

# PEDIATRIC PHARMACOTHERAPY

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## Clinical Applications for Botulinum Toxin Type A in Pediatric Patients

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While much attention has been paid to the cosmetic application of botulinum toxin type A recently, there are a number of other valuable uses for this agent. In both children and adults, botulinum toxin has been used to treat a wide range of muscular and autonomic disorders.<sup>1,2</sup> This issue of *Pediatric Pharmacotherapy* will review the uses of botulinum toxin type A in pediatrics, focusing on its use in children with cerebral palsy.

### Mechanism of Action

Botulinum toxins are produced by the bacterium *Clostridium botulinum*. There are seven distinct botulinum toxin serotypes (A through G). Of these, only A and B are commercially available. Most of the research conducted to date with botulinum toxin in children has involved the A serotype. Botulinum toxin type A blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting release of acetylcholine (ACh). The mechanism for this inhibition involves cleavage of SNAP-25, a protein necessary for the release of ACh from vesicles within nerve endings. The resulting effect of this partial chemical denervation is a localized paralysis, typically lasting 3 to 6 months.<sup>1-4</sup>

### Indications

Botulinum toxin type A (Botox®; Allergan) is currently approved by the Food and Drug Administration for the treatment of cervical dystonia in patients ≥ 16 years of age and the treatment blepharospasm (focal dystonia of the orbicularis oculi muscles) or strabismus in patients ≥ 12 years of age. A separate product, Botox Cosmetic®, is indicated for improvement in the appearance of glabellar lines.<sup>4</sup>

### Additional Uses

#### *Spasticity in Children with Cerebral Palsy*

Since its introduction in 1989, botulinum toxin type A has been used in a variety of clinical

settings. One of the most well-studied is the treatment of spasticity in children with cerebral palsy.<sup>1,5-12</sup> Spasticity can result in an imbalance in tone between agonist and antagonist muscles, interfering with their function and possibly leading to the development of fixed contractures. Selective destruction of muscle, by injection of alcohol or phenol, has been used for several decades to provide pain relief and delay the need for surgical intervention in these patients. Complications from these agents, including muscle damage and fibrosis, have led to the use of botulinum toxin type A.

The most frequent sites for administration of botulinum toxin type A in children with spasticity are the lower extremities. Injections are often given into the gastrocnemius-soleus muscle complex to improve walking in children with equinus gait, but may also be given into the hip adductors and hamstrings to improve positioning in nonambulatory children.<sup>11</sup>

Over a dozen studies, including seven randomized, double-blind, placebo-controlled trials, have documented the beneficial effects of botulinum toxin type A on lower limb spasticity.<sup>5-12</sup> In 2000, Koman and colleagues conducted the largest trial to date in the United States, enrolling 114 children (2 to 16 years of age) with spasticity resulting in dynamic equinus foot deformity.<sup>5</sup> Patients were randomized to receive either 4 units/kg botulinum toxin type A (Botox®) or placebo injected into the proximal one third of the gastrocnemius muscle. Injections were performed after baseline assessment and again at 4 weeks, if indicated. At 3 months, patients receiving botulinum toxin had significant improvement in gait function and range of motion.

Last year, Baker and colleagues, representing a multicenter European study group, published a dose-ranging study of 125 patients, ages 2 to 9 years, randomized to receive either botulinum

toxin type A (Dysport®) in doses of either 10, 20, or 30 units/kg or placebo injected into the gastrocnemius muscle of both legs.<sup>9</sup> Units of Dysport®, a product not available in the United States, are not considered equivalent to units of Botox®. At 4 weeks, clinically and statistically significant improvements were seen in all of the botulinum-treated groups. Mean improvement in the dynamic component of gastrocnemius shortening was most pronounced in the 20 units/kg group. Benefit in this group was maintained at 16 weeks. Increases in active gastrocnemius length were significantly greater than placebo in the 20 and 30 units/kg groups, but not in the 10 units/kg group. Although subjective evaluations by investigators and parents in all the botulinum toxin groups were favorable, in only the 20 and 30 units/kg groups were the evaluations statistically different than for children receiving placebo. Based on their results, the authors concluded that botulinum toxin type A is a safe and effective treatment in children with lower limb spasticity.

