Original Article

Safety of High-Dose Botulinum Toxin Type A Therapy for the Treatment of Pediatric Spasticity

Edward M. Goldstein, MD

ABSTRACT

This retrospective chart review examines the safety of high-dose (≥ 15 U/kg body weight or ≥ 800 total units) botulinum toxin type A (BOTOX, Allergan Inc., Irvine, CA) in children and young adults with spasticity. Ninety-four children weighing < 45 kg received a mean total dose of 334.1 U or 19.1 U/kg. Fourteen young adults weighing ≥ 45 kg received a mean total dose of 927.3 U or 15.2 U/kg. Adverse events were reported by 3 of the 108 patients (2.8%) and included single instances of rash and enuresis. The only serious adverse event consisted of mild, generalized botulism in a 13-year-old patient who received a 23 U/kg dose to the hamstrings and gastrocnemius/soleus bilaterally. No serious adverse events were noted in children weighing < 45 kg who received botulinum toxin type A doses of 15 to 22 U/kg of body weight or in young adults ≥ 45 kg who received total doses of 800 to 1200 U in a single injection protocol. High-dose botulinum toxin type A is safe for the treatment of spasticity in children and young adults. (*J Child Neurol* 2006;21:189–192; DOI 10.2310/7010.2006.00041).

Botulinum toxin type A is a naturally occurring neurotoxin that has been used therapeutically since the late 1970s.[1] When injected into muscles, botulinum toxin type A inhibits the release of acetylcholine at the neuromuscular junction, thereby reducing muscle contraction.[2] Over the past decade, botulinum toxin type A has become an increasingly popular treatment for pediatric spasticity and has been the subject of numerous clinical studies and review articles.[3–5]

In combination with appropriate rehabilitative therapies, botulinum toxin type A injections into specific spastic muscle groups have been found to reduce tone, increase range of motion, improve gait, and decrease pain in children with spasticity.[6–10] Botulinum toxin type A injections are typically well tolerated in this population. If adverse events do occur, they tend to be expected consequences of muscle relaxation, such as leg weakness or falls, which can occur as patients learn to readjust their postural control in response to altered muscle tone.[8,11]

As confidence with botulinum toxin type A has grown over the years, physicians have tended to use increasingly higher doses. Dose escalation of botulinum toxin type A proceeded cautiously through the 1990s on the basis of studies indicating a median lethal dose in subhuman primates of 39 U/kg of body weight.[12] In an effort to invoke a large safety factor, pilot studies in the early 1990s employed doses of 1 to 2 U/kg of body weight for children with spasticity.[13] However, by the late 1990s, dose recommendations had reached the range of 12 to 16 U/kg of body weight.[14–16] These dose increases have involved not only more botulinum toxin type A per injected muscle but also the injection of multiple muscle groups.

With increasing the dose of any drug comes an increased potential for adverse effects. However, few published studies have addressed the safety of high-dose botulinum toxin type A in the pediatric population. Therefore, the present retrospective

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From Child Neurology Associates, Children's Healthcare of Atlanta at Scottish Rite Children's Medical Center, Marcus Institute Division of Child Neurology, Atlanta, GA.

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Address correspondence to Dr Edward M. Goldstein, Child Neurology Associates, 5505 Peachtree-Dunwoody Road, Suite 500, Atlanta, GA 30342. Tel: 404-256-3535; fax: 404-847-9596; e-mail: egoldstein@child-

Table 1. Botulinum Toxin Type A Dosages Injected per Functional Muscle Group (Unilateral)

Functional Muscle Group	*Dose (U/kg)*	*Number of Injections*
Hip adductors	4–6	8–10
Knee flexors	4–6	8–10
Plantar flexors	4	8–10
Foot inverters	2	2–3
Shoulder adductors	3	6–8
Elbow flexors	2–3	8–10
Forearm pronators	2	4–6
Wrist flexors	2–3	8–10
Finger flexors	2–3	8–10
Thumb flexors	2	4–6
Thumb adductors	1	2–3

Table 2. Standardized Questions Asked at Follow-Up Visits 2 to 3 Months After Completion of Botulinum Toxin Type A Injections

Were these injections associated with the onset of…
Pain?
Infection?
Bleeding?
Cool feeling?
Flu-like symptoms?
Rash?
Allergic reaction?
Bladder or bowel problems?
Falls?
Weakness?
Fatigue?
Droopy eyelids?
Change in eye movements?
Double vision?
Difficulty swallowing?
Change in voice?
Constipation?
Other concerns?

study was undertaken to assess the safety of high-dose botulinum toxin type A therapy when treating children with spasticity.

