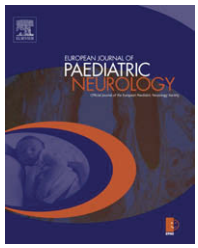
Official Journal of the European Paediatric Neurology Society



Original article

Safety of botulinum toxin type A in children younger than 2 years

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ARTICLE INFO

Article history:
Received 28 June 2008
Received in revised form
28 September 2008
Accepted 7 October 2008

Keywords:
Botulinum toxin type A
Safety
Infants
Cerebral palsy
Obstetric brachial palsy
Muscle spasticity

ABSTRACT

Background: Botulinum toxin type A (BoNT-A) has been used in many indications and is licensed for the treatment of spasticity in children older than 2 years. However, there are few reports of BoNT-A treatment in patients younger than 2 years of age.

Aims: To review retrospectively the safety data from all infants treated with botulinum toxin type A (BoNT-A) before 2 years of age in a paediatric neurology unit.

Methods: There were 74 infants: 28 received the first dose before 1 year of age, and 46 between the ages of 1 and 2 years.

Results: In the first year of life, the most frequent indication was obstetric brachial palsy (OBP) (71.4% of cases) and in the second year, cerebral palsy (CP) (73.9%). Both Botox® and Dysport®, the two commercially-available BoNT-A products in Spain, were used. The average starting dose by session was 6.55 U/kg body weight Botox in infants in their first year of life, and 8.4 U/kg body weight Botox and 21.1 U/kg body weight Dysport in the second year of life. Only 3.6% of cases treated in the first year and 6.5% of those treated in the second experienced adverse events (AEs), which consisted of mild weakness or tiredness lasting 1–4 days.

Conclusions: BoNT-A has a good safety profile in infants younger than 2 years old. AEs are similar to those found in older children.

1. Introduction

Botulinum toxin type A (BoNT-A) has been used in many indications, several of which are off-label, in patients older than 2 years. There are, however, few reports of BoNT-A treatment in patients younger than 2 years, unless reported as part of an older patient series. From the neuropaediatric perspective, the consensus is for the early treatment of spasticity, dystonia and brachial palsy to prevent complications, but the consequences of treating relatively immature muscles are not known.

There are some disorders that require very early treatment. For example, the spastic hip in bilateral cerebral palsy (CP) leads to early and dangerous lateral migration of the femoral head and to subluxation.[1–3] This can occur even in the first year of life, and early treatment with botulinum toxin has been proven useful.[2,4] Obstetric brachial palsy (OBP), particularly with partial impairment of the upper trunk (C5–C6) with no primary indication for surgery can be improved by BoNT-A in the first months of life, which can prevent the shoulder joint limitation that may otherwise occur.[5,6]

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1090-3798/$ – see front matter
doi:10.1016/j.ejpn.2008.10.006

BoNT-A has been widely studied as a treatment of muscle movement disorders, with a large body of supporting literature. The safety of BoNT-A in children and adults has been the subject of a recent meta-analysis[7] and review.[8] It has a good safety profile,[9–11] superior to that of many drugs used in neurology[7,8] and the rate of adverse events (AEs), most of which are mild and transient, is less than 15% in adults and children.[12–14]

A recent European consensus report, from an interdisciplinary group with considerable collective experience in the treatment of CP with BoNT-A, considers that BoNT-A, when used in appropriate doses, has an acceptable efficacy and safety profile.[15]

To demonstrate the safety of BoNT-A in patients younger than 2 years, we present a review of all cases treated in our hospital with BoNT-A in this age group.

2. Patients and methods

All patients treated with BoNT-A before 2 years of age from 1995 to June 2007 in the paediatric neurology department of the University Hospital La Paz, Madrid, Spain, were reviewed. Written informed consent was obtained from the parents in each case. BoNT-A (Botox® or Dysport®) was injected in each muscle at doses appropriate for the treatment of spasticity according to the reported guidelines,[16] or in OBP at doses of 1.5 U Botox or 3–5 U Dysport per muscle.[6] Patients may have received one or more treatment sessions.

The dilution used was always the same: 100 U/cc for Botox and 200 U/cc for Dysport. Injections were performed under local anaesthesia (lidocaine cream, EMLA® or ethyl chloride spray 100 g/100 ml), without sedation. Large muscles were injected in 2–3 points and smaller muscles in one point. Muscles were localized by palpation (most of them) or with guide EMG.

As part of the clinical protocol, every patient was examined 1.5–2 months after each infiltration, or earlier if necessary. For example, families were encouraged to return for re-examination if any symptoms were observed. Assessments included a movement examination appropriate to the disorder (spasticity scale, physician rating scale, joint motion assessment) and a global assessment of AEs as reported by parents and therapists.

