Cerebral palsy is the most common motor disorder in children, occurring in 2 to 2.5 per 1000 live births. It is the result of abnormal development of or injury to both gray and white matter within the central nervous system. Most children with CP experience hypertonia with components of spasticity and dystonia. This mixed hypertonicity limits muscle movement around a joint, interferes with voluntary motor movement, and decreases longitudinal muscle growth. As a result, CP commonly interferes with functional mobility, positioning, and self-care.

There are numerous treatment options for the hypertonicity that is characteristic of CP, including physical and occupational therapy, oral medications, baclofen pumps, chemodenervation, tendon lengthening, and dorsal rhizotomy. Chemodenervation is most commonly performed using BTA and has the potential advantages of a relatively focal effect and wide safety margin. Numerous researchers have assessed the safety and efficacy of this intervention by using a wide variety of delivery techniques and outcome assessment scales.

Despite the large body of promising evidence and more than 10 years of use in clinical practice, there are few treatment guidelines for the use of BTA in children. In this article, we will review the evidence for the use of BTA and outline proposed algorithms for management of hypertonicity in children with CP.

**Mechanism of Action for Botulinum Toxin A**

Botulinum toxin A provides a pharmacological neuromuscular blockade that results in temporary muscle paralysis. There are seven botulinum neurotoxin serotypes (A, B, C1, D, E, F, and G), all of which inhibit acetylcholine release at the neuromuscular junction. Both BTA and botulinum toxin E cleave the C terminus of SNAP-25, but BTA has the longest therapeutic effect. There is a lack of consensus as to whether the extended action of BTA is due to persistence of catalytic activity or prolonged blocking action by the cleaved SNAP-25. Cleaved SNAP-25 remains associated with the vesicle-docking protein syntaxin for prolonged periods, suggesting that it plays a continuing role in blocking vesicle fusion. However, this is likely not the only mechanism. The very long duration of effect of BTA results in the formation of temporary sprouts that substitute for the paralyzed nerve terminal. Sprout formation appears to correlate with the wearing off of clinical effect. A longer-term reinnervation of the parent terminal occurs eventually as the sprouts die back. There are two commercially available BTA preparations: Botox and Dysport. Although the exact dose equivalent of these two toxins is not known, a 1:3 ratio of the former to the latter produced the same clinical benefit and caused approximately the same number of side effects, as demonstrated by objective measures.

**Contraindications and Complications for BTA**

Contraindications to the use of BTA are based on theoretical interactions or conditions that could prolong neuromuscular blockade or lead to poor toleration of the proce-
Joint deformity or fixed contracture near the region of injection is a relative contraindication, although it is often difficult to determine the degree to which a contracture is fixed. If there is a fixed contracture or a structural cause for a limitation in ROM, chemodenervation is unlikely to be effective. Having recently received BTA injections is a relative contraindication because early reinnervation increases the risk of developing neutralizing antibodies that render further BTA treatment ineffective. Typically, BTA injections should be separated by at least 3 months to avoid the development of antibodies.

Complications from the use of BTA can be local or systemic. Local complications at the injection site can include pain, edema, erythema, ecchymosis, and short-term hyperesthesia. Systemic reactions can include nausea, fatigue, malaise, other flulike symptoms, and distant rashes. The most common adverse event is excessive weakness. Patients who use increased muscle tone for stability can potentially experience a functional decline following chemodenervation, which is the result of an “unmasking” of weakness. Thus, patients should have adequate compensatory muscle strength before being considered for BTA injections. Systemic weakness is rare in adults, but children are at greater risk because of the higher dose per kg of body weight they receive for therapeutic botulinum toxin injections.

**Effect of Botulinum Toxin on Impairment and Function**

To date, most randomized controlled trials on the effects of botulinum toxin injections have focused on treatment of the lower extremities, including the ankle flexors (gastrocnemius and soleus), knee flexors, and hip adductors in children with spastic diplegia and hemiplegia. Authors examining the effect of BTA in children with CP have assessed outcomes pertaining to a variety of impairments as well as function. The two most common impairments studied are spasticity and limitations in ROM. The level of function has been assessed by observing gait or reviewing the results of motor and functional outcome scales.