In 2001, Koman and colleagues published a larger, open-label trial of botulinum toxin type A in children with lower limb spasticity.<sup>10</sup> In this prospective multicenter trial, 207 children (mean age 5.6±2.8 years) were treated with 4 units/kg botulinum toxin type A (Botox®), up to a maximum of 200 units, every three months as needed. Seventy-five percent of the patients completed at least one year of evaluation. Dynamic gait pattern improved in 46% of the patients by the first follow-up visit and continued to show improvement at subsequent visits. The most common adverse effects reported were stumbling, leg cramps, leg weakness, and calf atrophy. No serious treatment-related adverse effects were reported.

Based on these studies and others, the use of botulinum toxin type A in children with spasticity has become an accepted addition to standard antispasmodic medications and physical and/or occupational therapy. In the February 2001 issue of the *Journal of Child Neurology*, Gormley and colleagues reviewed the cases of 270 children with spasticity or dystonia treated with botulinum toxin type A (Botox®) over a two year period at their three centers.<sup>11</sup> The average age of the patients at the time of their first injection was 6.2 years, with a range from 1.3 to 17.9 years. The average dose administered by each institution ranged from 7.7 to 10.8 units/kg, with a total amount per visit ranging from 154 to 205 units. The average length of time between injections ranged from 134 to 199 days among the centers. From this assessment of their clinical practice, the authors identified a trend

towards initiation of therapy at younger ages and with higher doses over the review period, reflecting a desire to maximize motor movement during early life.

In addition to decreasing lower limb spasticity, botulinum toxin type A has been shown to improve upper extremity function in children with hemiplegic cerebral palsy. Fehlings and colleagues of the Hospital for Sick Children in Toronto conducted a randomized, single-blind trial of botulinum toxin type A (Botox®) plus occupational therapy versus occupational therapy alone in 30 children ages 2.5 to 10 years.<sup>12</sup> Patients randomized to the botulinum toxin group received 2 to 6 units/kg into at least 1 of 3 muscle groups (biceps, forearm muscles, or the adductor pollicis muscle). Assessments were made at 1, 3, and 6 months. Twenty-nine children completed the study. Scores on the Quality of Upper Extremity Skills Test (QUEST) and self-care testing showed significantly greater improvement in the botulinum toxin-treated patients. Parents of the patients in this group also reported positive changes in their children's self-care skills.

#### *Other Pediatric Uses*

Children and adults with neuropathic bladders may also benefit from botulinum toxin type A injections. In a study of 17 children with myelomeningocele (average age 10 years), Schulte-Baukloh and colleagues studied the efficacy of a dose of 85 to 300 units botulinum toxin type A (Botox®), divided and given into 30 to 40 sites in the detrusor muscle to improve bladder compliance.<sup>13</sup> Urodynamic studies showed a 112.1% increase in mean reflex volume (from 95.00±34.54 to 201.45±68.57 ml). Maximal bladder capacity increased by 56.5%, from an average of 137.53±59.96 to 215.25±96.36 ml. Maximal detrusor pressure decreased by 32.6%, and detrusor compliance increased by 121.6%. The authors suggested that this technique may offer an alternative to long-term anticholinergic therapy.

Botulinum toxin has also been used in a variety of muscular disorders of the gastrointestinal tract. Doses of 80 to 100 units of botulinum toxin type A have been used to relieve achalasia, a disorder of increased lower esophageal sphincter tone, in pediatric patients.<sup>14</sup> In children with Hirschsprung's disease, botulinum toxin has been used to relieve internal anal sphincter hypertonicity. In 2000, Minkes and Langer reported the results of a prospective study of 18 children (ages 1-13 years) who were given 15 to 60 units of botulinum toxin type A (Botox®), divided and injected into the four

quadrants of the sphincter.<sup>15</sup> Four patients had no improvement in bowel function, two had temporary improvement (lasting less than one month), seven had improvement lasting up to 6 months, and five had improvement lasting over 6 months. No adverse effects were noted.

At the neuroglandular junction, botulinum toxin can produce a blockade of abnormal autonomic function. This blockade has been successful in the treatment of several autonomic disorders, including palmar hyperhidrosis and hyperlacrimation. In children with cerebral palsy and other neurologic impairments, botulinum toxin type A has been studied as a treatment for drooling.<sup>16-18</sup> In an open-label, dose-escalation study of 22 children (ages 8-21 years) with cerebral palsy, Suskind and Tilton found a clinical benefit from botulinum toxin.<sup>17</sup> The first 12 patients were randomized to receive a dose of either 10, 20, or 30 units of botulinum toxin type A (Botox<sup>®</sup>) into the submandibular gland. The second group (10 patients) received injections of 30 units into the submandibular gland and either 20, 30, or 40 units into the parotid gland. Objective assessment of drooling (saturation of dental rolls) as well as subjective assessments were favorable. No adverse effects on swallowing or other complications were reported.