We asked specifically in every case for fever, weakness, hypotonia, tiredness, mild distress, or other negative effects that could have happened in injected muscles, in other muscles in close or distant proximity to the injected muscle, and the duration of these symptoms. Parents answered the questions in a face- to- face open interview at the hospital, and therapists answered them through a written form because they usually worked outside our hospital. Both in the oral interview and in the written form we asked the same questions: (1) Did you observe any positive effects in the functionality of muscles injected? (2) Did you observe any positive effects in other muscles or limbs not injected? (3) Did you observe any adverse effects in the muscles injected? or (4) Did you observe any adverse effects in other muscles not injected, like fever, weakness, hypotonia, tiredness, mild distress, or others? They were graded subjectively if the AE was mild, moderate or severe according to the impairment of function or of general well-being.

Efficacy data from some of the identified cases have been previously reported.[2,6,17]

3. Results

Of 620 cases treated with BoNT-A in the unit in the review period, 74 (11.9%) were patients aged younger than 2 years. Most cases were treated after 2002. A summary of these cases is shown in Table 1.

The most frequent indication in infants younger than 1 year was OBP (71.4%). Spastic CP (mostly for hip spasticity) was the next most common indication (25%). In the second year of life, the most frequent indication was CP (73.9% of cases).

Average doses/kg body weight were lower in the group of patients treated in the first year of life compared with those treated in their second year (Botox, 6.55 vs. 8.40 U; Dysport, 17.04 vs. 21.10 U). This difference was mainly due to the clinical disorder treated, as OBP was more common in the first year. Average doses in the 0–1 year-olds were 6.3 U/kg Botox and 15 U/kg Dysport for OBP, and 7.2 U/kg Botox and 19.5 U/kg Dysport for other disorders. In the second year of age the average doses were 5.7 U/kg Botox and 10.9 U/kg Dysport for OBP, and 8.8 U/kg Botox and 23.6 U/kg Dysport for other disorders. The maximum doses used were 14.29 U/kg for Botox or 37.5 U/kg for Dysport.

More than one BoNT-A session was given before the age of 2 in 40% of cases, and many patients continued treatment beyond their second year, mostly those with CP: 21/28 cases first treated before 1 year of age and 42/46 whose treatment started between 1 and 2 years of age received additional injections after the age of 2 years.

The only AE reported by parents or therapists was focal or generalized weakness which was mild and lasted only 1–4 days. This was noted in 5.4% of cases. No AEs were reported by staff (rehabilitation and neurological) when patients returned to hospital for clinical assessment.

No differences in AEs were found between Botox and Dysport. Only two cases treated with Botox (one younger than 1 year and the other aged 1–2) and two cases treated with Dysport (both aged 1–2) reported an AE, and there appeared to be no relationship to total dose or dose by muscles.

No long-term AEs have been noted throughout the treatment period under review.

4. Discussion

BoNT-A is licensed for the treatment of spasticity in children older than 2 years. However, as occurs with other drugs, it is not uncommon to encounter off-label use, either for different indications or in patients younger than specified in the product license. A meta-analysis of 36 studies has shown that BoNT-A has a good safety profile when used in accordance with defined protocols.[7]

The toxicity of BoNT-A relates not only to the total dose received by session but also with the number of muscles

Please cite this article in press as: Samuel Ignacio Pascual-Pascual, Pascual-Castroviejo I, Safety of botulinum toxin type A in children younger than 2 years, European Journal of Paediatric Neurology (2008), doi:10.1016/j.ejpn.2008.10.006

Table 1 – – Treatment details with botulinum toxin type A (BoNT-A) in patients younger than 2 years

	Age at start of BoNT-A treatment		Total
	>1 year	1–2 years	
Cases treated, *n*	28	46	74
>3 months of age	4		
3–6 months of age	12		
6 months–1 year of age	12		
Diagnosis, *n* (%)			
Obstetric brachial palsy	20 (71.4)	10 (21.7)	30
Torticollis congenital	1 (3.5)	1	2
Spastic cerebral palsy[27]	7 (25)	34 (73.9)	41
Bilateral (levels IV or V of GMFCS[28]):			
Tetraplegia	3	14	
Diplegia	2	10	
Unilateral (hemiplegia), levels I–II of GMFCS	2	10	
Idiopathic toe gait	0	1 (2.1)	1
Type of BoNT-A used			
Botox®	10	29	39
Dysport®	18	17	35
Doses used in the first infiltration			
Botox			
Mean total dose (U)	52.50	88.62	
Range (U)	25–90	25–180	
Mean dose by weight (U/kg)	6.55	8.40	
Range (U/kg)	3–11.25	2.08–14.29	
Dysport			
Mean total dose (U)	124.44	211.88	
Range (U)	80–200	70–360	
Mean dose by weight (U/kg)	17.04	21.10	
Range (U/kg)	10–25	7–37.5	
Cases receiving 25–30 U/kg (*n*)	0	1	
Cases receiving >30 U/kg (*n*)	0	5	
Number of sessions before 2 years of age	1–3	1–2	
Botox, cases with 2 or 3 sessions, *n* (%)	9 (23) with 2 sessions 7 (18) with 3 sessions		
Dysport, cases with 2 or 3 sessions, *n* (%)	9 (25.7) with 2 sessions 3 (8.5) with 3 sessions		
Adverse events			
Weakness, tiredness lasting 1–4 days	1 (3.6%)	3 (6.5%)	4 (5.4%)
Lasting more than 4 days	0	0	

