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Use of Rimabotulinum Toxin for Focal Hypertonicity Management in Children with Cerebral Palsy with Nonresponse to Onabotulinum Toxin

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Abstract

Objective—The aim of this study was to review the effect of rimabotulinum toxin (BoNT-B) for focal hypertonicity management in children with cerebral palsy and secondary nonresponse to onabotulinum toxin treated at the authors' tertiary care academic medical center.

Design—A retrospective review of the medical treatment of children was conducted at the authors' institution (March 16, 2001, to August 2, 2002) using the key words *botulinum toxin B* and *Myobloc* (Solstice Neurosciences Inc, South San Francisco, CA). Demographic information was analyzed using descriptive statistics (number [percentage] and mean [range]). The Pearson χ^2 test was used to evaluate differences in incidence of adverse events.

Results—Eighty-two children had BoNT-B injections (116 treatments). Overall, 26.8% (19/71) of the children or their parents/guardians reported no or minimal response to the injections, with 89.5% (17/19) of these children having secondary nonresponse to onabotulinum toxin. Adverse events were frequent but did not require hospitalization of any patient. No significant differences were found in incidence of adverse events related to BoNT-B dosing, medical fragility, or Gross Motor Function Classification System level.

Conclusions—More than one-fourth of the children receiving BoNT-B injections had nonresponse, with most having previous nonresponse to onabotulinum toxin. Adverse events related to BoNT-B injections were frequent and unpredictable but not severe.

Keywords

Adverse Events; Botulinum Toxins; Cerebral Palsy; Muscle Spasticity

Onabotulinum toxin (BoNT-A) is considered the standard of care for the focal management of hypertonicity in children.¹ In a joint position paper from the American Academy of

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Neurology and the Child Neurology Society in 2010, BoNT-A was considered a safe, effective treatment of focal spasticity and dystonia in children with cerebral palsy (CP).² However, the decreased responsiveness to BoNT-A with repeated dosing in some children with CP has resulted in providers using rimabotulinum toxin (BoNT-B), despite limited evidence supporting its use for spasticity management in this group.^{2,3}

With regard to the use of BoNT-B in adults with cervical dystonia and BoNT-A in secondary nonresponse, some individuals rapidly develop nonresponse to BoNT-B.^{4,5} This is also a potential concern for children with CP. In a pilot study of 29 children, functional improvements lagged in the children receiving BoNT-B who had a secondary nonresponse to BoNT-A.³ Although this was suggestive of decreased efficacy, identification of nonresponse to BoNT-B was not done. Therefore, understanding the responsiveness to and the effectiveness of BoNT-B in children with CP who have nonresponse to BoNT-A is necessary to evaluate the benefit of BoNT-B treatment of focal spasticity management in this group.

Both the benefits of BoNT-B and the safety of its use in children with CP have not been thoroughly evaluated. In adults with cervical dystonia, the increased incidence of adverse effects (AEs) ranges from 0% to 89%, with most studies showing the incidence⁶⁻⁹ to be greater than 50%. Currently, all botulinum toxins approved by the United States Food and Drug Administration have a boxed warning regarding the potential for spread to noninjected muscles, based on AE reports, including one randomized study involving BoNT-A use in children with CP that reported a death.¹⁰ The overall incidence of AEs with BoNT-A in children with CP^{11,12} ranges from 6.2% to 10%. A recent study evaluating potential factors contributing to the development of AEs of BoNT-A injections in children with CP found that those with greater medical fragility and Gross Motor Function Classification System (GMFCS) level IV or V had an increased incidence of AEs.¹¹ The incidence of AEs in children receiving BoNT-B seems to be greater than that for BoNT-A, with two studies showing AEs at 24.2% (15/62 injection sessions)³ and 28.6% (2/7 individuals).¹³ However, these studies had limited numbers of individuals and did not include evaluation of the potential risk factors of susceptibility to AEs. A third study evaluating botulinum neurotoxin use in children with CP found the incidence of AEs to be 6.8% (51/748), although few children received BoNT-B injections.¹⁴ Further evaluation of AEs with the use of BoNT-B in children with CP, particularly with regard to potential risk factors of AEs, is needed to further one's understanding of the safety of this intervention in these children.

