult and pediatric patients 4 years or older. Various complications of baclofen pumps are described in the literature. Immediately after surgery, problems from infection can arise and range from superficial skin infections to meningitis and bacteremia. Another early complication includes cerebrospinal fluid leak that can be observed by notable swelling beneath the lumbar incision. Additional problems that arise later are usually from the mechanics of the pump and catheter. Pump-related complications include failure, migration, and flipping. Catheter-related complications include disconnection, occlusion, fracture, or kink. Most of these complications typically lead to baclofen withdrawal, although there are a few case reports of overdose due to mechanical causes. Here we describe 2 cases of individuals experiencing complications of excessive baclofen exposure after significant changes in the atmospheric pressure due to travel involving ambient altitude change. These cases reflect the need to discuss this potential complication with families and patients with baclofen pumps before travel to high elevations.

Intrathecal baclofen (ITB) pumps are commonly used in pediatric patients with spastic cerebral palsy (CP). Baclofen, sold under the trade names Lioresal and others, binds to γ-aminobutyric acid (GABA) receptors to inhibit both monosynaptic and polysynaptic reflexes at the spinal cord level. The blockade stops the release of excitatory transmitters and thereby decreases muscle contraction. It is commonly used for lower limb spasticity and has been shown to improve postural ability and functional status.[1] The US Food and Drug Administration has approved baclofen for the treatment of spasticity of cerebral or spinal origin in adult and pediatric patients 4 years or older.[2] There are off-label uses including children younger than 4 years who have progressive myelopathies or autonomic dysregulation.[2] Various complications of baclofen pumps are described in the literature. Immediately after surgery, problems from infection can arise and range from superficial skin infections to meningitis and bacteremia.[2] Another early complication includes cerebrospinal fluid leak that can be observed by notable swelling beneath the lumbar incision.[3] Additional problems that arise later are usually from the mechanics of the pump and catheter. Pump-related complications include failure, migration, and flipping. Catheter-related complications include disconnection, occlusion, fracture, or kink.[2] Most of these complications

[a]Division of Pediatric Emergency Medicine, [b]Department of Pediatrics, Primary Children's Hospital, University of Utah, Salt Lake City, Utah; and [c]Department of Pediatric Emergency Medicine, Rady Children's Hospital, San Diego, California

Dr Jackman made the decision to write the case reports initially, drafted the manuscript, and contributed substantially to the essential edits and revisions of the manuscript; Dr Ryan made the decision to write the case reports initially and drafted the manuscript; Dr Green drafted the manuscript; Drs Dudley and Pruitt contributed substantially to the essential edits and revisions of the manuscript; and all authors approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2017-3973

Accepted for publication Apr 20, 2018

Address correspondence to Sydney Ryan, MD, Division of Emergency Medicine, Department of Pediatrics, Primary Children's Hospital, 295 Chipeta Way, Salt Lake City, UT 84108. E-mail: sydney.ryan@hsc.utah.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Ryan S, Dudley N, Green M, et al. Altered Mental Status at High Altitude. *Pediatrics.* 2018;142(2):e20173973

typically lead to baclofen withdrawal, although there are a few case reports of overdose due to mechanical causes.[4–6] Here we describe 2 cases of individuals experiencing complications of excessive baclofen exposure after significant changes in the atmospheric pressure due to travel involving ambient altitude change. These cases reflect the need to discuss this potential complication with families and patients with baclofen pumps before travel to high elevations.

The prevalence of moderate to severe CP is ~1.5 to 3 per 1000 live births, with half of those having hemiplegia.[3,7] ITB pumps have been shown to improve spasticity, dystonia, and ambulation in patients with ambulant CP.[1,3]

ITB pump systems are devices that deliver a programmed dose of baclofen directly to the intrathecal space, allowing the body to better respond to baclofen when compared with the oral route of administration. The pump stores and releases a programmed amount hourly and allows for intermittent bolus administration of the medication throughout the day and/or night. With this type of administration, the individual should be able to obtain more consistent symptom relief (ie, decreased spasticity). Because the baclofen is delivered directly to the spinal cord, the individual may only need a relatively small amount of medicine for effective treatment, reducing side effects. Adverse effects of ITB are less common than oral baclofen; however, the effects of overdose or withdrawal can be more severe.

Here we review 2 cases of adolescent patients with overinfusion of baclofen via ITB pump after travel to high altitude resulting in altered mental status, hypotonia, hypoventilation, and vomiting.