METHODS

This was a retrospective review of charts from children who were treated with high-dose botulinum toxin type A (BOTOX, Allergan, Inc., Irvine, CA) for spasticity at Child Neurology Associates, PC, in Atlanta, Georgia, between 1998 and 2000. High-dose was defined as ≥ 15 U/kg body weight or ≥ 800 total units of botulinum toxin type A in a single injection protocol. It is important to note that all doses in this article refer to the botulinum toxin type A product from Allergan (ie, BOTOX). Doses of other botulinum neurotoxin products are not equivalent, and dose confusion could result in serious adverse consequences. Further, BOTOX is not approved by the US Food and Drug Administration for the treatment of spasticity.

Patients received injections of botulinum toxin type A into the upper and/or lower limb muscles under general inhalant anesthesia. General anesthesia was used to minimize the discomfort associated with performing multiple intramuscular injections. The muscles injected were determined by the investigator based on the patient's presenting pattern of spasticity. Doses injected into each functional muscle group are provided in Table 1. All doses were administered at a concentration of 100 U/mL, and multiple injections were administered into each muscle (maximum dose of 50 U per injection site). Injections were performed using electromyographic guidance or electrical stimulation as appropriate for the muscle group. Informed consent was obtained prior to all injection protocols and included a thorough discussion of the potential side effects of botulinum toxin type A.

Following injections, the muscles were massaged and subjected to range of motion exercise. Patients were observed for 2 hours postinjection to evaluate possible adverse events. On discharge from the day surgery area, patients were instructed to contact the investigator directly by telephone with concerns regarding possible side effects. Patients and their caregivers returned 2 to 3 months following each injection protocol to answer a standardized series of questions regarding the potential side effects of botulinum toxin type A (Table 2). Patients and caregivers were specifically queried about the following: pain, infection, bleeding, cool feeling, flulike symptoms, rash, allergic reaction, incontinence, weakness, fatigue, falls, ptosis, diplopia, dysphagia, dysphonia, constipation, or other concerns.

The patients' charts were reviewed for date of birth, weight, diagnosis, date of injection protocol(s), muscle groups injected, botulinum toxin type A dose per limb, total botulinum toxin type A dose, and adverse events. Analysis of dosage was stratified by patient weights into subgroups of children < 45 kg and young adults ≥ 45 kg. Although the young adult patients received high total botulinum toxin type A doses, their per kilogram doses might be relatively low owing to their body weight. This stratification avoided a dilutional effect on the per kilogram dose figures for children weighing < 45 kg.

RESULTS

One hundred nineteen charts were identified from patients who received high-dose botulinum toxin type A injections at our practice between 1998 and 2000. Of these 119 charts, 11 were excluded owing to a lack of follow-up. Apart from their failure to return, nothing unique was evident about these excluded patients. Thus, charts from 108 patients were included in the analysis, with ages ranging from 0 to 19 years (median 5 years). Ninety-four children (87%) weighed less than 45 kg, and 14 young adults (13%) weighed 45 kg or more. Most of the patients (84 of 108; 78%) were diagnosed with cerebral palsy, with the next most common diagnosis being traumatic brain injury (16 of 108; 15%), followed by hypoxic-ischemic encephalopathy (3 of 108; 3%), mitochondrial encephalomyopathy (2 of 108; 2%), stroke (1 of 108; 1%), progressive spastic paraparesis (1 of 108; 1%), and arteriovenous malformation (1 of 108; 1%).

Patients received a total of 209 injection protocols, with a median of 2 per patient (range 1 to 7) at a median interval of 5 months. Fifty-three patients (49%) received injections into the lower extremities, 17 patients (16%) received injections into the upper extremities, and 38 patients (35%) received injections into both the upper and lower extremities.