At the authors' institution, BoNT-A and phenol neurolysis are used to manage focal hypertonicity in children with CP. The use of BoNT-B for focal hypertonicity management in children with CP was initiated in March 2001 and discontinued in August 2002 because of concern regarding AEs. However, interest in reinstating the use of BoNT-B has remained high, prompting further review and analysis of this treatment. Herein, the authors report their experience with the use of BoNT-B for the management of focal hypertonicity (defined as spasticity, dystonia, or both) in children with CP.

METHODS

After approval of this study by the University of Minnesota Institutional Review Board, a retrospective review was conducted of medical records for patients treated between March 16, 2001, and August 2, 2002. All patients and/or their legally authorized representatives had previously agreed to allow the use of the patients' records for research; individual consent was therefore not required by the institutional review board for this study. The inclusion criteria were as follows: a diagnosis of CP; age younger than 18 yrs at the time of

the first injection; and at least one BoNT-B injection. The exclusion criterion was lack of consent to use the patient's medical records for research.

A search of the institution's medical records was conducted using a computerized document management system with the keywords *Myobloc* (Solstice Neurosciences Inc, South San Francisco, CA) and *botulinum toxin B*. Abstracted information included the child's name, medical record number, date of birth, sex, type of CP (hemiplegic, diplegic, triplegic, or quadriplegic), tone type (spasticity, spasticity and dystonia, or dystonia), GMFCS level (either in the medical record or determined upon review of information provided in the record at or near the time of the initial injection), other medical diagnoses, previous use of BoNT-A, and development of clinical resistance to BoNT-A. Clinical resistance was defined as decreasing effectiveness or reduced duration of response at the same or an increased dosage. Response to injections was based on family perceptions of the child's function, daily care, and physical examination. There was no single standardized method of reporting of the response to injections, with one or more of the previously mentioned elements used to determine response. In the individuals with minimal or no response, further injections were not performed. For each BoNT-B injection episode, data were abstracted that included the identity of the healthcare provider performing the injections, the child's weight, the dose of BoNT-B, the dose and dilution of BoNT-A (if concurrently used), the dose of phenol (if concurrently used), the muscles injected, the clinical setting for injections, and the self-reported or parent-/guardian-reported AEs at follow-up. AEs were determined either by open-ended or directed questioning at the clinic visit or by telephone follow-up. An injection episode was defined as all injections a child received in a single clinical encounter.

Descriptive statistics were used for age, weight, type of CP, tone type, GMFCS level, BoNT-B dosing, BoNT-A dosing, phenol dosing, AEs, and perceived effects of injections. The Pearson χ^2 test was used to evaluate differences in AEs regarding type of CP, tone type, GMFCS level (I/II, III, or IV/V), location of injections (upper extremities, lower extremities, or both), medical fragility (defined as having a gastrostomy tube and/or seizures), provider performing the injection, setting in which the injections were performed (clinic, operating room, or rural clinic), reported benefit from injections as reported by the patient or the caregiver and physician, number of muscles injected (1–2, 3–4, or 5), use of low-dose (<10,000 U) vs. high-dose (≥10,000 U) BoNT-B, and concomitant use of BoNT-A and/or phenol. Differences between the patients who received one episode of injections and those who received two or more episodes were evaluated using the McNemar test.

RESULTS

Between March 2001 and August 2002, a total of 82 children with a diagnosis of CP underwent 116 episodes of injections with BoNT-B (Table 1). Of the 82 children, 61 (74%) had secondary nonresponse to BoNT-A, 18 (22%) had no previous exposure to BoNT-A or lacked documentation regarding BoNT-A exposure, and 3 (4%) had AEs with BoNT-A injections. Overall, of the 82 children, 60 participated in one episode of injections, 13 had two episodes, 7 had three episodes, 1 had four episodes, and 1 had five episodes (Table 2). With regard to BoNT-B, the mean dose was 8,959 U (range, 3,000–22,000 U) and the mean units per kilogram dose was 343.4 U/kg (range, 73.7–657.9 U/kg). The number of muscles injected with BoNT-B in an individual subject in a single injection episode ranged from 1 to 10. For the first episode of injections, 67 subjects (81.7%) had BoNT-B; 9 (11.0%) had BoNT-B and phenol; 4 had both BoNT-A and BoNT-B; and 2 had BoNT-A, BoNT-B, and phenol.