PRESENTATION

Case 1

A 15 year old with a history of mild right-sided CP due to perinatal ischemic injury presented via air transport to our tertiary care pediatric emergency department (ED) with altered mental status. For the past 2 days, he was on a backpacking trip in the nearby mountains, above an elevation of 9000 ft. Approximately 4 to 5 days before presentation, he traveled from sea level to an area at 4500 ft altitude to acclimate. During the second day of his visit, before beginning his backpacking and camping trip, he took a day hike to >9000 ft. The day before his presentation at our facility, he hiked 6 miles at 9500 ft and was in his usual state of health that night before going to sleep in the tent. On the morning of presentation, his family member checked on him at 10 AM for breakfast, but he was somnolent and mumbling. His family assumed he was tired, so they allowed him to sleep for another 2 hours. At approximately noon they tried to wake him, but he was difficult to arouse and responded to a sternal rub with only limited movement of his extremities. His family initiated rescue via a flight crew, and he was given 1 L normal saline and placed on a nonrebreather mask for shallow breathing. There was no reported hypoxemia, new exposures, recent illness, or trauma. His only medication was baclofen through a pump, which had been increased by 10%, up to 599 μg per day. It was increased the week before in anticipation of the backpacking trip to allow for increased mobility. In the ED, he was somnolent, hypothermic to 34.5°C, hypotonic, and with mydriasis to 5 to 6 mm. He had a Glasgow Coma Scale (GCS) of 9 (eye response 2, verbal response 2, and motor response 5). His respiratory effort was shallow, his heart rate was 50 with some variability, and his blood pressure was 103/52.

Our differential diagnosis included high-altitude cerebral edema, trauma, ingestion, electrolyte abnormality, infection, or baclofen overdose. He was placed on nasal cannula oxygen while a workup was initiated. His laboratory results revealed a normal creatinine kinase, negative urine and serum drug screen, normal complete blood count, slight respiratory acidosis with a pH of 7.29 and P_{CO_2} of 48, normal electrolytes, and normal glucose. He was given maintenance intravenous fluids of normal saline at a rate of 100 mL/hour. A head computed tomography scan revealed chronic changes of slight left-sided asymmetry adjacent to parenchymal brain loss without hydrocephalus, and a small amount of air was noted within the suprasellar cistern, which likely reflected his recent access to the baclofen pump when they increased the dose. He was admitted to the PICU after a baclofen pump interrogation by the physical medicine and rehabilitation consultant. There were no signs of baclofen pump malfunction. However, his baclofen dose was reduced by 10%, 540 μg/day, which was the dose he was on before leaving his home at sea level. On admission to the ICU, his mental status improved with a GCS of 14. With improvement in his mental status, he no longer required oxygen support. He was transferred to the medical floor team several hours later with continued improvement and was discharged the next day.

Case 2

A 17-year-old with spastic CP presented to our tertiary care pediatric ED with altered mental status and vomiting via ambulance. She was in her usual state of health until that morning when she started having multiple episodes of nonbloody, nonbilious emesis. She traveled from sea level to 7000 ft 9 days before presentation. She had been participating in outdoor

activities including hiking above an elevation of 8000 ft and horseback riding. She had progressive somnolence throughout the day and was found in her bedroom unresponsive. She did not have recent illness, medication changes, trauma, or new exposures. In the ambulance, her vital signs remained stable and she did not require oxygen support. Her last change in baclofen dose occurred 4 years ago. Her baseline rate was 419 μg/day and she took no other medications.

On arrival to the ED, she was hypoventilating with a rate of 10, hypothermic to 35.4°C, hypotonic, and aroused to voice. Her GCS was 14 on arrival, with eye opening to command, clear and appropriate speech, and movement spontaneously of all extremities. Her laboratory results revealed normal electrolytes, normal glucose, and normal complete blood count. Physical medicine and rehabilitation professionals were consulted, and the decision was made to admit her to the 24-hour observation unit without changes to her baclofen pump. Over the course of 6 hours, she returned completely to baseline, and the family drove home the next day.

DISCUSSION

To the best of our knowledge, these are the first reported cases of baclofen overinfusion in patients with CP that is attributable to exposure to high elevation. Both patients experienced symptoms of excessive baclofen after traveling to high altitude. The etiology may be multifactorial. There may be an increased sensitivity of the brain to baclofen, related to the effect of altitude on GABA, with reports of increased GABA in mild hypoxia.[8,9] Additionally, high altitude and changes in the ambient atmospheric pressure may alter the infusion rate in baclofen pumps. In situations of an increased atmospheric pressure, it is thought that the infusion rate slows.[10] There is 1 case report of a scuba diver who went to a depth of 30 m and had the pump shield collapse, causing damage to the drug reservoir. The authors of this case report also describe a decrease of ~3% in the baclofen flow rate at depths of 49 ft and inability of the pump to release baclofen at depths of 66 ft.[11] The authors of another case report describe increased intrathecal pressure during hyperbaric oxygen therapy producing retrograde flow of cerebrospinal fluid into the baclofen pump and dilution of the baclofen in the reservoir of the pump.[12] On the other hand, user manuals for the baclofen pumps contain lists of potential problems at elevations >6000 ft above sea level that may result in an increased flow rate by up to 35%.[13–15] The manuals mention that changes in atmospheric pressure can potentially alter the infusion rate, although there is no specific reference to studies or case reports.[14,15] The authors of 1 report describe a patient who was able to fly for 18 hours in a 24-hour period without adverse effects, which may be because of the pressurized cabin. Airplanes are commonly pressurized to ~8000 ft, with newer airplanes pressurized to 6000 ft.[13,16] A lower cabin pressure in newer planes may allow patients with baclofen pumps a greater ability to travel. In a literature search, we could not find specific trials in which baclofen pump infusion rates at various elevations were compared.