**Range of Motion**

Injection of BTA has been demonstrated to improve passive and active ankle dorsiflexion. Baker and colleagues injected BTA into the ankle flexors of 125 children with dynamic equinus spasticity. They found a statistically significant increase in active ROM in all treatment groups (10, 20, or 30 U/kg Dysport) when compared with placebo groups. Passive ROM was significantly improved at the 30 U/kg dose. Similarly, Sätilä and colleagues injected the ankle flexors of 19 children who were divided into groups that received injections at distal and proximal locations. They found that both groups demonstrated improvement from baseline at 3, 6, and 16 weeks posttreatment. Interestingly, several studies that failed to show improvement in passive ROM by using goniometric measures did demonstrate improvement in active ROM during gait assessment. There have been no randomized controlled trials in which the effects of BTA were evaluated after isolated hamstring injections. However, Wissel and colleagues found a significant mean increase in knee ROM (passive 15°, active 20°) after BTA injections in multiple muscle groups, including the hamstrings, hip adductors, and ankle flexors. Mall, et al., performed a double-blind randomized controlled trial of combined BTA injections in the hamstrings and hip adductors of 61 children with CP (39 with leg-dominant tetraparesis and 22 with tetraparesis). They found a statistically significant improvement in knee–ankle distance (hip abduction) when comparing the BTA group with the placebo group. These studies demonstrated that active and passive ROM is typically increased following BTA injection but that variability in response may be due to variation in hypertonicity within the study population.

**Effect of BTA on Spasticity**

The effect of BTA on spasticity in patients with CP has been widely studied. The most commonly used tool to assess spasticity is the modified Ashworth Scale. An important limitation of using spasticity as a clinical endpoint is that it cannot be correlated with functional change. For example, if a given dose of BTA is too great, there can be marked improvement in spasticity but substantial functional decline. Multiple randomized controlled trials have demonstrated reduced modified Ashworth Scale scores after injection of BTA in ankle flexors, hamstrings, and hip adductors. Typically, modified Ashworth Scale scores were reduced by 1 to 2 points from baseline following injection. In most studies the modified Ashworth Scale scores remained below baseline for up to 3 to 4 months after injection, but in one study the scores remained lower for up to 6 months following injection. Spasticity in children with CP also can be measured using the modified Tardieu Scale. This scale has been demonstrated to be more reliable and sensitive to changes following treatment in children with CP when compared with the modified Ashworth Scale. Unfortunately, no researchers who conducted randomized controlled trials in which BTA was evaluated as a treatment for children with CP used modified Tardieu Scale scores as a primary outcome.

**Function and Gait**

Many randomized controlled trials have focused on functional outcomes, including gait assessment. Typical methods of gait assessment include three-dimensional gait analyses, videotaped gait analysis, and the Physician Rating Scale. Koman and colleagues demonstrated improvement in Physician Rating Scale scores in a double-blind randomized controlled trial in which BTA injections were compared with placebo injections in multiple muscle groups in the lower extremities. These benefits were maintained in 41 to 58% of patients in an open-label follow-up study at 2 years. Authors of several studies have used gait analysis to demonstrate improvements in gait following BTA injections in the ankle flexors, hamstrings, and hip adductors. Ubhi and colleagues found a significant improvement in the heel strike of children with CP at 6 and 12 weeks after BTA injections in the ankle.
Botulinum toxin for spasticity in children

flexors compared with those in a placebo group. Wissel, et al.,\(^4\) compared a high dose of BTA (11.62 U/kg of body weight) to a low dose (6.08 U/kg of body weight) in a randomized controlled trial in which gait analysis was used for assessment. The children demonstrated a significant dose-dependent improvement in stride length and velocity after injections to the gastrocnemius, hamstrings, adductors, and rectus femoris. By using ankle kinematics, Corry and colleagues\(^7\) found improvements in ankle dorsiflexion during swing or stance and reduced maximal plantar flexion following BTA injections to the ankle flexors, hamstrings, and adductors. Although the patients in most of these studies already were independent ambulators with or without an assistive device, BTA injections to the heel cords, hamstrings, and adductors improved both kinetic and kinematic gait variables.

