Intrathecal baclofen therapy in children

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Since its introduction in the late 1980s, intrathecal baclofen (ITB) therapy has become the standard treatment for severe generalized spasticity and dystonia in children. Treatment with ITB decreases spasticity in the upper and lower extremities and has been associated with improved function and decreased musculoskeletal contractures. In addition, ITB decreases generalized secondary dystonia and has been associated with improved comfort and ease of care in approximately 85% and with improved function in approximately 33% of patients. Continued effectiveness of ITB in treating spasticity has been observed for up to 17 years, and its effectiveness in treating dystonia has been observed for up to 10 years. Although ITB therapy is frequently associated with complications such as infections, catheter malfunctions, and cerebrospinal fluid leaks, the benefits of therapy appear to outweigh the risks. Additional investigation is needed to determine the effects of ITB on other movement disorders such as athetosis and chorea.

Key Words • movement disorder • spasticity • dystonia • cerebral palsy • intrathecal baclofen

Baclofen was initially synthesized in the 1920s as a GABA agonist to treat epilepsy. In the course of treating adults with epilepsy who also had spasticity, physicians observed that seizure frequency was minimally affected but that spasticity was decreased. Baclofen was given only orally until the mid-1980s, when Penn and Kroin first reported the use of ITB. Penn and colleagues subsequently confirmed its efficacy in a landmark double-blind study. The first report of the use of ITB therapy to treat children was published in 1985 by Dralle, et al., who used it to treat a 4-year-old child who suffered from hypertonicity after a near-drowning. In 1991, we reported a double-blinded screening trial of ITB therapy in children with spastic CP, and confirmed the short-term effect of bolus injections on spasticity. In 1992, Müller reported that ITB improved spasticity in approximately 20 patients (children and young adults) younger than 20 years of age who were studied in a European multicenter trial. Since then, ITB therapy has been shown to diminish both spasticity and dystonia in children, and at times it improves function.

Although other medications such as clonidine and morphine have been given intrathecally to treat spasticity in adults, they have been used minimally in children, and evidence about their effectiveness is anecdotal.

Pharmacology of Baclofen

Baclofen, 4-amino-3-(4-chlorophenyl)-butanoic acid, is an agonist of the inhibitory neurotransmitter GABA. Baclofen acts primarily in the superficial layers of the spinal cord in treating spasticity, in essence replacing GABA that is not being released because of deficient descending inhibitory impulses. Baclofen’s site of action in treating dystonia is unknown; it may be at the spinal cord level or the cortical level, or both. It has been postulated that the site of action is at the cortical level, with inhibition of excessively stimulated premotor and supplementary motor cortex. That postulate was based on the observation that a single lumbar bolus of ITB often does not diminish dystonia the same way it does spasticity (where the site of action is known to be in the spinal cord), and the observation that a continuous infusion of ITB often takes 24 to 48 hours before dystonia begins to improve, long enough for baclofen to enter the intracranial subarachnoid space and ascend over the convexitites.

Oral baclofen is absorbed rapidly and well from the gastrointestinal tract, but little of it crosses the blood–brain barrier to enter the CSF. Oral baclofen doses of 30 to 60 mg are associated with CSF levels of 12 to 96 µg, whereas intrathecal doses of 400 µg are associated with levels of nearly 400 µg/ml in the CSF. Baclofen injected into CSF is distributed within the fluid and is cleared at CSF clearance rates. The effects of a bolus dose on spasticity are maximal 4 hours after injection and disappear within 8 hours. Serum baclofen levels are virtually undetectable in children receiving ITB therapy.

Criteria for ITB Therapy in Childhood

Patient Selection

Most children with moderate or severe spasticity, particularly those who are younger than 4 years of age, can be helped appreciably with oral medications, with or without accompanying botulinum toxin injections. For children older than 6 years who have severe spasticity or dystonia, the likelihood of obtaining the desired improvement with oral medications is small, and sometimes the initial rec-
ommendation is for ITB, even if oral medications have not been given first.