Other uses of botulinum toxin type A include treatment of nystagmus, laryngeal dystonia or spasmodic dysphonia, severe bruxism, muscle spasms and cramps, as well as migraine headaches and myofascial pain.<sup>2</sup>

#### Drug Interactions

Concurrent use of botulinum toxin and other drugs that affect neuromuscular function may produce additive effects. Aminoglycosides and neuromuscular blocking agents (eg, curare-like compounds such as pancuronium, vecuronium, or rocuronium) may potentiate the weakness produced by botulinum toxin.<sup>3,4</sup>

#### Adverse Effects

The most commonly reported adverse effects with botulinum toxin are excessive weakness of the target muscle or adjacent muscles and local reactions such as tenderness or pain. In patients with cervical dystonia, other frequently observed adverse effects include dysphagia (in 19% of patients) with or without dyspnea, respiratory tract infections (12%), and headache (11%). In patients receiving treatment for blepharospasm, ptosis has been the most commonly reported adverse effect, occurring in 20% of patients, followed by keratitis or eye dryness in 6.3%. In patients receiving treatment for strabismus, the

most common adverse effects are ptosis or vertical eye deviation (0.3 to 18% depending on dose and injection site). Rare, but serious, adverse effects reported after botulinum toxin injection consist of hypersensitivity reactions (including anaphylaxis), pneumonia, arrhythmias, and myocardial infarction.<sup>3,4</sup>

The use of botulinum toxin type A for spasticity appears to be well tolerated. Bakheit and colleagues found a 7% overall incidence of adverse effects in a retrospective review of 758 children with spastic cerebral palsy who were treated with 1,594 doses of botulinum toxin type A (Dysport<sup>®</sup>).<sup>19</sup> Focal muscle weakness was the most frequently reported adverse effect, followed by urinary incontinence. Both occurred in approximately 1% of patients. Less common adverse effects included pain at the injection site, fatigue, somnolence, influenza-like symptoms, fever, and rash. In another retrospective analysis, Mohamed and colleagues reported 21 adverse effects in 37 children given 143 injections of botulinum toxin type A (Dysport<sup>®</sup>) for spasticity.<sup>20</sup> The most commonly observed adverse effects were weakness, dysphagia, worsening strabismus, and urinary incontinence.

In addition to these adverse effects, one of the concerns with repeated administration of botulinum toxin is the development of neutralizing antibodies that may reduce effectiveness. In studies of adults receiving multiple injections for cervical dystonia, 2% of patients were found to have a positive assay for neutralizing antibody.<sup>4</sup> In the open-label trial by Koman, 6% of the children had detectable neutralizing antibody and subsequent treatment failure.<sup>10</sup> Because of difficulties in performing the assay and interpretation of the results, the clinical significance and relative risks associated with antibody development to botulinum toxin are not yet well understood. To minimize the potential for antibody development, it is recommended that no more than 12 units/kg or 400 units (whichever is smaller) be administered at one time and that there be a minimum interval of 3 months between treatments.<sup>1,2</sup>

#### Administration

Botulinum toxin should only be administered by a physician knowledgeable of the anatomy and function of the affected muscles. Dose selection is determined by the indication. In children with spasticity associated with cerebral palsy, a dose of 2 to 10 units/kg is recommended per target muscle, with a maximum of 400 units.

Botulinum toxin type A (Botox®) is available in vials containing 100 units of neurotoxin, 0.5 mg albumin, and 0.9 mg sodium chloride. The powder should be reconstituted with preservative-free sodium chloride to make a dilution ranging between 1.25 unit/0.1 ml to 10 units/0.1 ml. The powder should remain frozen until reconstituted, after which the solution should be refrigerated until use. The reconstituted product should be used within 4 hours. Solutions that are discolored or contain particulate matter should be discarded.<sup>3,4</sup>

### Cost

According to the current issue of the Drug Topics Red Book, the average wholesale price for a 100 unit vial of Botox® is \$490.00.

### Summary

Botulinum toxin type A has a number of uses in the pediatric population. The greatest experience to date has been in the treatment of spasticity in children with cerebral palsy. While more experience is needed to further refine dosing strategies and identify any long-term complications, initial research with this drug in children has been promising.