**Motor and Function Scales and Disability**

In addition to studying specific impairments or gait kinetic and kinematic data, authors of several trials have examined the effects of BTA therapy by using function and disability scales such as parental questionnaires of functional improvement,\(^11,18,29\) Gross Motor Function Measure,\(^30\) Global Scoring Scale,\(^11\) and Goal Attainment Scale.\(^27\) As shown by survey questionnaires, parents view BTA treatments as significantly improving the functional ability of their children when compared with treatment with a placebo.\(^11,18,29\) However, questionnaires as measurements of outcome provide information on the perception of treatment by children and parents but lack the objectivity and reproducibility of more formal motor function scales. The Gross Motor Function Measure,\(^14,21,30\) Global Attainment Scale,\(^23,34\) and Global Scoring Scale\(^31\) all have been used to demonstrate significant improvements in function after injection of BTA in the ankle flexors, adductors, and hamstrings, but each measurement device has limitations. Although the Gross Motor Function Measure is a widely used tool for assessment of motor performance and has shown good reliability and validity in children with CP,\(^9\) it is of limited benefit in severely affected children.\(^22\) Although the Global Attainment Scale may provide better results for the severely affected children, it remains limited by subjective goal setting and limited generalization to the entire CP population. Scales such as the Global Scoring Scale have been used in limited studies in children with CP but lack reliability and validity for this population. Nevertheless, these scales provide the best objective evidence that children with CP demonstrate improvement in function and reduction of their disabilities after receiving BTA.

**Serial Casts and BTA**

Randomized controlled trials in which the benefits of BTA and the placement of serial casts have been examined include five in which the effects of the interventions separately or in combination were compared.\(^4,7,11,14\) In most studies, injections were given in the ankle flexors (gastrocnemius and soleus muscles), although authors of one study investigated the effect of BTA injections in multiple sites.\(^9\) In two studies, outcomes were compared for placement of serial casts and BTA injections as separate treatments. Corry, et al.,\(^7\) compared BTA injections in the ankle flexors to placement of serial casts and found that the children in the BTA group demonstrated a greater increase in dorsiflexion ROM, greater dorsiflexion in the stance phase of gait, and prolonged improvements in ankle kinematics compared with those in the serial cast group. Both groups demonstrated an increase in the foot contact score of the Physician Rating Scale.\(^7\) Flett, et al.,\(^11\) performed a similar study with patients randomized to groups whose members either received BTA injections in the gastrocnemius or underwent serial casting. They found improvements in scores on the Gross Motor Function Measure, Physician Rating Scale, and modified Ashworth Scale as well as in the ankle ROM in both groups. Although they reported no difference between the two groups in the degree of improvement on outcome measures, 17 of 20 parents preferred BTA injections to serial casting. In three studies, the effects of serial casting combined with BTA were examined. Bottos, et al.,\(^4\) found that BTA in addition to placement of serial casts was superior to BTA alone, and that the group that received both demonstrated more sustained improvements in Gross Motor Function Measure scores, gait speed, and reduction of spasticity. Interestingly, there was no change in ankle kinematics for either group. Kay, et al.,\(^14\) compared the placement of serial casts alone with BTA plus serial casts in children with fixed plantar flexion or equinus contractures at the ankle. They found that both groups showed increased Gross Motor Function Measure scores through 12 months of follow up. Both groups also improved in ROM and peak dorsiflexion during the swing phase of gait, but the group that received both BTA and serial casts showed fewer sustained benefits than the group that received serial casts alone.\(^14\) The researchers concluded that the addition of BTA injection to the placement of serial casts results in an earlier return of dynamic equinus contractures. Desloovere, et al.,\(^9\) compared children who received serial casts for the lower legs prior to BTA injections in multiple lower-extremity muscle groups with those who received the two treatments in the reverse order. They found significant changes in the walking patterns of both groups, with the most significant changes at the ankle joint. Children who received casts after injections demonstrated a slightly more pronounced benefit, mainly in the proximal joints. On balance, BTA and serial casts appear to be equally effective in treating dynamic lower-extremity contractures. Higher parent satisfaction scores are found with BTA, although the combination of both therapies may be slightly more efficacious. Serial casting may be more effective for fixed contractures.