Since the introduction of the smaller Synchronized II pumps (Medtronic, Inc., Minneapolis, MN), practically no size or age limitations exist for pump implantation. Although most children who undergo pump implantation are at least 6 years of age, and few children younger than 4 years of age need a pump, we have implanted a pump into a 9-month-old, 18-lb infant who suffered from severe hypertonicity after an anoxic event.

Treatment recommendations for ITB should come ideally from a multidisciplinary team with expertise in all of the various treatment modalities, including oral medications, botulinum toxins, selective dorsal rhizotomies, orthopedic procedures, and ITB.

Common Indications

Spasticity. Most candidates for ITB therapy to treat spasticity have generalized moderate or severe symptoms, with Ashworth scores of 3 to 4 in the upper and lower extremities. Their spasticity is either impeding care, causing progressive contractures, or impeding function. Children with spastic diplegia associated with spinal cord injuries or with familial spastic paraparesis are typically benefited by ITB therapy, but very few children with spastic diplegia associated with CP are candidates for ITB; they can usually be treated more definitively with selective dorsal rhizotomy. Sometimes ITB is used in children with severe spastic hemiplegia, in whom it appears to relax the spastic side but not to cause hypotonicity of the normal side.

Treatment goals must be clarified before a pump is inserted. Decreasing spasticity per se is not a treatment goal; facilitating care, increasing comfort, decreasing contractures, or improving function are treatment goals.

Contraindications to pump implantation include unrealistic expectations about ITB benefits (for example, normal function) and evidence that the family will not return for the indicated refills, therefore risking baclofen withdrawal. The presence of a gastrostomy stoma in the left upper quadrant is not a contraindication to pump implantation.

Dystonia. Candidates for ITB treatment for dystonia have moderate or severe generalized dystonia that is impeding care, causing discomfort, or impeding function. Secondary dystonia (secondary to a structural brain lesion, as in CP) seems to respond best to ITB. Heredodegenerative dystonia (for example, that associated with disorders such as Hallervorden–Spatz or Wilson disease) seems to respond less well. Primary dystonia (associated with no structural abnormality but at times with the DYT-1 gene) has the worst response. Children with primary dystonia, even those as young as 8 years of age, are usually treated more effectively with deep brain stimulation than with ITB therapy.

Children with severe hemidystonia can be treated with ITB; as is the case with spastic hemiparesis, tone in the affected side improves and tone in the normal side appears to be unaffected. Some children have substantial dystonia in their upper and lower extremities but low tone in their trunk and neck. The decision to use ITB in these children is more difficult; some of them have such severe dystonia in the extremities that ITB is appropriate even if their neck and trunk are more hypotonic postoperatively.

Screening for ITB Therapy

Since the introduction of ITB for clinical use, patient responsiveness to this therapy has traditionally been tested before a pump is implanted. Responsiveness of spasticity has been tested with bolus baclofen doses injected via lumbar punctures, using doses of 25 µg for children weighing less than 40 lbs and 50 µg for those weighing more than 40 lbs. Ashworth scores in the lower extremity have been graded at baseline and every 2 hours for 6 to 8 hours after injection. Decreases of one point or greater in the mean Ashworth scores in the lower extremities have been considered to be clinically significant for children with spasticity of cerebral origin, and two points or greater for those with spasticity of spinal origin. For the few children whose spasticity does not respond to a 50-µg bolus, a bolus of 75 to 100 µg can be given the next day.

If patients or observers note improved function after a bolus dose, that improvement is usually maintained if the patients undergo pump insertion; conversely, if function does not improve after a bolus, it may improve during long-term infusion as doses are fine-tuned. Bolus doses are not a good way to see what will happen to gait after a pump implantation; gait often worsens after such a dose because the bolus is a larger dose than that needed to optimize gait. Indeed, some have used infusion via an external pump to evaluate gait after ITB therapy in ambulatory children with CP.

In our experience with ITB, virtually all patients with spasticity respond to bolus doses, and we no longer give a screening bolus before implanting a pump if the child has spasticity. Other practitioners in the US with considerable ITB experience have also discontinued screening trials. The great majority of children who “do not respond” to bolus doses have dystonia, which takes higher doses and often requires continuous infusions to evaluate response.

