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CLINICAL NOTES

Effect of Intrathecal Baclofen Concentration on Spasticity Control: Case Series

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Abstract

Background/Objective: Intrathecal baclofen (ITB) has been shown to be an effective treatment for severe spasticity of spinal or cerebral origin. Although most patients respond well to an ITB trial, there are often difficulties in achieving and/or maintaining such effectiveness with ITB pump treatment. There are few published guidelines for dosing efficacy and no studies looking at the effect of concentration of ITB on spasticity management.

Methods: Case series of 3 adults with severe spasticity treated with ITB pump: a 44-year-old man with C7 tetraplegia using a 40-mL Medtronic SynchroMed II pump with 500-μg/mL concentration; a 35-year-old woman with traumatic brain injury with right spastic hemiplegia using a 18-mL Medtronic SynchroMed EL pump with 2,000-μg/mL concentration; and a 43-year-old woman with spastic diplegic cerebral palsy using a 40-mL Medtronic SynchroMed II pump with 2,000-μg/mL concentration.

Results: After reducing ITB concentrations in the pump, either as part of a standard protocol for dye study to assess the integrity of pump and catheter system or secondary to plateau in therapeutic efficacy, patients experienced temporary, significant reduction in spasticity based on range of motion, Modified Ashworth scores, and verbal feedback.

Conclusions: Decreasing the concentration of ITB seems to affect spasticity control. Further research in this area is needed for those patients with refractory spasticity to optimize efficacy of ITB therapy.

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Key Words: Spasticity; Baclofen; Intrathecal; Tetraplegia; Hemiplegia; Cerebral palsy; Traumatic brain injury

INTRODUCTION

Baclofen is a centrally acting gamma-amino-butyric acid B ($GABA_B$) agonist used to treat spasticity in upper motor neuron syndromes such as spinal cord injuries (SCI) and spasticity of cerebral origin (1–3). As intrathecal baclofen (ITB) therapy has evolved, the challenges associated with optimizing treatment have grown. An important component of this challenge is improving our understanding of how ITB distributes in the cerebral spinal fluid (CSF). Research has shown that ITB seems to gradually decrease in concentration as it goes from lumbar to thoracic cord level (4). More recent studies propose that CSF is poorly distributed in the spinal canal, resulting in limited to no movement of the CSF in some regions of the spinal cord (5,6). Techniques to overcome these difficulties in the course of ITB would include varying catheter tip placement and bolus dosing to enhance clinical efficacy. These strategies have been applied with mixed clinical results (1–4,7).

Pharmokinetic studies have shown that, for moderately hydrophilic drugs such as baclofen, the drug concentration in the cisternal CSF is considerably lower (1/3 to 1/7) than that of the lumbar CSF levels (4). Research data suggested that a lumbar to cisternal gradient of approximately 4:1 is established along the neuroaxis during infusion of baclofen injection, based on simultaneous CSF sampling through lumbar and cisternal taps. The rate of decline seems to be gradual based on the study done by Kroin et al (4), which showed a 43% reduction in hydrophilic tracer from T12 to T2 within 72 hours when equilibrium was reached and a 24% reduction of tracer in the lumbar CSF when extrapolated to the C1 level (4). The decline in ITB concentration is thought to be related to interchange of CSF as it ascends from the spinal CSF space to the cranial CSF space, with additional loss to areas outside the spinal cord (4).

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Using the aforementioned theoretical base for distribution of ITB, researchers have looked at catheter tip placement and how it may influence the distribution of ITB. This is especially salient in the management of the patient with upper extremity spasticity. Secondary to poor bulk flow, researchers have advocated for higher placement of catheters above T12/L1 for patients with upper extremity spasticity, with the goal of maintaining a more even distribution of ITB to assist in reducing tone for upper and lower extremity spasticity and reducing dosage of ITB (4,7–9). Hugenholtz et al (9) also hypothesized increasing the dosage with the catheter tip at the lumbar level could control spasticity equally as well as for upper extremities, but may be toxic to the muscles of the lower extremities by making them too loose, especially in ambulatory patients. Bolus injections may diffuse baclofen even further up from the catheter tip, affecting trunk and upper extremity tone, whereas chronic infusion is good for a stable gradient when trying to assist with tone in lower extremities (7–9).