After the first episode of injections, 12 (16.9%) of the 71 children for whom AE data were available experienced no or minimal tone reduction. Five children had nonresponse after the

second injection episode. For all injection episodes, 19 (26.8%) children had no or minimal response. In 17 (89.5%) of these 19 children, secondary nonresponse to BoNT-A had been reported. No significant differences were found between responsiveness of the subjects who had no or minimal benefit from the first episode of injections and the presence or absence of previous BoNT-A exposure ($P = 0.67$). Of the 116 injection episodes, 74 episodes (63.8%) had documented reports of response from both the parent/guardian or the patient and the physician. Agreement with regard to response to the injections occurred in 65 (87.8%) of 74 of these injection episodes.

For all children, reported AEs included bowel function changes (constipation or diarrhea), urinary changes (retention or incontinence), dry mouth, new or increased difficulties with oral motor function (chewing/swallowing/drooling), new or increased frequency of seizures, generalized weakness or hypotonia, visual disturbances, and nausea (Table 3). Reports concerning AEs after the first episode of injections were available for 71 children (86.6%). Of these 71 children, 48 (67.6%) had no AEs, 16 (22.5%) had 1 AE, 5 (7.0%) had 2 AEs, and 2 (2.8%) had 3 AEs, for a total of 32 AEs experienced by 23 children (32.4%). With respect to the two children who had three AEs, BoNT-B was administered to both the upper and lower extremities: one child received injections to the right arm and the right leg and one child received injections to both arms and both legs. For those with nonresponse to the first injection episode, 1 (8.3%) of 12 children experienced an AE (dry mouth). Of all 19 children with report of nonresponse to injections, 3 experienced AEs (3/19 [15.8%]), with 2 experiencing dry mouth and 1 having a new-onset seizure (after the fifth injection episode). No significant differences were noted in AEs related to response to injections ($P = 0.09$), GMFCS level ($P = 0.53$), type of CP ($P = 0.99$), or muscle tone ($P = 0.94$); degree of medical fragility ($P = 0.90$); injection site ($P = 0.26$); number of muscles injected ($P = 0.87$); healthcare provider performing the injection ($P = 0.10$); medical setting in which the injection was performed ($P = 0.74$); high-dose vs. low-dose BoNT-B ($P = 0.18$); or concomitant use of BoNT-A and/or phenol ($P = 0.92$). No AE was severe enough to require hospitalization.

For all 116 injection episodes, documentation of the presence or the absence of AEs was identified in 104 episodes (89.7%). Of these 104 episodes with documentation, 31 (29.8%) had AEs. No significant difference was found in the AEs between the patients who had one episode of injections and the patients who had a second episode of injections ($P = 0.84$). Further statistical analysis of the subsequent injection episodes was not performed because of the small numbers of patients who received more than two episodes of injections.

DISCUSSION

Overall, 26.8% (19/71) of the children with documented AEs in this study experienced no response or minimal response to BoNT-B injections, suggestive of nonresponse to BoNT-B. Most (89.5% [17/19]) of the children with no or minimal response to BoNT-B had clinical resistance to BoNT-A. Statistical significance was not achieved between the groups with regard to previous BoNT-A clinical resistance and response to BoNT-B injections. In fact, if the proportions of the groups were kept the same and the study was powered to 80%, it would require between 9,000 and 18,000 children to detect a difference between these groups. Other studies have differences in responses in those with BoNT-A clinical resistance. One pilot study of children with CP found lesser functional improvement after BoNT-B injections in those with nonresponse to BoNT-A compared with those with no previous exposure to BoNT-A.³ In adults with cervical dystonia, the responsiveness to BoNT-B injections in BoNT-A nonresponders has been mixed.^{4,5,8} Overall, this is suggestive that some children with CP who do not respond to BoNT-A may respond to

BoNT-B. Further evaluation of this possibility with a standardized prospective study should be considered to further characterize this relationship.

