Use of botulinum toxin type A in the management of patients with neurological disorders: a national survey

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Summary

The aim of this survey was to provide an overview of important issues relating to therapeutic strategies based on botulinum toxin type A injection for the treatment of patients with neurological disorders. Two hundred and ten physicians from neurology and neurorehabilitation units in Italian hospitals answered a questionnaire exploring some clinical aspects of the use of botulinum toxin type A in patients with spasticity/dystonia. 66% of the physicians treated patients with dystonia, 80% treated adults with spasticity, and 35% treated children with cerebral palsy. Palpation with no instrumental guidance was the injection technique most commonly used for treating patients with dystonia, spasticity and cerebral palsy; 57% of the physicians evaluated patients instrumentally before toxin injection, while 45% assessed post-injection improvements by instrumental means; 78% of the physicians prescribed (when appropriate) rehabilitation procedures after toxin injection. Our results seem to show that the routine use of botulinum toxin in clinics is far from standardized.

KEY WORDS: botulinum toxin, cerebral palsy, dystonia, injection, spasticity, survey.

Introduction

Botulinum toxin type A (BoNT-A) is a neurotoxin produced by the obligate anaerobic bacterium *Clostridium Botulinum*, which acts in the cytosol of nerve endings to cleave the SNAP-25 protein (Lim and Seet, 2010; Naumann et al., 2008; Esquenazi et al., 2010; Ward et al., 2006). This target protein mediates the docking and fusion of neurotransmitter-containing vesicles to the presynaptic membrane (Lim and Seet, 2010). Therefore, cleavage of SNAP-25 by BoNT-A prevents exocytosis of acetylcholine from the presynaptic terminal of neuromuscular junctions, resulting in a temporary, reversible block of the motor fibers and weakened muscle contraction (Lim and Seet, 2010; Ward et al., 2006). BoNT-A is widely used in patients with neurological impairments characterized by skeletal muscle overactivity (such as movement disorders and spasticity) to provide a targeted paralytic effect, which normally lasts 3-4 months (Lim and Seet, 2010; Esquenazi et al., 2010; Ward et al., 2006). Other clinical indications for this intervention are conditions involving glandular and smooth muscle overactivity (Lim and Seet, 2010; Esquenazi et al., 2010).

In clinical practice, several issues have to be considered when planning a treatment strategy that includes the injection of BoNT-A (Lim and Seet, 2010). The treatment goals and methods that are to be used to assess clinical improvement need to be outlined in the treatment plan. The injection schedule also needs to be planned, detailing the muscles to be injected, the injection technique, the number of injection sites per muscle, the dosage and the dilution. Furthermore, other treatment modalities, such as rehabilitation procedures, that may need to be integrated with BoNT-A should also be carefully planned.

Three commercial preparations of BoNT-A are currently available in Italy: abobotulinumtoxinA (Dysport®, Ipsen, France), incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Germany) and onabotulinumoxinA (Botox®, Allergan Inc., United States) (Albanese, 2011). Although BoNT-A is being used by a growing number of physicians to treat a range of neurological conditions, to the best of our knowledge no study has yet provided an overview of important issues relating to BoNT-A injection-based therapeutic strategies for treating patients with neurological disorders. In an attempt to fill this gap in knowledge, we conducted the Best in Injection Training (BIT) project, which was aimed at understanding and improving clinical practice involving the use of BoNT-A in neurology and neurorehabilitation clinics. The present paper reports the

main findings of the BIT project.

Materials and methods

Two hundred and ten neurology/neurorehabilitation units in Italian hospitals (selected from the Italian Society of Neurological Rehabilitation database) qualified for inclusion in this survey. One physician from each unit included in the survey was required to complete a self-administered questionnaire on the use of BoNT-A for the treatment of patients with neurological disorders (Table I). The following aspects were investigated: i) the use of BoNT-A in clinical practice; ii) the presence of a specific service for treating patients with BoNT-A in the unit; iii) years of clinical experience in the use of BoNT-A in patients with neurological disorders; iv) clinical conditions treated with BoNT-A; v) BoNT-A treatment of muscle overactivity associated with painful conditions; vi) evaluation procedures used for planning a treatment strategy based on the injection of BoNT-A; vii) frequency of BoNT-A re-injections; viii) BoNT-A dilution; ix) BoNT-A dosages; x) BoNT-A injection techniques; xi) rehabilitation procedures after BoNT-A injection; xii) evaluation procedures used for assessing clinical improvements after BoNT-A injection; xiii) adverse reactions to BoNT-A; xiv) clinical updates on the use of BoNT-A.

Statistical analysis

Descriptive statistics were used for all the items investigated. Statistical analysis was performed using the SPSS for Windows statistical package, version 20.0 (SPSS Inc., Chicago, IL, USA).