The responsiveness of dystonia to ITB therapy in young, small children (<7 years of age, <40 lbs) can often be evaluated using bolus lumbar injections, particularly doses of 50 to 100 µg. For older, larger children, however, screening is probably better done with continuous infusions—using an intrathecal catheter and an external microinfusion pump—than with bolus injections. In our screening protocol, infusions began at 200 µg/day and increased by 50 µg every 8 hours until one of the following occurred: 1) dystonia improved (25% decrease on the Barry–Albright Dystonia Scale); 2) unacceptable side effects occurred; or 3) there was no significant response at 900 µg/day.

In our experience with more than 200 patients who had dystonia and whose response to ITB was tested before pump implantation, more than 90% responded with decreased dystonia scores. (Data from the first 89 cases were published in 2002.) Given that experience, we no longer do screening trials (either bolus or infusion) for children with severe secondary dystonia or for children who have mixed spasticity and dystonia. Nevertheless, we do use infusion trials for patients with other mixed movement disorders, for example, for a child whose hyperkinetic movements appear to be a combination of dystonia, athetosis, and chorea, and whose response to ITB is unknown. We also use screening infusion trials for older children and young adults who have severe generalized athetosis or cho-
Pumps placed in children and who have not responded to any oral medication, although too few such patients have been treated to know their likelihood of responding to ITB.

**Pump Implantation**

Techniques of pump implantation have been summarized recently, including techniques designed to decrease the risk of common complications. Pumps placed in children are inserted after induction of general anesthesia, in operations lasting 1 to 1.5 hours, and are now almost always inserted subfascially, usually on the right side. The presence of a gastrostomy tube in the left upper quadrant has not been found to increase the risk of a pump infection. Intrathecal catheters are inserted obliquely in the lumbar region into the thecal sac and are advanced cephalad to a level depending on the underlying disorder: T10–11 to treat familial spastic paraparesis, C6–T2 to treat spastic quadriplegia, and C1–4 to treat generalized secondary dystonia. The higher catheter tip placement is based on the following considerations: 1) the demonstration by Kroin, et al., that drug concentrations at the foramen magnum has not been found to increase the risk of a pump infection. Intrathecal catheters are inserted obliquely in the lumbar region into the thecal sac and are advanced cephalad to a level depending on the underlying disorder: T10–11 to treat familial spastic paraparesis, C6–T2 to treat spastic quadriplegia, and C1–4 to treat generalized secondary dystonia. The higher catheter tip placement is based on the following considerations: 1) the demonstration by Kroin, et al., that drug concentrations at the foramen magnum are approximately one fourth those at T-12 after infusions in the lumbar region; 2) data reporting less upper-extremity spasticity with higher catheter placement; and 3) data reporting less dystonia with higher placement.

Commercially available pumps can be obtained in either fixed- or adjustable-rate models. Because ITB doses are so frequently changed to treat either spasticity or dystonia in children, adjustable-rate pumps are used far more often than fixed-rate models. Implanted pumps can be secured either by sutures running between the suture eyelets on the pump and the adjacent fascia/muscle, which is the technique we strongly prefer, or by inserting the pump into a Dacron pouch and suturing the pouch to the surrounding tissues. The pouches induce intense fibrosis; they are difficult to remove if an infection occurs, and they are also difficult to enlarge if a bigger pump needs to be implanted within the pouch.

In patients who have undergone a spinal fusion and need ITB, we initially drilled a tunnel through the fusion mass in the lumbar region, inserted the catheter through a Tuohy needle, and then filled the space in the bone around the catheter with muscle, Gelfoam, and fibrin glue. Several CSF leaks ensued and were particularly challenging to treat. For the past 3 to 4 years, in children with or who were scheduled to undergo spinal fusions, we have tunneled the catheters subcutaneously, paramedian to the cervical level, and inserted them into the thecal sac through a small laminectomy with a purse-string suture at the insertion site, and no CSF leaks have occurred.

