Journal of Pediatric Rehabilitation Medicine: An Interdisciplinary Approach Throughout the Lifespan 16 (2023) 19–24
DOI:10.3233/PRM-230005
IOS Press

Invited Position Paper

Benefit of enteral baclofen in the management of spasticity in cerebral palsy

Rajashree Srinivasan*
Department of Physical Medicine and Rehabilitation, University of Texas Southwestern, Dallas, TX, USA

Received 21 February 2023
Accepted 1 March 2023

Keywords: Spasticity, cerebral palsy, baclofen

Abbreviations

CP	Cerebral Palsy
FDA	Federal Drug and Administration
GERD	Gastroesophageal reflux disease

Spasticity is a movement disorder that is commonly associated with cerebral palsy (CP) and can be managed by various treatment options. It can be increased or worsened by any noxious stimulus like infection, constipation, gastroesophageal reflux disease (GERD), tight clothes, and growth spurts.

Indications to treat spasticity include decreasing muscle spasms, improving posture, improving mobility, decreasing pain, improving use and tolerability of adequate braces, decreasing risk of pressure ulcers, preventing or decreasing the rate of contracture formation, and improving quality of life [1].

There are several pharmacologic treatment options used to treat spasticity which include chemodenervation with botulinum toxin injections; chemoneurolysis with phenol or alcohol; oral medications like diazepam, baclofen, tizanidine, and dantrolene; and intrathecal baclofen (ITB) [1]. Baclofen has been used as a mainstay for treatment of spasticity and was approved by the U.S. Food and Drug Administration (FDA) for the same recently on December 7, 2021, in the form of granules [2]. Though baclofen is not specifically approved by the U.S. FDA for CP-associated spasticity, it has been a first line oral treatment for children with spastic CP since the 1960 s [3]. Baclofen can be given orally, intravenously, and intrathecally. Side effects are described in Table 2.

1. Baclofen

Although oral baclofen is not as effective for cerebral spasticity as it is for spinal spasticity, it is nonetheless one of the most commonly used medications to treat cerebral spasticity in children [4]. Of its side effects, drowsiness is by far the most common [5]. Baclofen can also promote epileptogenesis by blocking inhibitory interneurons, shifting the balance in neuronal networks toward excitation [6]. Tolerance has been reported after prolonged oral administration but is infrequently a clinically significant problem.

The effect of baclofen is due to a balance between inhibition of neurotransmitter release, mediated by presynaptic $GABA_B$ receptors, and inhibition of neuronal excitability, mediated by postsynaptic $GABA_A$ receptors [7]. Baclofen decreases muscle spasticity, which can help ease caregiving, improve range of

*Corresponding author: Rajashree Srinivasan, MBBS, Department of Physical Medicine and Rehabilitation, 2222 Medical District Drive, Dallas, TX, 75235, USA. Tel.: +1 469 401 5639; E-mail: Rajashree.Srinivasan@Childrens.com.

Table 1
Benefits of baclofen

Decreased spasticity
Improved range of motion
Improved pain and sleep
Decreased contracture formation
Better fit of bracing

motion, and optimize positioning. The highest density of $GABA_B$ binding sites is found in thalamic nuclei, the molecular layer of the cerebellum, the cerebral cortex, the interpeduncular nucleus, and the dorsal horn of the spinal cord [8]. $GABA_B$ receptor agonists have several pharmacological effects in the central nervous system (CNS): central muscle relaxation, suppression of cocaine and narcotic drug self-administration, antinociception, cognitive impairment, inhibition of hormone release, synaptic plasticity, development of some neuronal pathways, as well as improvement of conduction in demyelinated axons [8].

While baclofen is rapidly absorbed after enteral administration, it has low lipid solubility and 30% is bound to protein, thereby making the crossover via the blood-brain barrier very poor [4]. At high oral doses (in adults, more than 120 mg/day), CNS drug levels are low [9]. Serum levels peak two to three hours after oral administration; the half-life is three to four hours, requiring repeated daily doses. Approximately 70% to 85% of the drug is excreted in the urine within 24 hours, hence the need to be dosed daily [1, 4]. It also has moderate systemic side effects listed in Table 2. Variability in response to oral baclofen can be multifactorial, including genetic causes [10, 11].

