Case report

Intrathecal baclofen for the treatment of spinal myoclonus: a case series

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Context/objective: To demonstrate the utility of intrathecal baclofen in the treatment of secondary myoclonus of spinal origin.
Design: Case series.
Setting: University medical center.
Participants: Two patients with spinal myoclonus who required the use of an assistive device because of difficulty walking resulting in falls.
Interventions: Intrathecal baclofen management.
Outcome measures: Symptom management and mobility function.
Results: Both experienced resolution of their spinal myoclonus and became community-level ambulators without the need of an assistive device.
Conclusion: Intrathecal baclofen is an effective treatment of secondary myoclonus of spinal origin.

Keywords: Spinal myoclonus, Assistive devices, Intrathecal baclofen, Spinal cord injuries, Stiff person syndrome, Transverse myelitis

Introduction

Spinal myoclonus is characterized by sudden involuntary rhythmic or semi-rhythmic muscle contractions in a muscle or group of muscles. The myoclonus may be unilateral or bilateral and may be stimulus sensitive. Propriospinal myoclonus is characterized by more widespread motor neuron activation as the stimulus is propagated up and down the spinal cord from a central generator.[1] Most patients with propriospinal myoclonus have had minor spinal cord trauma with normal MRI findings. However, it has been reported in severe spinal cord injury, multiple sclerosis, human immunodeficiency virus infection, Lyme infection, spinal cord syrinx, spinal cord tumors, spinal cord infarction,[2] arteriovenous malformations, spondylosis, amyotrophic lateral sclerosis, and viral infection.[3] Electromyography shows synchronous activation of the affected muscles with a typical frequency in the range of 0.5–3 Hz. The duration of contraction varies between 50 and 500 ms[2].

The pathophysiology of spinal myoclonus is postulated to be the spontaneous discharge of motor neurons in a limited area of the spinal cord.[2] These discharges may reflect increased excitability of facilitatory mechanisms or reduced activity of inhibitory mechanisms at the level of the inter-neurons or motor neurons.[3] However, the type of neuronal defect that creates these movements in the brainstem or spinal cord is unknown. It is known that when a partial lesion or denervation of brainstem or spinal gray matter occurs, abnormal firing of some remaining neurons occurs. The pattern of abnormal firing is typically rhythmic or irregular bursting. It has been postulated that this abnormal excitation overflows to motor neurons, which in turn causes the segmental myoclonus.[2] Post-mortem study of three adult human cases of viral infection of the spinal cord showed preferential loss of small- to medium-sized neurons in the spinal gray matter with little motor neuron loss, giving some credence to this hypothesis. It is also possible that the mechanism may have to do with neuroplasticity of remaining inter-neurons in response to abnormal neurological input after disease or injury of the spinal cord.[3] Other postulated mechanisms have included ephaptic activation of motor neurons, axonal irritation secondary to excitatory inflammatory factors, or ion channel dysfunction.[4]

There is little in the literature that details the neurochemistry of this disorder as it relates to myoclonus of

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spinal origin. In post-hypoxic myoclonus, cerebrospinal fluid studies have shown low levels of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin. A role for gamma-amino-butyric acid (GABA) in this disorder is suggested by producing these symptoms by injecting GABA antagonists into the rat thalamus. Although damage in these areas of the brain in post-mortem studies in humans has not been seen, GABA-ergic drugs such as valproic acid and clonazepam are usually used in the treatment of post-hypoxic myoclonus. Each is associated with improvement in approximately 50% of treated patients. Levetiracetam has been recently reported to be effective in an open-label trial as well. Other GABAergic drugs such as vigabatrin and gabapentin have not shown promise. No report of the use of tizanidine or other alpha-2 sympathetic agonists has been published. The importance of serotonin metabolism and release in this disorder is uncertain with speculation of why some serotonin agonists improve symptoms in the rat in spite of normal cerebrospinal fluid serotonin levels.[1]

Intrathecal baclofen has been utilized for stiff person syndrome and progressive encephalomyelopathy with rigidity and myoclonus. The latter is considered a variant of stiff person syndrome in which 60% of patients have autoantibodies against glutamic acid decarboxylase, which converts glutamate to GABA. The initial treatment is high-dose diazepam. The use of intrathecal baclofen, a GABA agonist, also requires a high dose similar to patients with stiff person syndrome.[5]

This paper presents our experience treating this disorder with intrathecal baclofen.