More recent findings by Bernards et al (10) have enhanced our understanding of baclofen distribution in the CSF. With the application of magnetic resonance imaging techniques, CSF has been shown to oscillate back and forth along the rostrocaudal axis with decreased force of flow caudally. Bernards et al (10) also hypothesized that drug distribution would be aided by the kinetic energy created during the act of bolusing. Using a slow infusion rate similar to that used in actual ITB therapy of 20 mL/h, they observed most of the distribution of ITB (at a concentration of 7.5 mg/mL) within the CSF of pigs was located within 1 cm of the catheter tip, specifically at the posterior surface of the spinal cord (10). This seems to support the findings of poor distribution within the CSF. Drug concentration decreased dramatically as a function of distance from the administration site. Interestingly, with an increased rate of infusion (1,000 μg/h) and with bolus dosing (1,000 μg over 5 minutes) at supratherapeutic doses, more uniform and broader distribution of ITB was noted (10).

Additionally, Albright et al (11) looked at the concentration of ITB and dosing. They found significant intra-individual variations in the pharmacokinetic properties (half-life/clearance) of ITB with marked differences in response to a given dose of drug. There were no correlations between either ITB dosages or catheter tip placement and CSF concentration levels of baclofen (11).

The anatomy of the spinal cord may also play a role in the distribution of ITB, further complicating our ability to optimize outcomes. Treatment effectiveness may be altered especially if there is a syrinx, tumor, or other obstruction in spinal canal affecting flow of CSF and thus ITB (11). Cystic cord lesions such as congenital syringohydromyelia and posttraumatic spinal cord cysts may show pulsatile flow of CSF (12). Review of the literature failed to show literature on the effect of changing dose concentration on spasticity management.

Case 1

A 44-year-old man with C7 ASIA level A tetraplegia and a medical history of myasthenia gravis presented with severe spasticity. After placement of a Medtronic SynchroMed II pump (Medtronic Corp, Minneapolis, MN), he reported overall reduced spasticity with 100 μg on simple continuous basis at 500 μg/mL concentration, but did intermittently take oral baclofen 20 mg once or twice a week. Sixteen months after placement, he presented with worsened spasticity. He reported taking 7 to 8 oral baclofen 20-mg tablets a day, with increased fatigue and ongoing problematic tone. Physical examination showed a Modified Ashworth Score (MAS) of 3 to 4/5 in the bilateral lower extremities, 4+ patellar deep tendon reflexes with sustained ankle clonus, abdominal spasms, and significant difficulty with transfers. Other sources for increased tone were ruled out including skin, bladder, and/or bowel complications. Radiological study of his catheter and pump system was normal. Initially, his dosage was increased from 100 to 215 μg/d over several visits. His pump was refilled, confirming that the pump was distributing medicine. In subsequent follow-up, bolus dosing was used, which helped relieve his spasticity temporarily. However, the patient continued to require oral baclofen supplementation 5 to 6 times a day to maintain an MAS of 1+ to 2. Tone was still problematic, interfering with transfers. A dye study was planned, and his baclofen concentration was decreased from 500 to 250 μg/mL to minimize the risk of overdose during the dye study. On the day of the study, the patient had an MAS of 0/5 and had not taken any oral baclofen for several days. His dosage was unchanged at 215 μg/d, with 4 boluses of 25 μg. As his tone was well managed, the dye study was postponed, and his baclofen concentration was maintained at 250 μg/mL.

Approximately 3 days later, his tone returned, ultimately requiring oral baclofen supplementation of 20 mg 3 to 4 times a day. The MASs were 1+/5. His ITB pump daily dose was raised to 230 μg, and his dye study was done, decreasing his concentration to 250 μg/mL. Again, spasticity improved to an MAS of 0/5 for 1 week, only to return to baseline. The dye study was normal, including a postinfusion computerized tomography scan. Dosage was maintained at 250 μg/mL for the rest of the month; however, he still noted problematic tone, requiring 100 to 120 mg of oral baclofen per day, with resulting fatigue. The concentration was subsequently increased to 500 μg/mL, and his dosage was increased to 300 μg/d with 4 boluses of baclofen 40 μg spaced throughout the day. His dosage continues to be adjusted.

Case 2

A 35-year-old woman with a history of traumatic brain injury as an adolescent presented with severe right-sided spasticity. A Medtronic SynchroMed EL 18-mL ITB pump was placed. Spasticity was well controlled in her lower extremities but difficult to treat in the right upper