**Side Effects and Complications of ITB Therapy**

The most common early side effect of ITB is the inability to urinate for 2 to 3 days, which is never a permanent condition. The most common chronic side effect of ITB is increased constipation, and this is often treated with Miralax. Lassitude or tiredness may occur if slightly higher ITB doses are being given than are needed. Decreased spasticity in the lower extremities may be associated with greater difficulty doing pivot transfers. The relationship between ITB therapy and seizures has been debated. There are a few anecdotal reports of increased seizure frequency after pump implantation, but no good data confirming such an increase, and in one pediatric multicenter study, no change in seizure frequency was observed.

The three most common complications of ITB therapy are infections, catheter problems (breaks, kinks, migration), and CSF leaks. Infections occur in approximately 10% of patients; most are caused by *Staphylococcus aureus* and occur within 6 weeks after pump insertion. Treatment usually involves removal of the pump and intravenous antibiotics for 2 weeks. However, if the infection is limited to the pump site and the CSF is sterile, an alternative treatment method is to return the child to the operating room, remove the pump and cleanse it thoroughly, cleanse and pulse-irrigate the pump pocket, and reimplant the device. We have used that technique three times, twice with success.

Catheter problems develop in 5 to 15% of cases and require minor surgical procedures to correct them. There appear to be fewer complications with a single-piece catheter (lacking a straight connector posteriorly in the lumbar region), because disconnections and breaks at the straight connector are far less frequent. Catheters may migrate completely out of the thecal sac and become coiled in the subcutaneous region, or may even on occasion migrate completely around anteriorly and become coiled in the pump pocket. Such migrations usually occur within the first 3 months after implantation.

When CSF leaks occur, they develop outward around the intrathecal catheter, particularly within the first 2 weeks after insertion. The risk of CSF leaks is apparently higher in children with untreated hydrocephalus. These leaks are treated initially with bed rest and pressure dressings. If they persist, external lumbar CSF drains can be inserted percutaneously below the pump catheter for 3 to 5 days of external CSF drainage. In the few cases in which patients do not respond to external drainage, reoperation and insertion of a purse-string suture at the site where the catheter penetrates the dura mater is required.

**Long-Term Care of Individuals With ITB, Troubleshooting, and Side Effects**

When treating spasticity, the initial ITB dose is usually 100 µg/day, a dose twice the amount the child responded to when most screening boluses were given. Dosages are adjusted daily while the patient is hospitalized, often increasing by 5 to 10% a day, then again at the visit for infusion check and suture removal. When treating dystonia, the usual starting dose is 200 to 300 µg/day, depending on the severity of the condition, and the daily increases during hospitalization are often 50 to 100 µg/day.

For children with marked hypertonia, ITB doses are adjusted frequently over the first 2 to 4 months to reach an optimum level of tone control. Most children require dose increases of 10 to 15% to effect meaningful changes in tone; however the individual child’s response to changes and his or her underlying tone should guide subsequent dose adjustments. When there has been no meaningful change in tone after several dose adjustments, malfunction of the delivery system should be considered.

Most children begin infusions in a simple continuous

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mode. After hypertonia has been acceptably reduced generally, fine-tuning of the dose by using complex continuous or flex programming can optimize function, care, or comfort for each individual. Children who require increased lower-extremity tone to support standing or assisted ambulation may benefit from lower doses during the daytime. Boluses given 2 to 3 hours before bathing or dressing may improve comfort and ease of care during these activities of daily living.

The intervals between refills depend on three factors: pump reservoir size, baclofen concentration, and daily dosage. Intervals range from every 3 weeks to every 6 months; refills are recommended at no more than 6-month intervals because of uncertainty about baclofen stability beyond that time. Because stability in concentrations of ITB greater than 2700 \( \mu \)g/ml has been unreliable, we do not advocate use of concentrations higher than those currently commercially available; a 40-ml pump filled with 2000 \( \mu \)g/ml will allow an infusion of 1000 \( \mu \)g/day for almost 3 months. Pumps are refilled percutaneously with a sterile technique by inserting a Huber needle into the pump’s central septum. At each refill, the provider should elicit an interval history, assess tone, and record the amount of baclofen aspirated from the reservoir.