Case 1

A 47-year-old white woman presented with a several-week history of gait abnormality including tightness and difficulty with balance. When she developed difficulty with urination with stress incontinence and difficulty with bladder emptying, she presented to the emergency department. Physical examination revealed at T6 incomplete pin level with lower extremity spasticity, brisk reflexes, and extensor plantar responses. Magnetic resonance imaging revealed abnormal high T2 and low T1 signals extending from T2 to T11. Abnormal signal was somewhat more pronounced in the right side and central aspects of the cord with post-contrast enhancement. Laboratory test showed cerebrospinal pleocytosis with 11% polymorphonucleocytes, 7% lymphocytes, and 82% histiocytes; glucose was 152 mg/dl and protein 74 mg/dl. Viral and bacterial studies were negative. Flow cytometry revealed no evidence of aberrant lymphoid cells and was negative for neoplasm. Myelin basic protein and oligoclonal bands were normal. Cerebrospinal fluid albumin and IgG were elevated. Serum testing showed a C-reactive protein of 1.9 mg/dl, rheumatoid factor of 104 IU/ml, nuclear antibody titer of greater than 1:2560 speckled, and extractable nuclear antibodies ro and la were positive. A clinical and laboratory diagnosis of Sjögren's syndrome with transverse myelitis was made, and she was started on a monthly course of pulsed cyclophosphamide and subsequent oral cyclophosphamide therapy with complete resolution of her neurological symptoms.

Cyclophosphamide therapy was stopped 4 months later when a coronary artery bypass graft was completed due to unstable angina that failed conservative treatment. However, her symptoms returned 8 months later with MRI and serum laboratory concurrence. Treatment with intravenous methylprednisolone 1 g daily for 3 days resulted in no improvement and cyclophosphamide infusions resumed with excellent effect. Persistent right leg weakness and bladder dysfunction required inpatient rehabilitation for 14 days. She was discharged with persistent right leg weakness, ambulating independently with a walker and requiring intermittent catheterization twice daily to monitor post-void residuals that remained elevated in spite of the ability to sense and initiate voiding. Follow-up thoracic MRI showed no definite signal aberration in the thoracic cord on the sagittal images with possible increased T2 signal within the central cord, slightly more to the right at the T6–T7 level on axial view, without associated contrast enhancement.

She did well for 2 months at which point she began to have periodic leg spasms, right greater than left. These episodes would last 15–45 seconds and occurred 5–8 times per hour. They were painful and inhibited her mobility, requiring inpatient hospitalization. Her modified Ashworth scores in between these episodes were 1+ throughout the left lower extremity and 1 on the right. Sensation was decreased to touch, pin, vibration, and proprioception in the lower extremities bilaterally. Sensation to touch was decreased more in the left lower extremity than the right, and her reflexes were 1+ at the biceps, 1+ at the triceps and symmetric. She had absent lower extremity reflexes and flexor plantar responses. Her strength in upper extremities was 5/5 diffusely; in her lower extremities, she had 2/5 hip strength on the right and 3/5 on the left with knee extension and ankle dorsiflexion 4/5 bilaterally. Oral baclofen at 100 mg daily did not change these episodes, nor did gabapentin or clonazepam. Three hours after a loading dose of phenytoin, these episodes abated.

Managing her symptoms with phenytoin allowed weaning of her clonazepam and decreasing her baclofen to 30 mg daily. She had several exacerbations of her myoclonus over the next year related to changes in the generic brand of her phenytoin provided by her pharmacy, resulting in fluctuating drug levels. She required a drug level of 20–25 to achieve optimal control. She did well for several years at which time she was switched from cyclophosphamide to mycophenolate for disease control. Upon titrating up her mycophenolate dose, she had an additional exacerbation of her transverse myelitis with increased weakness and sensory loss and increased spasms. Increased immunological control reversed the motor and sensory symptoms but the intermittent spasms were not longer well managed by phenytoin with oral baclofen and gabapentin. With her worsening symptom management and her continuous complaints of fatigue from her medications, an intrathecal baclofen trial was conducted. A 50 μg intrathecal test dose eliminated her myoclonus and resulted in no significant decline in her strength. Pump placement was pursued. Within 6 months, she was ambulating without an assistive device and independent in all activities of daily living, driving, and community activities. Bowel and bladder control were essentially normal. Lower extremity reflexes were trace. Lower extremity-modified Ashworth scores were 0. Strength testing showed ankle dorsiflexion 5/5 bilaterally, knee extension 5/5 bilaterally, hip flexion 3/5 on the right and 4/5 on the left, and hip abduction 4/5. She has remained free of myoclonus for 3 years on a daily intrathecal baclofen dose of 131.34 μg.