2. Clinical presentation of spasticity

Spasticity, an increase in tone, can present with delayed motor milestones, difficulty with and/or decreased range of motion, poor ability to maintain optimal hygiene, difficulty with performing activities of daily living, and increased exertion with mobility, transfers, proper positioning, and optimal fitting of braces. It is important to differentiate between severe spasticity or dystonia and GERD presenting as increased tone as the management differs. Spasticity increases metabolic rates, contributing to poor weight gain. It can also present as a cause of pain, negatively impact sleep, and greatly affect a person's quality of life.

3. Indications for use in children and adults and side effects

The decision to treat spasticity is always based on in-depth discussion with the provider(s), with the patient (if able to communicate), and/or with the family/caregiver(s). The focus of treatment is to improve function, help improve pain, allow for a better fit with bracing, enable better quality sleep, improve positioning, and/or improve caregiver ease (See Table 1).

The decision to use certain options to treat spasticity is based on the provider's personal preferences, an understanding of the literature, the clinician's training, and the history of what has worked well for the patient in the past and what has not. After obtaining clinical history, physical examination is performed, and spasticity is identified using either the Modified Ashworth Scale (MAS) or Modified Tardieu Scale (MTS). Treatment is determined based on functional impact, positioning, caregiving, and hygiene. The choice of options utilized is dependent upon the presentation of spasticity. Usually, if the presentation is focal, recommendations include local chemodenervation followed by (or in combination with) therapies and other localized treatments (e.g., serial

Table 2
Side effects of baclofen

Sedation, drowsiness
Ataxia
Respiratory and cardiovascular depression
Abrupt withdrawal of baclofen causes rebound spasticity, motor hyperactivity, headache, insomnia, hallucinations, seizures, and fever.
Overdose is rare (seen in intrathecal pump malfunction or human error); effects include weakness, areflexia, hypotonia, respiratory depression, seizures and rarely death.
Infrequently, neuropsychiatric impairment, hypotension, peripheral edema, dyspnea, hypoventilation, pneumonia, seizures, insomnia, pain, sleep alteration, depression, agitation, constipation, diarrhea, urinary frequency, incontinence, acute urinary retention, impotence, tremor, weakness, amblyopia urticaria and pruritis are seen [5].

Please see references 1, 5, 12, 13, and 14 for more information.

casting or splinting). For generalized hypertonicity, enteral medications such as baclofen are preferable as botulinum toxin injections and/or casting or splinting do not help with generalized hypertonia. Other enteral medications that are used to manage spasticity include diazepam, tizanidine, dantrolene, and gabapentin. Providers can control severe diffuse hypertonia with a combination of enteral medications to avoid adverse events but to maximize the efficacy. Sometimes, enteral baclofen is also used to manage focal spasticity or dystonia. Interventions to address spasticity have a better response when followed up with therapy via outpatient, home health, or home exercise programs.