Overdosage of ITB is characterized by hypotonia, decreased alertness, depressed respiration, bradycardia, and coma. Death can ensue in severe overdoses if respiration is not supported. Most incidents of overdose are iatrogenic; a mild overdose may occur after a large dose increase, whereas a severe overdose may result from an error in programming. There have been instances of overdose that are thought to have resulted from a subdural catheter placement; in these cases, it is postulated that the baclofen infuses into the subdural space, then the subdural accumulation is suddenly released into the intrathecal space because of a change in the patient’s position. Baclofen is not neurotoxic, and overdosed patients recover completely if supportive care is given. Although baclofen has a half-life of 4 to 5 hours, a large overdose typically will require 12 hours before improvement is observed. Treatment of an overdose involves turning off the pump temporarily and supporting the patient’s oxygenation and respiration until the drug has been metabolized. For a significant overdose, CSF barbotage can hasten the recovery. If the overdose was not iatrogenically induced, an extensive workup of the ITB delivery system should be done.

Baclofen withdrawal occurs much more commonly than overdosage, and it can be mild to life-threatening.\(^2\) Mild withdrawal is characterized by pruritis (without exanthem), agitation, diaphoresis, and increased tone. In moderate withdrawal, fever, tachycardia, spontaneous clonus, and painful muscle spasms also occur. Severe withdrawal is characterized by a worsening of the preceding symptoms and by seizures, hallucinations, delirium, rhahdomyolysis, and death. Treatment of withdrawal involves administering GABAergic and evaluating the cause. In mild to moderate withdrawal, enteral baclofen may resolve symptoms; dosages depend on the severity of withdrawal symptoms and range from 10 mg three times a day to 30 mg every 4 hours. If the patient cannot absorb enteral baclofen, intravenous benzodiazepines (for example, diazepam) are effective. Rarely, patients require intrathecal injections of baclofen through a lumbar puncture or a lumbar catheter to treat withdrawal effectively. In instances in which withdrawal is suspected, supplemental GABAergics should be administered before and during evaluation for a delivery system malfunction. Patients receiving ITB should have an up-to-date supply of oral baclofen available at all times.

Recognition and evaluation of suspected system malfunctions are among the most challenging aspects of ITB therapy. In many instances, baclofen withdrawal, even in its severe form, has gone undiagnosed, causing extreme discomfort as well as danger to the child. When the history or physical examination suggests withdrawal or there is a lack of effect after substantial dose increases, the system should be thoroughly evaluated. A meaningful bolus (that is, a dose large enough to give unequivocal results) should be given. In most children, this bolus should be from 50 to 150 \( \mu \)g programmed through the pump in the shortest time possible. Over the 3 to 4 hours that the effect is being monitored, anteroposterior and lateral x-ray films of the pump and catheter system should be obtained to rule out any disconnections. It is important that the connection of the catheter to the pump be well visualized; this sometimes requires addition of an oblique view. If there is no response to a meaningful bolus and the x-ray film is negative, then a flow study evaluating the catheter should follow.

Two methods of studying catheter function are available: injection of the pump’s side port with a fluoroscopic contrast agent or instillation of radionuclide into the pump and observation of its progress over real time through the catheter. Fluoroscopic studies may aid in the observation of flow throughout the intrathecal sac and can help define loculations; however, pinhole leaks in the catheter may not be identified because of the laminar flow at high pressure through the device after injection through the side port. Radionuclide studies reveal pinhole leaks more readily but require serial observations over 1 to 4 days to document distribution of the marker in the CSF. The pump roller can be visualized either fluoroscopically or on x-ray films to determine function after a programmed bolus. At times, documenting CSF baclofen levels helps in diagnosing system failures: a CSF baclofen level of zero documents such a failure even though the aforementioned testing may not demonstrate the cause. So-called toxic levels of baclofen in the CSF of an alert patient may indicate a loculated baclofen infusion rather than one that diffuses through the subarachnoid space. If a subdural location of the catheter tip is suspected, a computed tomography myelogram performed at the region of the catheter tip after injection of iohexal into the sideport can be useful (Fig. 1).