Case 2

A 44-year-old woman presented 3 years after an episode of idiopathic transverse myelitis. She presented with intermittent low back and right greater than left leg spasms and shaking. These episodes occurred with as few as 2 episodes a day to 6 to 7 episodes an hour which lasted for a few seconds only, resulting in tightening up and jerking of her legs. These episodes were painful and resulted in falls. They occurred in any position and at any time of the day or night. Her neurological examination revealed 3+ bilateral lower extremity reflexes with bilateral flexor plantar responses. Her strength was 5/5. Modified Ashworth score bilaterally was noted to be 1+ at hamstrings, 1 at the gluteus medius, and the rest was 0. She reported intact light touch and pin sensation. There was no edema noted at the lower extremities. She continued to use a cane in the left hand with no noted spasticity or gait deviations. Oral baclofen did not change these episodes at a dosage of 100 mg per day and pregabalin was aborted due to lower extremity swelling. Divalproex sodium resulted in some improvement but she did not tolerate higher doses due to lethargy. Carbamazepine was not tolerated due to lethargy and gabapentin was avoided due to nightmares. An intrathecal test dose of baclofen 50 μg eliminated these episodes. Pump placement and a daily dose of 207 μg resulted in elimination of these episodes. She ambulates without an assistive device and is independent in the community. She has used intrathecal baclofen therapy for 3 years without complication.

Discussion

Spinal myoclonus has been reported in transverse myelitis,[4] with presentation similar to the cases presented here. Given that both the patients presented in this case study experienced myoclonus at times when their disease was not active would argue against inflammatory mechanisms as the trigger for these episodes. The fact that phenytoin was dramatically effective in one case and divalproex showed some efficacy in the other would favor abnormal nerve firing influenced by ion channel abnormalities. However, the response to intrathecal baclofen, a GABA agonist, would favor the notion that spinal injury decreases inter-neuron inhibition leading to myoclonus. The relatively higher cerebrospinal fluid concentrations of baclofen obtained by the intrathecal delivery method were required to achieve motor neuron inhibition to alleviate the myoclonus. Focal treatment in the form of botulinum toxin or phenol block was not considered. Neither would address the underlying pathophysiology suggested for this problem. But, more importantly, the increase in tone is both generalized and paroxysmal. The generalized nature of the myoclonus episodes would have required many muscles to be targeted for chemo-denervation. The use of phenol or botulinum toxin would result in a risk of weakness to the muscles injected, muscles that do not experience increased tone most of the time. Many of the muscles involved in the two case presentations were weight-bearing muscles. Chemo-denervation of these muscles could have a detrimental impact on mobility skills.

The dose of intrathecal medication required to achieve clinical effectiveness is far smaller than that seen in stiff person syndrome[4] and our experience with that disorder would support this statement. This would seem to indicate a different pathophysiology for these two disorders. The treatment of spinal myoclonus in these two cases showed a far more complete resolution of symptoms than is commonly achieved with stiff person syndrome.

It should also be noted that the result of treatment was not merely the elimination of symptoms. In both cases, serious motor disability was reversed by treatment. Both required an assistive device before intrathecal baclofen therapy and both had a history of falls with injury. Intrathecal baclofen has allowed both patients to resume their lives as community ambulators without an assistive device. Neither has had a pump or catheter complication for greater than 3 years.

In these cases, the functional loss and pain experienced by the patients was the compelling reason to pursue intrathecal pump placement. It should be recalled that such placement is not without cost or risk. There is the high cost of the pump with the requirement of day surgery for placement, dosage adjustments, and refills done at least every 6 months. The pump has a limited life of 7 years with rare pump failures. Catheter failures in the form of kinks, leaks, and migrations are much more common than pump failures, with up to 10% of patients requiring surgical correction.

Conclusion

Intrathecal baclofen is an effective therapy for the treatment of myoclonus of spinal origin. The limited experience described shows a dose range between 125 and 207 μg per day. Treatment resulted in resolution of myoclonus episodes at a level of effectiveness much higher than other traditional treatments attempted. The ability to discontinue oral antispasmodic medications for this disorder eliminated the cognitive side effects. Dramatic improvement in motor function and safety can be seen.

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