**Effects of Dose and Dilution of BTA**

In their preliminary investigation, Koman, et al.,\(^17\) performed a prospective cohort study to determine the dose needed to produce weakness in the targeted muscle. Improvement was noted in those who received Botox at a dose of 1 to 2 U/kg of body weight for each of the targeted muscles, the improvement lasted 3 to 6 months and the benefits were repeatable. In a subsequent multicenter, open-label clinical trial, they demonstrated benefit without adverse reactions by using a higher dose of Botox (4 U/kg of body weight).\(^16\) Wissel and colleagues\(^40\) performed
a randomized controlled trial in which they compared the effects on spasticity, ROM, and gait analysis in patients who received a high dose of Botox (mean 11.62 U/kg body weight) with those who received a low dose (mean 6.08 U/kg) in the ankle plantar flexors, hamstrings, hip adductors, and rectus femoris. They found that both groups improved on all measures, with the high-dose group showing greater improvement in gait speed and stride length. Baker and colleagues studied the safety and efficacy of three doses of Dysport (10, 20, and 30 U/kg of body weight) on the dynamic component of gastrocnemius length during gait. They found that all doses resulted in improvement compared with a placebo, with the group that received the 20 U/kg dose demonstrating the greatest effect relative to groups receiving other doses. The beneficial effects were still present at a follow up at 4 months.

To be injected, BTA must be reconstituted in preservative-free saline. Therefore, the effect of dilution of toxin must be considered when planning BTA injections. In a single-blinded study, Lee and colleagues examined the effects of high-volume (4 ml) compared with low-volume (1 ml) BTA injections on patients with lower-extremity spasticity by using a fixed dose of 100 U of Botox (3–6 U/kg) injected in the gastrocnemius muscle. Spasticity was reduced in both lower extremities; however, dilution was not correlated to reduction in spasticity or change in ROM. The high-volume preparation did not cause greater pain or any change in adverse events. Both dilutions appeared to be a safe method of delivery for BTA. No study has addressed the effect of dilution on injections in proximal lower-extremity muscles.

**Practical Use of Botulinum Toxin Injections in Children Who Have CP**

The Cerebral Palsy Center at Washington University in St. Louis uses a multidisciplinary treatment approach that is coordinated by a pediatric neurologist and includes neurosurgeons, orthopedic surgeons, orthotists, physical and occupational therapists, and staff members from the botulinum toxin clinic (Fig. 1). Before treatment, the pediatric neurologist defines the objectives of treatment with the parents and the child. Common treatment goals include improved gait and balance, facilitation of patient care (for example, diapering), increased comfort with therapy, improved tolerance of bracing, and prevention of musculoskeletal complications. Baseline scores on the Gross Motor Function Measure and modified Ashworth Scale as well as a determination of ROM by using the modified Tardieu Scale are obtained in all patients. This is done to permit an assessment of treatment results that is as objective as possible. For the modified Tardieu Scale, we measure R1 as the first “catch” in a spastic limb and R2 as the passive end ROM. Treatment decisions also are predicated on an assessment of all children that is based on a review of their videotaped gait, their progress in physical therapy, and formal gait analysis where appropriate.

**Injection Procedure**

Each patient is evaluated in our botulinum toxin clinic by a pediatric physical therapist and a physician. Goals developed by the pediatric neurologist and therapists are reviewed, and the patient's gait and ROM are reassessed. The patient's body weight must be obtained before each pediatric botulinum toxin injection to prevent systemic toxicity from overdosing. We do not use oral sedatives or anesthesia because we feel that this prolongs the procedure and exposes the child to additional risks. A child life specialist provides distraction (such as toys, music, and games) during the procedure and rewards afterwards. We have found this technique to be superior to both sedatives and topical anesthesia. When they are not sedated, most school-age children return to class the same day.