Table I - Survey questionnaire

Item	Question	Answer
Experience		
1	Do you currently use BoNT-A in your clinical practice?	Yes / No
2	Is there a specific service for treating patients with BoNT-A in your unit?	Yes / No
3	How long is your clinical experience with BoNT-A?	<2 years / 2-5 years / 5-10 years / >10 years
4	What clinical conditions do you treat with BoNT-A?	spasticity / dystonia / cerebral palsy / other
5	How many patients/year do you treat with BoNT-A?	patients/year for each of the above-mentioned conditions
6	Do you use BoNT-A to treat muscle overactivity associated with painful conditions?	Yes / No
Clinical practice		
1	How do you evaluate patients in order to plan a treatment strategy based on the injection of BoNT-A?	clinical evaluation / validated scales / instrumental evaluation
2	How do you evaluate patients after BoNT-A injection?	clinical evaluation / validated scales / instrumental evaluation
3	How frequently do you re-inject patients with BoNT-A?	injections / year
4	Do you inject BoNT-A according to the recommended dilutions?	Yes / No
5	Do you consider the recommended BoNT-A doses adequate?	Yes / No
6	Do you initiate BoNT-A therapy at low doses, titrating them upwards as effects become evident?	Yes / No
7	Do you alter BoNT-A dosages during the course of BoNT-A treatments?	Yes / No
8	Which technique do you use for injecting BoNT-A in the above-mentioned clinical conditions?	palpation / electrical stimulation / electromyography / ultrasonography
9	Do you prescribe (when appropriate) rehabilitation procedures after BoNT-A injection?	Yes / No
10	Have you ever reported at least one adverse reaction to BoNT-A in your clinical practice? If so, why did it occur?	Yes / No
Education		
1	How many courses on the use of BoNT-A have you attended in the past year?	number
2	How many courses on the use of BoNT-A have you attended in the past five years?	number
3	What kind of courses on BoNT-A would you like to attend in the future?	description

BoNT-A=botulinum toxin type A

Results

All the physicians included in the survey (one physician per clinical unit) completed the questionnaire during the period from March to June 2011. Two hundred and three (97%) physicians usually used BoNT-A in their clinical practice. One hundred and eighty (86%) physicians worked in a specific service for the treatment of patients with BoNT-A. The clinical experience in BoNT-A treatment of the physicians involved in the survey was as follows: 18 physicians (9%) had less than two years' experience; 44 physicians (21%) had between two and five years' experience; 70 physicians (33%) had between five and ten years' experience; 78 physicians (37%) had more than ten years' experience. Data on the clinical conditions treated with BoNT-A are shown in table II. Seventy-two physicians (34%) used BoNT-A to treat muscle overactivity associated with pain.

As regards the evaluation procedures used for planning a treatment strategy based on the injection of BoNT-A, 197 physicians (93%) assessed patients by means of a detailed clinical examination, 158 (75%) evaluated patients with specific validated scales, while 120 (57%) used an instrumental evaluation, such as motion analysis or electromyography (EMG). As regards the assessment of clinical improvements after BoNT-A injection, 185 (88%) physicians evaluated patients by means of a detailed clinical examination, 147 (70%) assessed patients by means of specific scales, while ninety-six (45%) used an instrumental evaluation.

Table II gives data on the frequency of BoNT-A re-injections. One hundred and seventy-six physicians (83%) injected BoNT-A according to the recommended dilutions, while 163 (77%) considered the recommended BoNT-A doses to be adequate. Moreover, 160 physicians (76%) initiated therapy at low doses, titrating doses upwards as effects become evident, while 24% of physicians involved in this survey did not alter BoNT-A dosages during the course of BoNT-A injections. Data on the BoNT-A injection techniques used are shown in table III.

One hundred and sixty-five (78%) physicians prescribed, when appropriate, rehabilitation procedures (such as electrical stimulation, casting, splinting, taping or physical therapy) after BoNT-A injection. As regards the occurrence of adverse reactions to BoNT-A, eleven (5%) physicians reported at least one event, which in half the cases might have been due to an inaccurate injection technique.

As for BoNT-A-related medical education, the physicians involved in this survey had attended a mean of 0.9 courses (range 0-5) on the use of BoNT-A in patients with neurological disorders in the previous year and a mean of 2.9 courses (range 0-16) in the previous five years. One hundred and fifty-four (73%) physicians were interested in courses on BoNT-A injection techniques, while 68 (32%) were interested in courses on the neurorehabilitation management of patients with neurological disorders.

Table II - Clinical conditions treated with BoNT-A.

Clinical condition	Units n (%)	Patients/year (median)	Re-injections/year (mean)
Dystonia	140 (66)	30	3.3
Spasticity	170 (80)	50	3.0
Cerebral palsy	74 (35)	20	2.4
Other	78 (37)	20	2

Abbreviations: BoNT-A=botulinum toxin type A; n=number

Table III - BoNT-A injection techniques.