Despite the high incidence of nonresponse to BoNT-B and the large number of children with previous BoNT-A exposure, the incidence of AEs was found to be 29.8%. This is similar to the incidence of AEs found in two other studies involving children with CP receiving BoNT-B,^{3,13} slightly lower than that reported for adults with cervical dystonia,⁶⁻⁹ and much greater than that reported for children having BoNT-A injections.^{11,12} Interestingly, there was no significant difference with regard to experiencing an AE and the presence or the absence of a clinical response to the injections. This may be because of the relatively small number of persons in the BoNT-B nonresponder group compared with the number of BoNT-B responders. Detecting a difference with 80% power would have required 142 children with CP. Another possible explanation may be a different mechanism of action with regard to AEs, particularly autonomic effects, for BoNT-A vs. BoNT-B. In adults with cervical dystonia and BoNT-A nonresponse, those receiving BoNT-B experienced more autonomic AEs, thought to be the result of differing receptor or receptor-site interactions for the autonomic nervous system with BoNT-B compared with BoNT-A.¹⁵ If there is a difference in receptor or receptor-site action of BoNT-A and BoNT-B, this may explain why some of the nonresponders in this study experienced AEs because these were primarily autonomic (dry mouth). In addition, the slightly lower incidence of AEs with BoNT-B in children with CP compared with that in adults with cervical dystonia may be caused by differences in the location of the muscles that were injected. Overall, with the high incidence of AEs and with AEs occurring in children who did not respond to the injections, the authors suggest educating patients and families about the possibility of experiencing AEs, even without any change in spasticity or function.

The most frequently noted AEs in this study were new seizures or increased frequency of seizures, visual disturbance, and dry mouth, with none of the AEs mandating hospitalization. Visual disturbance and dry mouth have been found in multiple studies^{3,7,8,16,17} and have been hypothesized to be caused by a difference in the interaction of BoNT-B with the receptors in the autonomic nervous system, as noted above.¹⁵ The association of new or increased seizure frequency in those receiving BoNT-B injections is challenging to determine. Seizures have not been reported in adults with cervical dystonia receiving BoNT-B. Reports of seizures as related to AEs are mixed in children with CP receiving BoNT-A injections.^{10,18,19} The mechanism behind the association between seizures and both BoNT-A and BoNT-B injections is unknown and may be more reflective of predisposition to seizures caused by the underlying brain abnormality in these children than of an association with the injections. Clearly, further research and evaluation are needed in this area.

The authors also found no significant difference in AEs by degree of medical fragility, GMFCS level, or dose of BoNT-B. Detecting these differences with 80% power would have required approximately 7960, 178, and 417 children in each group, respectively. Although these results stand in contradistinction to those in a 2010 report by Naidu et al. regarding the use of BoNT-A in children with CP, this difference may be a result of the number of children in this study. In the Naidu et al. study,¹¹ 1147 children with CP received BoNT-A injections. In addition, the relatively high incidence of AEs experienced by the children in this study may have masked small differences with regard to medical fragility, GMFCS level, or dosing. It seems that in children with CP, AEs from BoNT-B injections may not be predictable by medical fragility, GMFCS level, or BoNT-B dosing. Larger prospective studies to evaluate this would be beneficial. Recommendations for altering the dosing of BoNT-B on the basis of medical fragility or GMFCS level cannot be made and should be based on the individual needs of the patient and the muscles targeted.

In the patients in this study, AEs were not associated with the concurrent use of BoNT-A and/or phenol. The authors believe that this study is the first to show the simultaneous use of different types of botulinum toxins in children with CP. In children with CP, the use of two different types of botulinum neurotoxins may allow more muscles to be injected during an injection episode, or it may allow the same number of muscles to be injected but with a lower dose of each botulinum toxin. Further research is needed about these potential injection options and outcomes. In addition, there is little information available about adjusting botulinum toxin dosing on the basis of the concurrent use of other botulinum toxins or with other spasticity management regimens. Because only a few children in this study received both BoNT-B and BoNT-A during a single injection episode, the authors were not able to perform further statistical analysis on dosing and AEs in those receiving both neurotoxins in the same injection episode.

Limitations

This study has some limitations. First, it was a retrospective study, with all the limitations inherent to that structure. Of the patients whose records were retrieved, 13.4% (11/82) either had no documentation of AEs after BoNT-B injections or were lost to follow-up. In addition, there was no standardized reporting of AEs or the types of response to the injections. In the cases in which follow-up was delayed, the caregivers and/or the patients may have recall bias with regard to AEs. Some of the patients in this study had significant cognitive impairments that would make reporting of symptoms, including vision changes or dry mouth, difficult. Some subgroups in the analysis of this study had such small numbers that statistical analysis could not be performed. Lastly, this study did not have a control group or a matched group of children who received BoNT-A injections to compare directly with the BoNT-B group. However, the authors did review other reports of studies of BoNT-A injections in children with CP and found that these documented a much lower frequency of AEs.^{11,14}

CONCLUSIONS

Overall, there was a high incidence of nonresponse (26.8%) in children with CP receiving BoNT-B injections. An association between a history of nonresponse to BoNT-A and nonresponse to BoNT-B was not detected. AEs associated with BoNT-B occurred in almost one-third (29.8%) of the injection episodes but were not severe enough to mandate hospitalization. AEs were experienced by some children with nonresponse to BoNT-B. For all children, the most common AEs reported were visual disturbance, dry mouth, and seizures. No association was found between the concurrent use of BoNT-A and/or phenol, medical fragility, or GMFCS level and the occurrence of AEs.