### References

1. Edgar TS. Clinical utility of botulinum toxin in the treatment of cerebral palsy: comprehensive review. *J Child Neurol* 2001;16:37-46.
2. Verheyden J, Blitzer A, Brin MF. Other noncosmetic uses of BOTOX. *Sem Cutaneous Med Surg* 2001;20(2):121-6.
3. Burnham TH, ed. *Drug Facts and Comparisons*. 2003. St. Louis: Facts and Comparisons, Inc.:1122a-b.
4. Botox® product information. Allergan, Inc. Dec. 2000. Available at [www.botox.com/index.jsp?cc&prescribing-botox](http://www.botox.com/index.jsp?cc&prescribing-botox)
5. Koman LA, Mooney JF, Smith BP, et al. Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. *J Pediatr Orthop* 2000;20:108-15.
6. Ubhi T, Bhakta BB, Ives HL, et al. Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. *Arch Dis Child* 2000;83:481-7.
7. Suputtitida A. Managing spasticity in pediatric cerebral palsy using a very low dose of botulinum toxin type A: preliminary report. *Am J Phys Med Rehabil* 2000;79:320-6.
8. Polak F, Morton R, Ward C, et al. Double-blind comparison study of two doses of botulinum toxin A injected into the calf muscles in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2002;44:551-5.
9. Baker R, Jasinski M, Maciag-Tymecka I, et al. Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study. *Dev Med Child Neurol* 2002;44:666-75.
10. Koman LA, Brashear A, Rosenfeld S, et al. Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics* 2001;108:1062-71.
11. Gormley ME, Gaebler-Spira D, Delgado MR. Use of botulinum toxin type A in pediatric patients with cerebral palsy: a three-center retrospective chart review. *J Child Neurol* 2001;16:113-8.

12. Fehlings D, Rang M, Glazier J, et al. An evaluation of botulinum-A toxin injections to improve upper extremity function in children with cerebral palsy. *J Pediatr* 2000;137:331-7.

13. Schulte-Baukloh H, Michael T, Schobert J, et al. Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *Urology* 2002;59:325-8.

14. Hurwitz M, Bahar RJ, Ament ME, et al. Evaluation of the use of botulinum toxin in children with achalasia. *J Pediatr Gastroenterol Nutr* 2000;30:509-14.

15. Minkes RK, Langer JC. A prospective study of botulinum toxin for internal anal sphincter hypertonicity in children with Hirschsprung's disease. *J Pediatr Surg* 2000;35:1733-6.

16. Jongerius PH, Rotteveel JJ, van den Hoogen F, et al. Botulinum toxin A: a new option for treatment of drooling in children with cerebral palsy. *Eur J Pediatr* 2001;160:509-12.

17. Suskind DL, Tilton A. Clinical study of botulinum-A toxin in the treatment of sialorrhea in children with cerebral palsy. *Laryngoscope* 2002;112:73-81.

18. Bothwell JE, Clarke K, Dooley JM, et al. Botulinum toxin A as a treatment for excessive drooling in children. *Pediatr Neurol* 2002;27:18-22.

19. Bakheit AMO, Severa S, Cosgrove A, et al. Safety profile and efficacy of botulinum toxin A (Dysport) in children with muscle spasticity. *Dev Med Child Neurol* 2001;43:234-8.

20. Blair E. Adverse events following repeated injections with botulinum toxin A in children with spasticity. *Dev Med Child Neurol* 2001;43:791-2.

### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/28/03:

1. The bile acid sequestrants were reviewed. Cholestyramine light (generic) was added to the Formulary and colestipol was removed.
2. Intravenous liothyronine (Triostat®) was added to the Formulary for supplementation in children undergoing complex cardiac surgery.
3. Ezetimibe (Zetia®) was added for the management of hypercholesterolemia in patients intolerant of or with an inadequate response to HMG-CoA reductase inhibitors. It is currently approved for inpatient use. Availability for outpatients will be determined at a later date.
4. Lactulose powder for oral solution (Kristalose®) was added to the Formulary.
5. Pediarix®, a combination of diphtheria-tetanus-acellular pertussis, hepatitis B, and inactivated polio vaccines, was added to the Formulary for routine childhood immunization.
6. Adefovir dipivoxil (Hepsera®) was added for the treatment of hepatitis B.
7. Tirofiban was deleted.

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