Despite a thorough workup for system malfunction, some causes of failure to respond to ITB or continued symptoms of withdrawal are not identified. Some practitioners postulate that tachyphylaxis or tolerance to intrathecal baclofen may develop in children. Although this is theoretically possible, we have seen no children with spasticity in whom tolerance develops. In fact, virtually all children who fail to respond have an undiagnosed system malfunction. We have found that a very useful test to determine the presence of tolerance or of an undiagnosed system malfunction, despite “normal” test results as suggested earlier, is to instill a meaningful baclofen bolus through a lumbar puncture and observe the clinical res-
In most published series, spasticity in the upper extremities has been reported to improve, despite the fact that many of the catheters were positioned at the original T10–12 level. In the multicenter study by Gilmartin, et al., tone decreased in the lower extremities from 3.6 to 1.9, and in the upper extremities from 2.6 to 1.5.

We evaluated the effects of ITB in 37 patients with CP; 25 were functional and 12 were nonfunctional. In the functional group, 19 reported improved upper-extremity function and 10 reported improved ambulation and speech. The effects of ITB on gait were evaluated by Gerszten, et al., who graded ambulation in 24 patients with CP according to four functional levels (community, household, nonfunctional, and nonambulatory). The postoperative ambulation was considered by the authors to be improved by one level in nine patients, unchanged in 12, and worse in three. Interestingly, 20 of the 24 patients or their families thought their gait was better. Krach, et al., evaluated function with the Gross Motor Function Measure 1 year after ITB therapy in 31 patients with CP, and found significant improvements in the mean scores in two groups, those who were ambulatory with assistive devices and those with minimal or no purposeful motor activity.

The effects of ITB on function have not been evaluated in a Level I trial. In 2000, Butler and Campbell reviewed the results of 14 publications about ITB therapy and summarized them by saying that spasticity was improved and function was probably improved. In Level II and III studies, statistically significant improvements have been reported in gait, overall function, self-care, positioning, and ease of care. In our study of the frequency of orthopedic operations after ITB therapy, we suggested that although many patients need one orthopedic operation—often on multiple levels—virtually none require the multiple operations that were so common before spasticity could be controlled pharmacologically.

The effects of ITB on dystonia were reported first by Narayan, et al., in 1991. These authors used ITB effectively to treat an 18-year-old patient with dystonia caused by birth injury. In 1995, Penn, et al., reported that ITB improved focal dystonia in some adults, and in the following year we reported the use of ITB for generalized secondary dystonia in children. In the largest series of patients undergoing ITB therapy for generalized dystonia (86 patients treated with ITB for at least 1 year), dystonia scores had significantly improved at up to 36 months of follow up, ease of care and comfort improved in 85%, and speech and upper-extremity function improved in approximately one third. These results occurred in a population with secondary dystonia, many with Level IV or V status according to the Gross Motor Function Classification System before pump implantation; these are patients who would not have been expected to make functional gains.

A cost/benefit analysis conducted in adults found that treatment with ITB was associated with lower costs over a decade than if the spasticity had been left untreated. No good-quality cost/benefit analysis has been reported in children.

Conclusions

Intrathecal baclofen therapy is the treatment of choice for most children with moderate or severe spastic quadriparesis as well as for those with secondary generalized dystonia. It is far more effective than oral medications, it improves spasticity and dystonia in both the upper and lower extremities, and its effects (and side effects) can be adjusted. In our experience, ITB effectively treats spasticity for at least 17 years, and it is an effective treatment for dystonia for at least 10 years. Multiple studies have contained reports of improved function, but no randomized controlled studies have been done. The complications of ITB therapy are appreciable but the benefits appear to outweigh the complications; nearly all children who come to the end of pump battery life choose to have the pump replaced and the therapy continue. The costs of ITB treatment are also appreciable, both in terms of pump implantation and ongoing refills. Cost/benefit studies are needed.

Disclosure

Dr. Albright is a consultant, grant recipient, and shareholder in Medtronic, Inc.

References


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