For generalized spasticity, I use enteral medications like baclofen. Enteral baclofen has been widely used in the management of spasticity in CP in pediatric and adult patients. Tolerance to baclofen use can be seen in about 3–20% of cases [12]. Increasing the baclofen dose can cause the development of receptor saturation and severe downregulation, leading to unresponsiveness to baclofen. This can present as increasing spasticity in a previously well-controlled patient. Tolerance can be treated with a "baclofen holiday" of 3–37 days, during which another antispasticity medication can be used to manage the tone [12]. Baclofen can be restarted as a lower dose than was given before the drug holiday, necessitating a dose increase later due to receptor desensitization (start at a 30–80% lower dose than before the drug holiday with ITB) [12]. Baclofen must be weaned gradually, as stopping it abruptly can cause seizures which can be life-threatening. Despite concern about side effects such as somnolence, fatigue, weakness, and constipation, I usually recommend oral baclofen for children with diffuse spasticity or mixed tone with spasticity and dystonia, while recommending chemoneurolysis for children with focal spasticity to avoid systemic side effects such as constipation and fatigue. I usually start the medication at bedtime to avoid fatigue and help improve sleep, and I gradually increase and/or add doses during the day if spasticity gets better and requires a higher dose. Spasticity can cause pain/cramping in muscles. In the words of one of my patients, "It's like a charley horse that never goes away." Using the medicine at nighttime helps with sleep in addition to addressing spasticity, as that is when it is most often experienced. As the body adjusts to the dose at night, there may be a need to add doses during daytime. As half-life of baclofen is between 2–6 hours, its beneficial effect does not last through the day. Hence, doses are added during day with an interval of six to eight hours. I usually ask the family when the tone is most increased and will try to adjust dosing appropriately. Oral baclofen also is considered for patients with hepatic impairment since it is mainly excreted through the kidneys. As baclofen is renally excreted, baseline kidney function studies are obtained and monitored prior to starting this medication. For patients with renal impairment, renal function is monitored and medication is changed if there is worsening renal condition. I obtain both liver and kidney function tests prior to starting baclofen and monitor renal function every six months or, if stable, every year.

4. Why is baclofen my favorite enteral option?

Baclofen is a relatively safe drug when used judiciously. It has been used for a long time to manage spasticity. The side effect profile is manageable and easy to troubleshoot. It is affordable, as it is often approved by payers. It is not an invasive treatment option and is a good medication to use with other modalities. Usual side effects that I have seen include drowsiness, which can be managed by using the medication at times of naps/sleep. Constipation is managed with laxatives. Most other enteral medications for spasticity management have the same side effect profile with drowsiness. If a patient cannot tolerate oral baclofen or other enteral medications due to drowsiness, I may consider medication that does not cross blood-brain barriers such as dantrolene or local approaches with chemodenervation or chemoneurolysis. If patients respond well to enteral baclofen for diffuse hypertonia but side effects prevent them from continuing it, I consider ITB.

5. What are the positive things that I expect from baclofen when I prescribe it to a patient?

Enteral baclofen has several positives for clinicians to consider: 1) It is a less invasive approach. Some parents are reluctant to accept invasive approaches such as chemodenervation on chemoneurolysis. 2) Its effect is not selective but systemic, which is good for diffuse hypertonia. 3) It is useful as an adjunctive if chemodenervation and/or chemoneurolysis approaches are not sufficient to cover diffuse spasticity or dystonia. 4) It is good for mixed tone with spasticity and dystonia since baclofen is effective for

both. 5) It has an additional effect on external sphincters for spastic bladders and oromandibular dystonia. 6) Patients can be younger than two years old whereas botulinum toxins have not been approved for this age group. 7) It is associated with less hepatotoxicity.

6. Anecdotal use of enteral baclofen and its results

6.1. Case 1

A three-year-old female with spastic tetraplegic CP, Gross Motor Function Classification System (GMFCS) level V, Manual Ability Classification System (MACS) V, Communication Function Classification System (CFCS) V, and Eating and Drinking Ability Classification System (EDACS) V, scoliosis, and holoprosencephaly presented with spasticity. Per parent report, it was extremely difficult to stretch her extremities, position her in bed properly, and perform hygiene tasks (changing diapers, etc.) due to severe spasticity. She also had significant constipation, which caused worsening spasticity. After discussion with her parents and explaining the risks and benefits of anti-spasticity medications, she was started on a low dose of baclofen at 2.5 mg/day. Her constipation was also addressed by establishing a bowel program using polyethylene glycol and sennosides as needed. She initially responded to the baclofen but gradually started needing additional doses, which could be attributed to her growth. She was noted to have improved tone in her hip adductors, making it easier to address her diaper change, and improved positioning. Her parents also reported improved sleep and comfort with positioning in chairs and in bed. As she grew, she was also noted to have increased tone in her quadriceps. Using chemodenervation with botulinum toxin injections to her hip adductors and quadriceps improved her spasticity greatly. We attempted to wean enteral baclofen. However, this resulted in increased discomfort, increased tone, sleep disturbance, and crying. Once baclofen was restarted, improved positioning and possible pain relief was noted. She is currently 16 years old and has been doing well on the combination of 15 mg baclofen via G-tube 4x/day and chemodenervation every four months to bilateral quadriceps and hip adductors. Her parents report that they can tell when it is time for the next round of injections because they begin to note an increase in tone, particularly in the hip adductors. She has continued on baclofen and has not had any side effects from the medication. Parents have noted improvement in tone when she receives injections; however, after the injections wear off, they note worsening of tone when the patients misses a dose of baclofen.