Baclofen pumps are becoming more common in the pediatric population with use in CP for spasticity. Since the invention of the pumps in 1984, their use has continued to increase in patients with CP, allowing patients improved mobility and activity. Along with the increase in mobility, it is easier to travel to high altitude areas of the world.

Patients experiencing an ITB overdose typically present with decreased spasticity, dizziness, weakness, fatigue, lethargy, somnolence, nausea, and vomiting. Those with severe overdoses may present with abnormal vital signs including bradycardia and hypotension, as well as respiratory failure, hypothermia, seizures, coma, and even death. There is no specific treatment, but they do require supportive care until they are able to return to lower elevation or have their baclofen pumps changed to a lower dose. Our pediatric ED is located at 4300 ft in elevation, which may have played a factor in the patients' improvement.

Parents should be counseled on signs and symptoms of baclofen overdose and withdrawal so they can anticipate the need for medical management and baclofen pump assessment if necessary, particularly when traveling. Pediatricians managing these patients in their practice regularly should be aware of this potential problem and can counsel families who might be traveling to a high altitude. As an additional anticipatory measure, families can carry an action plan informing health care providers of potential problems.

ABBREVIATIONS

CP: cerebral palsy
ED: emergency department
GABA: γ-aminobutyric acid
GCS: Glasgow Coma Scale
ITB: intrathecal baclofen

REFERENCES

1. Brochard S, Remy-Neris O, Filipetti P, Bussel B. Intrathecal baclofen infusion for ambulant children with cerebral palsy. *Pediatr Neurol*. 2009;40(4):265–270
2. Woolf SM, Baum CR. Baclofen pumps: uses and complications. *Pediatr Emerg Care*. 2017;33(4):271–275

3. Motto F, Antonello CE. Analysis of complications in 430 consecutive pediatric patients treated with intrathecal baclofen therapy: 14-year experience [published correction appears in *J Neurosurg Pediatr*. 2014;13(5):588]. *J Neurosurg Pediatr*. 2014;13(3):301–306
4. Davanzo JR, Rizk E. Baclofen overdose from possible intrinsic malfunction of SynchroMed II pump. *J Neurosurgery Pediatr*. 2015;16(2):232–234
5. Lew SM, Psaty EL, Abbott R. An unusual cause of overdose after baclofen pump implantation: case report. *Neurosurgery*. 2005;56(3):E624; disc ussion E624
6. Sgouros S, Charalambides C, Matsota P, Tsangaris I, Kostopanagiotou G. Malfunction of SynchroMed II baclofen pump delivers a near-lethal baclofen overdose. *Pediatr Neurosurg*. 2010;46(1):62–65
7. Kuban KC, Leviton A. Cerebral palsy. *N Engl J Med*. 1994;330(3):188–195
8. Wood JD, Watson WJ, Ducker AJ. The effect of hypoxia on brain gamma-aminobutyric acid levels. *J Neurochem*. 1968;15(7):603–608
9. Kumar GK. Hypoxia. 3. Hypoxia and neurotransmitter synthesis. *Am J Physiol Cell Physiol*. 2011;300(4):C743–C751
10. Hsieh JC, Penn RD. Intrathecal baclofen in the treatment of adult spasticity. *Neurosurg Focus*. 2006;21(2):e5
11. Draulans N, Roels E, Kiekens C, Nuttin B, Peers K. Permanent mechanical deformation of an intrathecal baclofen pump secondary to scuba diving: a case report. *Spinal Cord*. 2013;51(11):868–869
12. Akman MN, Loubser PG, Fife CE, Donovan WH. Hyperbaric oxygen therapy: implications for spinal cord injury patients with intrathecal baclofen infusion pumps. Case report. *Paraplegia*. 1994;32(4):281–284
13. Ethans KD, Schryvers OI, Nance PW, Casey AR. Intrathecal drug therapy using the Codman Model 3000 Constant Flow Implantable Infusion Pumps: experience with 17 cases. *Spinal Cord*. 2005;43(4):214–218
14. Codman and Shurtleff, Inc. *Codman 3000 Series Constant Flow Implantable Pump With Bolus Safety Valve: Instructions for Use, TLB2862M*. Raynham, MA: Codman & Shurtleff, Inc; 2018
15. Medtronic. *SynchroMed II Infusion System Patient Manual*. Minneapolis, MN: Medtronic, Inc; 2003
16. Boeing. Boeing 787 dreamliner by design. Available at: www.boeing.com/commercial/787/by-design/#/lower-cabin-altitude. Accessed May 23, 2018

Altered Mental Status at High Altitude

Sydney Ryan, Nanette Dudley, Michael Green, Charles Pruitt and Geoffrey Jackman

Pediatrics 2018;142;
DOI: 10.1542/peds.2017-3973 originally published online July 5, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Altered Mental Status at High Altitude

Sydney Ryan, Nanette Dudley, Michael Green, Charles Pruitt and Geoffrey Jackman

Pediatrics 2018;142;
DOI: 10.1542/peds.2017-3973 originally published online July 5, 2018;