extremity. Numerous trials of nerve blocks and botulinum toxin A injections were performed to treat right upper extremity spasticity with minimal unsustained effect. A trial of reduced concentration of ITB from 2,000 to 500 μg/mL was initiated to improve spasticity and range of motion in the right upper extremity. A bridge bolus was done, and 5 mL of bacteriostatic preservative-free saline was used to wash the pump reservoir before the insertion of the 500 μg/mL concentration. After this reduction, measurements of MAS and range of motion (ROM) were performed at 2 weeks, 1 month, and 2 months. Patient and caregiver feedback was also obtained. Modified MASs were noted to drop by 2 points at the right hip adductors and 1 point at the right hip flexors, right biceps, and right shoulder internal rotators. Range of motion was improved modestly at shoulder abduction and external rotation and was relatively unchanged at the elbow. Moderate improvement in ROM was noted on wrist flexion and forearm supination (10 degrees). Care staff noted improvement in patient's level of energy and overall freedom of movement within ranges. Alignment of lower extremities was also greatly improved, with marked reduction in internal hip rotation and valgus positioning at the knee. It was necessary to resume the 2,000 μg/mL concentration for 10 weeks to extend time between refills until the implantation of her 40-mL pump. Therapists noted return to baseline function with the return to the higher concentration. Once she received her 40-mL pump, she resumed her prior dosing regimen with 500-μg/mL concentration of ITB. She has begun therapy and continues to show improvement in trunk spasticity and lower extremity tone, especially in the right internal hip rotators.

Case 3

A 42-year-old woman with diplegic spastic cerebral palsy presented with severe spasticity. Before her ITB pump placement, she noted difficulty with gait and activities of daily living secondary to spasticity in the lower extremities. She originally received a Medtronic SynchroMed 18-mL pump; 5 years later, this was replaced with a SynchroMed II 40-mL ITB pump. After pump placements, she experienced ongoing issues with fine tuning of her ITB dose. She had fluctuating symptoms of feeling too tight or too loose, affecting her ability to ambulate using an assistive device. Dosing varied from as high as 650 to 400 μg/d, with an ITB concentration of 2,000 μg/mL. Spasticity was also managed with accompanying periodic botox injections to the lower extremities. Additionally, she would regularly supplement with 10 to 20 mg of oral baclofen per day.

Approximately 1 year after implantation of her second pump, a dye study was performed secondary to concerns of a possible ITB withdrawal including increased tone and burning pain with itchiness. Before the dye study, her ITB concentration was decreased from 2,000 to 500 μg/mL to avoid overdosage during the study. Three days after the change in concentration, she returned to the clinic with symptoms of overdose including nausea, low tone, weakness with fatigue, and temporary loss of bladder control. Her baclofen dosage was decreased by 15% from 583 to 494 μg/d. For the next several days, she reported no symptoms of overdose and was pleased with her spasticity management. On her return to the clinic 3 weeks after her dye study to assess her pump catheter system, she reported the best 3 weeks of function in over a year, with no difficulty sleeping and no need for oral antispasticity medications. She continues on 500 μg/mL concentration and uses small and sporadic doses of oral baclofen to supplement her spasticity management.

DISCUSSION

These cases underscore the importance of dose and concentration with spasticity management with ITB. In these individuals, decreases in ITB concentration resulted in an apparent increase in spasticity control. In contrast, an increase in concentration leads to decreased spasticity control at the same dose rate. Despite the small volumes that are pumped on a daily basis for either concentration, these patients show that there does seem to be a difference in spasticity control when stratifying for concentration only. This is consistent with our findings in situations when we inject a much lower concentration of ITB during the ITB trial. This might be because of the volume change or it might be related to the concept of kinetic energy of Bernards et al (10), which may enhance the distribution and possibly efficacy of the drug. This phenomenon should be considered when looking at ITB trials as well.

Again, we noted a subpopulation of individuals who seem to have much better responses after their ITB trials than after the pump is placed and their dosage is optimized. It may be that, in these patients, increased spread of the antispasmodic medication is enough to allow further binding to GABA sites in a larger gap in the spinal cord or in more proximal segments, allowing for more optimal spasticity control. Based on the findings by Bernards et al (10), this seems less likely; however, the interaction between distribution of CSF and drug concentration of ITB in CSF has yet to be studied. The increased knowledge of CSF flow and distribution and its affect on concentration is an important aspect to consider. Regardless of the small volumes involved, for some patients, the use of lower concentration ITB makes a significant difference in their spasticity management,

For these patients, this phenomenon circumvents the advantage of the higher volume capability of the new generation of ITB pumps. Part of the attraction of these devices is to allow an increase in the interval time between refill appointments. If a low concentration of ITB is needed, frequent refills will be necessary. It is possible that the new 40-mL pumps will still demand frequent

refills, but pump refills would not be so frequent as to be a deterrent to continued therapy.

CONCLUSION

Our own hypothesis supports a clinical effect of decreased spasticity through reduction in concentration of ITB within a small subset of subjects. The mechanism behind these phenomena is unclear. This is an area to further study as we try to optimize our ability to treat spasticity and determine whether this is an isolated effect. Although the aforementioned case studies report temporary, significant reductions in tone, the clinical outcomes need to be evaluated to identify the underlying mechanism of action. Further evaluation of this hypothesis and mechanism of action to determine whether it can be generalized is needed.

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