6.2. Case 2

A four-month-old male born at term with complications of hypoxic ischemic encephalopathy and a maternal history of amniotic fluid embolism causing a cerebrovascular accident in the mother was seen in consultation on an inpatient unit for spasticity management. The child suffered respiratory insufficiency, dysphagia status post G-tube placement, tracheostomy and ventilator dependence, and developmental delay. He was significantly delayed, did not make any eye contact, and did not focus his eyes nor track. He was noted to have difficulty tolerating range of motion activities due to increased muscle tone evidenced by increased heart rate and grimacing with stretching. The patient was on diazepam on admission to the rehabilitation unit. He was continued on diazepam, and later baclofen was added to help treat his spasticity since botulinum toxin is not indicated for a four-month-old infant. He had regular blood work as he was seen in the ventilator clinic and noted to have stable kidney function tests. He responded to this treatment well, with better ability to have his joints ranged, improved positioning, and decreased tone. During follow-ups in the outpatient clinic, he was noted to have increased tone in bilateral elbow flexors and lower extremities for which he received weight-appropriate chemodenervation and responded well. When an increase in baclofen dose was recommended to manage increased spasticity, his mother was reluctant since she felt that the baclofen was making him sleepy. As a result, he is currently on a low dose of baclofen with additional diazepam.

The patient is currently 12 years old and functions at the following levels: GMFCS V, MACS V, CFCS V, and EDACS V. During the COVID pandemic, his spasticity was more frequently controlled by oral baclofen and diazepam with decreased chemodenervation treatments because of restrictions of hospital visits. He has had periodic blood work to check kidney and liver functions, which have been within normal limits. His family has been reluctant to add more interventions to his care. They feel he is comfortable on the current regimen.

6.3. Case 3

A two-year-old male with a history of abusive head injury resulting in right hemiparesis, spasticity, and gait abnormality had been admitted to the inpatient floor for rehabilitation. He was unable to tolerate any stretching and strengthening or functional activities on the right side of the body. He was also unable to use his right upper extremity to reach for objects, complete bimanual activities, or ambulate. He was started on a low dose of enteral baclofen of 2.5 mg at bedtime, which resulted in decreased spasticity and improved pain, improved tolerance to therapy, and increased time wearing his braces. He is currently 11 years old and is doing well overall. He is now able to ambulate independently, run, and complete activities of daily livings independently. He is in school and is able to participate in school-based activities, play with his siblings, and tolerate his ankle-foot orthosis on his right lower extremity. He has also received chemodenervation to upper and lower extremities and is currently doing well with baclofen and chemodenervation treatments. Enteral baclofen has kept his tone low overall, and chemodenervation has helped with focal increase in tone.

6.4. Case 4

A four-year-old male with CP, GMFCS II, MACS I, CFCS II, and EDACS I, was seen in the pediatric rehabilitation medicine clinic for spasticity management. He had a history of prematurity, with grade 2 intraventricular hemorrhage on the right more than left. He was noted to have increased tone in his right lower extremity, with increased tone in the right gastrocnemius (MAS II). He had difficulty with ambulation due to lack of getting his foot flat on the right side, impacting his balance. Upon discussion of options for management of spasticity, his parents did not feel comfortable pursuing chemodenervation with botulinum toxin, as they felt nervous about using "wrinkle treatment" to treat spasticity. They felt more comfortable with trying enteral baclofen at bedtime. His parents reported that they noted he was able to get his foot flat and maintain better balance while ambulating. They also reported that his gait improved while climbing stairs. They were pleased that he did not have any side effects from baclofen.