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TABLE 1

Characteristics of the children with CP who had one injection episode of BoNT-B and of the entire group over all injection episodes

Characteristic	Children	
	First Injection (<i>n</i> = 82)	All Injection Episodes (<i>n</i> = 116)
Age, mean (SD) [range], mos	119.6 (50.3) [36–213]	116.1 (51.7) [36–218]
Sex		
Female	38 (46.3)	46 (39.7)
Male	44 (53.7)	70 (60.3)
Weight, mean (SD) [range], kg	25.7 (13.9) [7.6–72.3]	24.8 (13.2) [7.6–72.3]
CP type		
Hemiplegia	13 (15.9) ^a	21 (18.1)
Diplegia	21 (25.6)	28 (24.1)
Triplegia	9 (11.0)	16 (13.8)
Quadriplegia	39 (47.6)	51 (44.0)
GMFCS		
I	21 (25.6)	32 (27.6) ^a
II	12 (14.6)	17 (14.7)
III	14 (17.1)	16 (13.8)
IV	16 (19.5)	25 (21.6)
V	19 (23.2)	26 (22.4)
Tone type		
Spastic	69 (84.1)	99 (85.3)
Mixed/dystonic	13 (15.9)	17 (14.7)

Values are presented as number (percentage) unless otherwise indicated.

^a Percentages total greater than 100% because of rounding.

TABLE 2

BoNT-B dosing and use for the first and all injection episodes in the children with CP

Variable	First Injection (<i>n</i> = 82)	All Injection Episodes (<i>n</i> = 116)
BoNT-B dose, mean (SD) [range], U	9,167.7 (3,311.5) [3,000–22,000]	8,959.1 (3,094.3) [3,000–22,000]
BoNT-B, mean (SD) [range], U/kg	340.5 (133.9) [101.6–657.9]	343.4 (130.0) [73.7–657.9]
No. muscles injected with BoNT-B		
1–2	43 (52.4)	63 (54.3)
3–4	25 (30.5)	29 (25.0)
5	14 (17.1)	24 (20.7)
Site of BoNT-B injection		
Upper extremity	11 (13.4)	12 (10.3)
Lower extremity	60 (73.2)	87 (75.0)
Both upper and lower extremities	11 (13.4)	17 (14.7)
Other types of injections		
BoNT-A	4 (4.9)	8 (6.9)
Phenol	9 (11.0)	11 (9.5)
BoNT-A and phenol	2 (2.4)	2 (1.7)
BoNT-A dose, mean (SD) [range], U	266.7 (81.6) [200–400]	234.0 (118.0) [40–400]
BoNT-A, mean (SD) [range], U/kg	7.9 (3.9) [4.7–13.3]	6.4 (3.7) [1.3–13.3]
Phenol dose, mean (SD) [range], ml	12.6 (6.1) [6–24]	13.4 (6.6) [6–24]
Phenol, mean (SD) [range], ml/kg	0.5 (0.3) [0.08–0.9]	0.6 (0.3) [0.08–0.9]

Values are presented as number (percentage) unless otherwise indicated.

TABLE 3

Adverse reactions to BoNT-B in 82 children with CP by injection episode

Adverse Events	Injection 1 (n = 32)	Injection 2 (n = 8)	Injection 3 (n = 1)	Injection 4 (n = 0)	Injection 5 (n = 1)	Total (N = 42)
Bowel changes	3	1	0	0	0	4
Bladder changes	1	1	0	0	0	2
Dry mouth	6	1	0	0	0	7
Difficulty swallowing or chewing; drooling	6	0	0	0	0	6
New/increased frequency of seizures	4	2	1	0	1	8
Generalized weakness/hypotonia	3	1	0	0	0	4
Visual disturbance	6	2	0	0	0	8
Nausea	3	0	0	0	0	3

Values are presented as number.