Intrathecal Therapies

Michael Saulino, MD, PhD[a,b,*]

KEYWORDS

• Intrathecal therapy • Intrathecal baclofen • Spasticity • Intraventricular baclofen

KEY POINTS

- Intrathecal baclofen therapy is an effective therapy for multifocal and global presentation of spasticity.
- Positive results have been seen in several diagnoses, including multiple sclerosis, spinal cord injury, brain injury, stroke, and cerebral palsy.
- The classic algorithm for intrathecal baclofen therapy is a sequence of patient selection, trialing, implantation of a permanent system, and chronic maintenance therapy.
- At times, derivation from the traditional treatment for intrathecal baclofen therapy is appropriate to achieve reasonable outcomes in selected patient populations.

INTRODUCTION

Intrathecal baclofen therapy (IBT) is a form of targeted drug delivery that has been used for three decades in the management of spastic hypertonia associated with the upper motor neuron syndrome.[1] This condition includes pathology affecting the spinal cord as well as the brain. Intrathecal baclofen infusion exerts its therapeutic effect by delivering liquid baclofen directly into the cerebrospinal fluid (CSF), thus affording enhanced access of this agent to target neurons in the spinal cord. This article provides a brief review of IBT because it is currently used in routine clinical practice as well as a series of hypothetical cases that will explore unusual techniques and strategies for targeted drug delivery in the management of the hypertonic condition. It is pertinent to recognize that the cases will explore treatment approaches that are not approved by Food and Drug Administration (FDA). Although clinicians are allowed to explore these "off-label" methodologies, they should fully acknowledge the risks and benefits of these procedures and apprize their patients accordingly.[2]

Disclosure Statement: Speakers bureau, fellowship support and research grant: Medtronic (19107). Speakers bureau, and research grant: Jazz Pharmaceuticals (19107). Speakers bureau: Ipsen. Patent compensation: Saol Therapeutics.

[a] MossRehab, 60 Township Line Road, Elkins Park, PA 19027, USA; [b] Department of Rehabilitation Medicine, Thomas Jefferson University, Philadelphia, PA, USA
* 60 Township Line Road, Elkins Park, PA 19027.
E-mail address: Docsaulino@msn.com

Phys Med Rehabil Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.pmr.2018.04.001 **pmr.theclinics.com**

PHARMACOLOGY OF INTRATHECAL BACLOFEN

Baclofen exerts its therapeutic effect by binding to gamma-aminobutyric acid (GABA) B receptors located in the laminae I–IV of the spinal cord, where primary sensory fibers end. After binding with the presynaptic terminal of GABAergic interneurons, membrane hyperpolarization arises, leading to a restriction of the influx of calcium into the presynaptic terminal. This leads to a reduction of endogenous transmitter release, which leads to inhibition of monosynaptic and polysynaptic spinal reflexes. Baclofen is rapidly absorbed after oral administration, partially metabolized by the liver, and mainly excreted by kidneys in unchanged form. Oral baclofen has several significant pharmacokinetic limitations, including restricted absorption in the upper small intestine by saturable active transport mechanism, a short half-life of 3 to 4 hours, partial hepatic metabolization, rapid renal clearance, and poor passage through the blood brain barrier.[3,4] There is also the possibility of pharmacogenomic variability with regard to baclofen metabolism.[5] Relatively common side effects of oral baclofen are sedation, respiratory depression, confusion, dizziness, headache, insomnia, depression, tremor, ataxia, paresthesia, hallucinations, orthostatic hypotension, dry mouth, visual accommodation troubles, nausea, vomiting, constipation, diarrhea, hyperhidrosis, rashes, and aggravation of a preexistent dysuria.[5] Significant adverse effects have been demonstrated with oral baclofen in both elderly stroke population and a mixed population with acquired brain injury.[6] Adherence to prescribed oral baclofen is often limited.[7] The rationale for intrathecal administration has been the delivery of the drug directly into the spinal fluid in order to allow higher concentrations in the spinal cord using lower doses than the oral route,[8] thus optimizing the benefit/risk ratio. This method of administration allows for GABA-mediated inhibition of spasticity while minimizing side effects secondary to high levels of baclofen in the brain. Although IBT can be tremendously beneficial for the management of spasticity related to central nervous system pathology, there is the potential for serious adverse effects related to this therapy. The improved potency of IBT compared with oral baclofen particularly predisposes patient to the possibilities of withdrawal and overdose syndromes.[9]

TRADITIONAL UTILIZATION OF INTRATHECAL BACLOFEN THERAPY

IBT is formally indicated for the management of severe spasticity of spinal and cerebral origins.[10] Despite its ubiquity, spasticity is a challenging entity to delineate with an evolving definition. Perhaps the best description that captures the depth and breath of this phenomenon is “a disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles.”[11] The next level of medical decision making for spasticity management is to determine the gravity of the condition. Colloquial definitions of “severe” include terminology such as “causing discomfort or hardship” as well as “very painful or harmful.” It is certainly reasonable to consider spasticity as severe when it is problematic, interfering with comfort, function, or caregiving. Spasticity intensity should include both the clinician’s impression as well as the patient’s perception. Clinicians should consider how problematic the spasticity is to the patient/caregiver, than solely relying on a numerical rating of a particular spasticity assessment measure. For example, modest resistance to passive motion, which could be evaluated as mild to the physician, may have a significant functional impact on the patient, who could describe the same phenomenon as severe. Given the diversity of spasticity presentations and the variety of diseases that create spasticity, it is not unexpected there are a multiplicity of treatment options. These therapeutic modalities can be divided into