7. Conclusion

In conclusion, enteral baclofen is a safe, effective medication which is easy to administer and has few side effects. It is a very useful adjunct in the treatment of spasticity in CP. As with any medication, it should be judiciously used and attention should be paid to any side effects.

Acknowledgments

There is no funding that was provided to the author and there is no conflict of interest to report. The author would like to acknowledge Drs. Heakyung Kim and Michael Green for their guidance.

References

[1] Navarrete-Opazo AA, Gonzalez W, Nahuelhual P. Effectiveness of Oral Baclofen in the Treatment of Spasticity in Children and Adolescents with Cerebral Palsy. Arch Phys Med Rehabil. 2016;97(4):604-18. doi: 10.1016/j.apmr.2015.08.417

[2] Stewart J. Lyvispah FDA Approval History. Drugs.com; 2021 [updated 25 November 2021]. Available from: https://www.drugs.com/history/lyvispah.html

[3] Reilly M, Liuzzo K, Blackmer AB. Pharmacological Management of Spasticity in Children with Cerebral Palsy. J Pediatr Health Care. 2020;34(5):495-509. doi: 10.1016/j.pedhc.2020.04.010

[4] Albright AL. Baclofen in the treatment of cerebral palsy. J Child Neurol. 1996;11(2):77-83. doi: 10.1177/088307389601100202

[5] Ghanavatian S, Derian A. Baclofen. Treasure Island, Florida; StatPearls Publishing LLC; 2022 [updated 1 May 2022]. Available from:

[6] Hansel DE, Hansel CRW, Shindle MK, et al. Oral baclofen in cerebral palsy: possible seizure potentiation? Pediatr Neurol. 2003;29(3):203-6. doi: 10.1016/s0887-8994(03)00208-x

[7] Misgeld U, Bijak M, Jarolimek W. A physiological role for $GABA_B$ receptors and the effects of baclofen in the mammalian central nervous system. Prog Neurobiol. 1995;46(4):423-62. doi: 10.1016/0301-0082(95)00012-k

[8] Dario A, Pisani R, Sangiorgi S, et al. Baclofen and potential therapeutic use: Studies of neuronal survival. Eur J Pharmacol. 2006;550(1-3):33-8. doi: 10.1016/j.ejphar.2006.08.068

[9] Knutsson E, Lindblom U, Mårtensson A. (1974): Plasma and cerebrospinal fluid level of baclofen (Lioresal) at optimal therapeutic responses in spastic paresis. J Neurolog Sci. 1974;23(3):473-84. doi: 10.1016/0022-510x(74)90163-4

[10] McLaughlin MJ, Abdel-Rahman S, Leeder JS. Examining the rol of precision medicine with oral baclofen in pediatric patients with cerebral palsy. Curr Phys Med Rehabil Rep. 2019;7(1):40-5.

[11] McLaughlin MJ, He Y, Brunstrom-Hernandez J, et al. Pharmacogenomic Variability of Oral Baclofen Clearance and

Clinical Response in Children with Cerebral Palsy. PM R. 2018;10(3):235-43. doi: 10.1016/j.pmrj.2017.08.441

[12] De Sousa N, Santos D, Monteiro S, Silva N, Barreiro-Iglesias A, Salgado AJ. Role of baclofen in Modulating Spasticity and Neuroprotection in Spinal Cord Injury. J Neurotrauma. 2022;39(3-4):249-58. doi: 10.1089/neu.2020.7591

[13] Terrence CF, Fromm GH, Roussan MS. Baclofen: its effect on seizure frequency. Arch Neurol. 1983;40(1):28-9. doi: 10.1001/archneur.1983.04050010048011

[14] Burgard EC, Sarvey JM. Long-lasting potentiation and epileptiform activity produced by GABAB receptor activation in the dentate gyrus of rat hippocampal slice. J Neurosci. 1991;11(5):1198-209. doi: 10.1523/JNEUROSCI.11-05-01198.1991