The 94 children who weighed < 45 kg received a total of 187 injection protocols. The mean total botulinum toxin type A dose for these patients was 334.1 U (± 132.5 U standard deviation [SD]), with a range from 160 to 800 U. The mean botulinum toxin type A dose per kilogram for these patients was 19.1 U/kg (± 2.1 U/kg SD), with a range from 15 to 30 U/kg. The 14 young adults who weighed ≥ 45 kg received a total of 22 injection protocols. The mean total dose for these patients was 927.3 U (± 103.2 U SD), with a range from 800 to 1200 U. The mean botulinum toxin type A dose per kilogram for these young adults was 15.2 U/kg (± 3.6 U/kg SD), with a range from 7 to 20 U/kg.

Adverse events were reported by 3 of the 108 patients (2.8%), all of whom were < 45 kg (3 of 94; 3.2%). One of the adverse events was a rash experienced by a 23-month-old child with cerebral palsy following the first injection protocol. The child had received 19 U/kg of botulinum toxin type A to the hamstrings and gastrocnemius/soleus bilaterally. The rash, which was unassociated with respiratory compromise or mucosal involvement, began less than 12 hours after the injection protocol. Diphenhydramine was initiated, and the rash cleared in less than 48 hours. This rash was deemed to be a mild adverse event. The second adverse event was urinary incontinence experienced by a 10-year-old child with cerebral palsy following the first injection protocol. This child received 18 U/kg botulinum toxin type A to the hamstrings bilaterally. The child sustained loss of bladder control "en route" to the bathroom. In eliciting the history from the patient and caregivers, it appeared that incontinence was secondary to excessive focal leg weakness and slowness in getting to the bathroom rather than a manifestation of botulinum toxin type A spread into the pelvic floor, with resultant sphincter weakness. This adverse event resolved by 6 weeks postinjection and was rated as moderate in severity.

The third and only serious adverse event was a case of mild, generalized botulism, which occurred in a 13-year-old child with cerebral palsy who received a second injection protocol of 23 U/kg botulinum toxin type A into the hamstrings and gastrocnemius/soleus bilaterally. Her first injection protocol involved 17 U/kg to the hamstrings bilaterally performed 6 months previously, with complete resolution of botulinum toxin type A effect prior to her second injection protocol. The symptoms of botulism included fatigue, ptosis, diplopia, and dysarthria, without associated dysphagia or respiratory compromise. These symptoms improved with the administration of pyridostigmine and resolved within 6 weeks, whereas a desired decrease in lower extremity tone persisted for 5 months. This patient has subsequently been reinjected with a lower dose of botulinum toxin type A and has sustained no adverse events.

No serious adverse events were noted in children < 45 kg who received botulinum toxin type A doses of 15 to 22 U/Kg of body weight or in young adults ≥ 45 kg who received total doses of 800 to 1200 U in a single injection protocol.

DISCUSSION

This retrospective study found that high-dose botulinum toxin type A (ie, ≥ 15 U/kg body weight or ≥ 800 total units per single injection protocol), with the total dose divided and administered into multiple muscle groups, was safe for the treatment of pediatric spasticity. Three of the 108 patients in this study reported an adverse event, two of which were mild or moderate and only one of which was serious. Despite the functional disability associated with enuresis and botulism in our two patients who sustained the most significant adverse events, these symptoms resolved by 6 weeks postinjection, and neither of these patients reported ongoing compromise of their systemic health or functional capabilities.

The results of this study are important because many children with central nervous system dysfunction require botulinum toxin type A injections into multiple muscle groups to control their spasticity, which necessitates the use of high total doses. The results of a randomized, double-blind study found that high-dose botulinum toxin type A (40–80 U/muscle for a mean dose of 11.62 U/kg body weight) produced significantly greater improvements than low-dose botulinum toxin type A (20–40 U/muscle for a mean dose of 6.08 U/kg body weight) in a population of children and young adults with cerebral palsy. Improvements were noted in lower extremity muscle tone, range of motion, and longitudinal gait parameters.[17] These observations suggest that high doses of botulinum toxin type A might be necessary to achieve sufficient clinical benefit in this population.