**Treatment Algorithms**

Although the Gross Motor Function Measure provides a useful research scale for quantifying each child’s functional status, we find it more practical to plan treatment algorithms based on a child’s presenting complaint and primary clinical goal. The three primary complaints we encounter in children with lower extremities affected by CP include toe walking (excessive ankle–plantar flexion), crouched gait (dynamic knee contracture with excessive knee flexion), and scissoring (excessive adductor tone).

**Toe Walking.** Although children who manifest toe walking generally have excessive plantar flexion tone, hamstring tone also can contribute to the condition. The selection of the muscle groups to be injected is somewhat empirical, and we use modified Tardieu Scale results and our assessment of the gait pattern to guide our selection. We try to distinguish spasticity from dystonia, although they commonly coexist. We consider children with excessive plantar flexion who demonstrate normal ROM and mild spasticity (modified Ashworth Scale Score 1, modified Tardieu Scale R2 > 10˚) to have hypertonicity primarily due to dystonia. These children typically receive sufficient benefit from BTA and physical therapy. Children with more prominent spasticity (modified Ashworth Scale Scores 2–4, modified Tardieu Scale R2 < 10˚) may receive...
Botulinum toxin for spasticity in children

orthotic devices in addition to BTA. Although we routinely evaluate patients’ conditions by using both the modified Ashworth Scale and the modified Tardieu Scale, we prefer using the latter for the basis of treatment decisions because the test–retest reliability is significantly higher. Measurements for the modified Tardieu Scale are obtained in both the knee flexed (soleus) and knee extended (gastrocnemius) positions by using a handheld goniometer with the patient lying prone. In general, measurements taken in the knee-extended position dictate the treatment plan. If the R2 on the modified Tardieu scale fails to reach neutral (R2 < 0°), the child is referred for serial casting after BTA therapy (Fig. 2).

Initial injection sites are divided between the ankle flexors (gastrocnemius and soleus). The gastrocnemius is injected in four locations: a proximal and distal injection in both the medial and lateral heads of the gastrocnemius muscle. The soleus is injected in two locations, with the first site just distal to the belly of the medial gastrocnemius and the second site 1 to 2 cm distal along the length of the muscle. We typically start with Botox at 5 U/kg of body weight for each heel cord. If the response is inadequate as determined by a failure to achieve predefined treatment goals, we typically increase the dose to 10 U/kg for each heel cord with a maximum total body dose of 20 U/kg. Although no randomized controlled trials have used this dose for children with CP, we have seen patients who received injections at this dosage more than 250 times and have seen no evidence of systemic toxicity. Patients are injected with a maximum of 50 U per site and must wait a minimum of 3 months between BTA treatments.

Crouched Gait. Patients who present with dynamic knee contracture usually have a crouched gait, although not such children are ambulatory. Like children who exhibit toe walking, children who have hypertonicity primarily caused by dystonia are also treated with BTA and physical therapy (Fig. 3). On the basis of modified Tardieu Scale criteria, the condition of patients for whom the majority of their hypertonicity is secondary to spasticity is classified into mild, moderate, or severe categories. Modified Tardieu Scale measurements are obtained with a handheld goniometer while the child lies supine with the hip flexed at 90° (90/90 position), and then the leg is fully extended (terminal knee extension). In the 90/90 position, the knee is extended to R1 (first catch) and R2 (end range). Patients who have mildly increased tone (modified Tardieu Scale R2 > –25) are treated with physical therapy and knee immobilizers. Patients who have moderately increased tone (modified Tardieu Scale R2 –25 to –40) are considered candidates for BTA injections, knee immobilizers, and physical therapy. Patients who have severely increased tone (modified Tardieu Scale R2 < –40) who are unable to reach a neutral position (R2 < 0) in terminal knee extension are referred for Ultraflex splints (Ultraflex Systems, Inc., Pottstown, PA) in addition to BTA and physical therapy.