injected and with the infiltration technique[15,18] The dosing used in this patient series was calculated by body weight and was within the dose range recommended in older children.[15,19,20]

This difference in dosing seen between age groups in our series was mainly due to the clinical disorder treated. In the first year, the most frequent disorder was OBP in which the affected muscles are atrophied. This requires a lower dose because the goal is to balance antagonistic muscle pairs to prevent joint limitation. In the second year of life there were high proportions of spasticity cases, which require higher dosing.

The series presented here found mild and brief global weakness and tiredness lasting less than 5 days as the only AE reported by parents and therapists, and was present only in 5.4% of cases. This rate is lower than previously reported in our series of children and adolescent patients (11% of cases, with only 1.5% lasting more than 1 week).[21] The AE profile was no different to that seen in other reports in children,[13,14,21–23] except perhaps being of shorter duration and lower frequency.

The low toxicity of BoNT-A in older children and adults has been extensively reported.[2,7,8,18] The rate of AEs is generally lower than 15% either in childhood or adulthood, and AEs are usually mild in severity. In a meta-analysis of 36 clinical studies comprising 2309 patients[7] an overall AE rate of 25% was found, and all AEs were mild or moderate. The authors of the meta-analysis concluded that BoNT-A has a more favourable safety profile (in adults) than other drugs in common neurological use, such as non-steroidal anti-inflammatory agents (NSAIDs) or gabapentin.[7]

Some isolated cases of mild botulism subsequent to BoNT-A treatment have been reported in adults.[24] We have found

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only a single case report of death. It was a 6-year-old Spanish girl with CP who was treated three times with BoNT-A at high doses. After the second infiltration she showed muscular weakness. After the third infiltration, using even higher dose, she developed symptoms of botulism and several septic processes and finally died 2 months later.[25]

These studies suggest that the rate and severity of AEs related to BoNT-A treatment are not higher in children, and are not related to age. Data from the current study show that BoNT-A treatment in infants is not associated with excess AEs or AE severity and has not noted any negative effects of BoNT-A. In addition, a high proportion of children who received treatment at this early age went on to continue treatment beyond 2 years of age, suggesting that the procedure was considered safe and that the periodic need for treatment had an acceptable risk profile to parents.

Despite the low AE risk, treatment with BoNT-A is more complex than an oral treatment, as AEs are not only due to the drug, but also to the procedure. It is vital that treatment should be carefully planned and only undertaken when, after a thorough clinical examination, the clinician considers that BoNT-A can improve the patient's abnormal muscular function. Muscle selection and localization must be carefully assessed, and intravenous injection of the toxin must be avoided. Dose calculation is dependent on the muscle characteristics, including the saturation dose,[10] and on the severity of spasticity or dystonia.[15,18] The efficacy and AE profile observed after previous sessions also contributes to treatment planning. It should also be noted that the absolute doses of commercially available BoNT-A preparations are not interchangeable.[11] Finally, BoNT-A treatment must be a part of a comprehensive management plan in which physiotherapy, orthotic, postural and other treatments play a complementary role.[15,18,26] For these reasons, the success or failure of BoNT-A treatment is heavily dependent on the skill of the practitioner. The treating clinician must be suitably trained and experienced, a factor emphasized in all published guidelines.[15,20,26] On the other hand, the physician must be aware of the complications that undertreated CP or brachial palsy have for the child, with progressive osteoarticular deformities that appear sooner in more impaired children, and frequently before 2 years of age.

With careful clinical procedures, BoNT-A has been shown to be one of the safest drugs in the field of neurology, with a low frequency and severity of AEs.

Acknowledgements

The authors thank Caudex Medical Ltd (supported by Ipsen Group) for editorial assistance.

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Please cite this article in press as: Samuel Ignacio Pascual-Pascual, Pascual-Castroviejo I, Safety of botulinum toxin type A in children younger than 2 years, European Journal of Paediatric Neurology (2008), doi:10.1016/j.ejpn.2008.10.006