Only a few other published reports have employed doses in the range of those used in the present study. Molenaers and colleagues studied a group of 156 children with spastic cerebral palsy who received a mean dose of 19.4 U/kg body weight of botulinum toxin type A, with a maximum individual dose of 29 U/kg.[18] The authors noted no major side effects related to botulinum toxin type A; however, the number and nature of side effects were not specified. In another study, 34 children with spastic cerebral palsy received a total mean dose of 24.4 U/kg body weight for diplegia or 16.4 U/kg body weight for hemiplegia.[19] The authors noted "minor complications" in 14 children, including 12 children who had generalized weakness of 1 to 2 weeks' duration and 3 children with incontinence. Weakness was not considered an adverse event in this study but rather an expected consequence of decreased muscle tone. Although excessive focal weakness in the area of injection can reasonably be considered an expected consequence of injection, generalized weakness suggests systemic spread of botulinum toxin type A. The symptoms of botulism secondary to systemic spread of the toxin should be considered a significant adverse event, as it was for the purposes of the present study. Regrettably, the authors of this article do not provide data regarding the relationship between the dose of botulinum toxin type A and the presence of adverse events. Such data might be helpful in confirming a "ceiling effect," which is suggested by the present study, in which no patient sustained symptoms of systemic botulism at botulinum toxin type A doses of ≤ 22 U/kg of body weight.

The only patient in the present study to develop generalized botulism had no risk factors suggesting increased susceptibility to botulinum toxin type A–induced neuromuscular blockade. This child developed mild, generalized botulism at a dose of 23 U/kg of body weight. Seven children in this study received doses of botulinum toxin type A that were equal to or higher than that received by the patient who developed botulism. Clearly, additional research is required to delineate a maximal tolerable botulinum toxin type A dose for the treatment of pediatric spasticity, beyond which patients uniformly develop symptoms of generalized botulism.

The child described in the current study who developed generalized botulism was treated with pyridostigmine, with the hope that blockade of acetylcholinesterase would augment neuromuscular transmission at functioning nerve terminals and reduce the severity of symptoms. The dramatic improvement in this child's fatigue, ptosis, diplopia, and dysarthria over the 48 hours following the initiation of pyridostigmine suggests that increased synaptic acetylcholine levels can reduce the severity of symptoms in a mild case of iatrogenic botulism. Otherwise, there is no medical literature supporting the use of pyridostigmine for the treatment of botulism. Rather, botulism is treated with supportive care and the administration of human botulism immune globulin or equine botulinum antitoxin.[20,21]

The 2.8% of patients reporting adverse events in the present study is lower than that reported in a number of previous studies. In a large, prospective, double-blind, placebo-controlled trial, 17% of subjects receiving 4 U/kg body weight of botulinum toxin type A reported adverse events including focal weakness, increased falls, and pain.[8] A retrospective review of 215 children who received botulinum toxin type A therapy for spasticity revealed adverse event rates of 9% for falls and 2% each for leg pain, leg weakness, and generalized weakness.[11] However, a number of randomized, controlled trials of children with spastic cerebral palsy have not reported any treatment-related adverse events with botulinum toxin type A.[6,9,10,22] In the present study, the 2- to 3-month period prior to review of potential side effects might limit recall of adverse events. Further, patients and their families were counseled while obtaining informed consent that functional capabilities might deteriorate temporarily while the patient adjusts to the postinjection changes in muscle strength and tone. As such, some of the adverse events noted in previous studies might be anticipated changes in our injected patients that were not reported to the investigator. Despite these limitations, the close longitudinal relationship between the investigator and his patients, coupled with the investigator's availability to receive reports of side effects, renders underreporting of significant adverse events unlikely. As such, this study is believed to accurately reflect the nature and frequency of significant adverse events sustained by a population of children and young adults receiving high-dose botulinum toxin type A therapy for the treatment of spasticity.

It is important to reiterate that the doses used in the present study refer to a specific preparation of botulinum toxin type A (BOTOX) and cannot be generalized to other botulinum neurotoxin preparations. Likewise, the low rate of adverse events observed in the present study cannot be generalized to other botulinum neurotoxin preparations, which have unique biologic properties.

In summary, this study is notable for a low frequency of reported adverse events, despite the administration of high doses of botulinum toxin type A for the treatment of spasticity. No serious adverse events were reported in any child < 45 kg who received botulinum toxin type A at a dose of 15 to 22 U/kg of body weight. Similarly, no adverse events were reported in young adults ≥ 45 kg who received doses of 800 to 1200 U. The results of this study provide additional support to an evolving literature regarding the safety of botulinum toxin type A therapy for the treatment of pediatric spasticity.

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