For patients who have crouched gait and are considered appropriate candidates for BTA injections, we begin treatment with injections in the hamstring. Injections are distributed every 1 to 2 cm along the length of the medial hamstrings, with up to 50 U injected at each site. The starting dose is Botox at 7.5 to 10 U/kg of body weight for each extremity, with a maximum total dose of 20 U/kg. Given the size of these muscles, BTA is diluted in 2 ml preservative-free normal saline for greater spread in the injected muscle. Patients who respond well to BTA are generally re.injected every 3 to 6 months. Patients who have no response are considered candidates for surgical release.

Scissoring. In patients who experience scissoring (excessive adductor tone), hypertonicity is categorized according to the clinician’s interpretation of movements. Patients who have prominent dystonia (nearly normal ROM on the modified Tardieu Scale) are treated with BTA and physical therapy. Patients primarily demonstrating spasticity (reduced ROM as shown by modified Tardieu Scale) are divided into categories of mild, moderate, or severe on the basis of modified Tardieu Scale criteria. Each child’s adductor ROM is measured using a handheld goniometer while the patient lies supine with the knee flexed and then extended. Patients suffering from moderate or severe spasticity are considered candidates for adductor BTA injection and physical therapy in addition to orthotic interventions. Patients experiencing moderately increased tone and hip dislocation and all patients who have severely increased tone receive Ultraflex splints, physical therapy, and BTA injections (Fig. 4). Adductor muscles are injected starting approximately 1 to 2 cm below the pubis symphysis and extending about two thirds of the distance along a line drawn to the medial epicondyle. The initial
dose is Botox at 5 to 10 U/kg of body weight in each extremity, with a maximum total dose of 20 U/kg. The BTA is diluted into 2 ml preservative-free normal saline for these injections, and no more than 50 U is injected at each site. Just as with those who have crouched gait, children with a good response receive injections every 3 to 6 months. Patients who fail to respond are referred for possible surgical intervention.

Evaluation of Treatment Response

All patients are scheduled for a 1-month follow-up visit. At this visit, physical therapists use repeated modified Tardieu Scale measurements, a modified Ashworth Scale, and the Gross Motor Function Measure to assess the effects of BTA at the time of peak benefit. Clinical goals are reviewed and updated with the parents. Patients who have a good response to BTA continue therapy with repeated injections on a 3- to 6-month injection schedule. Patients who do not are reassessed by the pediatric neurologist and may be referred for surgical intervention.

Conclusions

Injection of BTA alone or in conjunction with serial casting can result in positive outcomes for appropriate candidates. Authors of randomized controlled trials have demonstrated that BTA injections in the ankle flexors, hamstrings, and adductors result in improved passive and active ROM and spasticity. Improvements in gait and function after BTA therapy have been demonstrated in other randomized controlled trials, but the sensitivity of current outcome measures to clinically meaningful changes in function remains unclear. Doses of Botox in the range of 1 to 11 U/kg of body weight appear safe and effective in dilutions from 1 to 4 ml, but the optimal form of dose and dilution is unknown. Similarly, BTA appears equally as effective as the placement of serial casts for treatment of dynamic contractures, and the combination may be beneficial for a subset of patients. Although considerable progress has been made in the understanding of clinical benefits for BTA in children with CP, many unknown variables remain, including the following: 1) the selection of patients most likely to benefit from therapy; 2) the effect of larger doses of toxin on clinical outcomes; 3) the long-term efficacy of botulinum toxin therapy; 4) the long-term benefits of botulinum toxin therapy; 5) the relative advantages or disadvantages of therapy with botulinum toxin compared with surgical therapies; 6) the appropriate duration of therapy; and 7) the effect of early therapy on degenerative changes in soft tissues and joints in adult patients who have CP.

References


Fig. 4. Schematic diagram showing a treatment algorithm for patients who experience scissoring (excessive adductor tone).
Botulinum toxin for spasticity in children


This work was supported by NIH Grant Nos. K23NS43351 and R21HD048972 and a fellowship training grant from Allergan. Address reprint requests to: Brad A. Racette, M.D, Washington University School of Medicine, 660 South Euclid Ave, Box 8111, St. Louis, MO 63110. email: racetteb@neuro.wustl.edu.