Clinical condition	No instrumental guidance n (%)	Electrical stimulation guidance n (%)	Electromyography guidance n (%)	Ultrasonography guidance n (%)
Dystonia (total of 140 clinical units)	100 (71)	22 (16)	95 (68)	15 (11)
Spasticity (total of 170 clinical units)	140 (82)	57 (34)	110 (65)	35 (21)
Cerebral palsy (total of 74 clinical units)	59 (80)	14 (19)	23 (31)	25 (34)
Other (total of 78 clinical units)	16 (21)	22 (28)	8 (10)	20 (26)

Abbreviations: BoNT-A=botulinum toxin type A; n=clinical units that use this technique

Discussion

The main aim of this survey was to provide an overview of some important issues relating to the therapeutic strategies adopted by physicians who use BoNT-A injections to treat patients with neurological disorders. We investigated a representative sample of physicians (n=210) in Italy who use BoNT-A; of these 210 medical experts in the field of neurology and neurorehabilitation, 86% treated their patients with BoNT-A in a specific clinical service and 70% had more than five years' experience with botulinum toxin. The main neurological conditions treated with BoNT-A were dystonia (66%), spasticity in adults (80%) and cerebral palsy in children (35%).

In particular, 93% of the physicians involved in this survey performed a detailed clinical assessment prior to the injection every time they treated a patient with BoNT-A. Moreover, 75% of the physicians used specific, validated scales, while 57% performed an instrumental evaluation of patients before administering BoNT-A injections. As regards the assessment of the outcome of treatment, 88% of the physicians performed a full clinical assessment after BoNT-A injection, 70% evaluated patients clinically by means of validated scales, while 45% performed an instrumental evaluation. According to the international consensus on the use of BoNT-A for treating neurological disorders, patients should be regularly assessed both before and after injections so that the planning of the treatment strategy can be ongoing and the goals can be refined according to the improvements achieved (Novak et al., 2010; Heinen et al., 2010; Wissel et al., 2009; Sheean et al., 2010; Olver et al., 2010; Fehlings et al., 2010; Love et al., 2010; Simon and Yelnik, 2010). We observed, in this survey, that patients were not evaluated in the same way before and after BoNT-A injection. We interpret the discrepancy between the pre- and post-injection instrumental evaluations as being due to the fact that more time-consuming assessments, such as three-dimensional motion analysis with poly-EMG, are only performed in selected cases to correctly plan the treatment strategy before BoNT-A is injected.

Moreover, we recommend the use of specific, validated scales combined with simple instrumental evaluations (such as analysis of spatiotemporal gait parameters or video analysis of movement) to assess patients before and after BoNT-A injection, not only to improve the decision-making accuracy in the case of re-injections, but also to encourage physicians to speak the same language and evaluate interventions using more standardized instruments that correspond as closely as possible to the dimensions of the International Classification of Functioning, Disability and Health (Novak et al., 2010; Heinen et al., 2010; Wissel et al., 2009).

The re-injection intervals reported in this survey are in line with those recommended in the literature (Novak et al., 2010; Sheean et al., 2010; Olver et al., 2010; Fehlings et al., 2010; Love et al., 2010). In particular, we observed a mean re-injection time in patients with dystonia and adults with spasticity of about four months (Novak et al., 2010; Sheean et al., 2010; Olver et al., 2010), whereas the mean re-injection time in children with cerebral palsy was about six months (Fehlings et al., 2010; Love et al., 2010), which reflects the fact that intervals between BoNT-A injections should exceed three months in order to prevent the formation of neutralizing antibodies (Novak et al., 2010; Sheean et al., 2010; Olver et al., 2010; Fehlings et al., 2010; Love et al., 2010). As regards the BoNT-A dosage, it is noteworthy that about one quarter of the physicians involved in this survey did not alter the dosage of the toxin injections. This is in contrast to the international consensus, which instead recommends initiating therapy at low doses and titrating doses upwards as effects become evident (Novak et al., 2010; Heinen et al., 2010; Wissel et al., 2009). In particular, BoNT-A dosages should be determined on the basis of the patient's condition and treatment goals, with the latter being reassessed according to the response (Wissel et al., 2009). We believe that this point, combined with a proper assessment (see above), is crucial if an optimal treatment outcome is to be achieved.

As regards BoNT-A injection techniques, it is noteworthy that most of the physicians enrolled in this survey used no guidance for needle positioning (Table III). This is, we believe, a critical issue in the use of BoNT-A for the treatment of patients with neurological disorders, as an inaccurate injection technique is reported to be one of the main reasons for a lack of BoNT-A response and may reduce the safety profile of BoNT-A injections (Wissel et al., 2009; Lim et al., 2011). The importance of this issue is confirmed by the findings regarding adverse reactions reported by the physicians in this survey, which may, in half the cases, be ascribed to an inaccurate injection technique.

In patients with dystonia, EMG has been reported to be a useful tool in the assessment and planning of BoNT-A treatment as it can be used to identify muscles that are contracting inappropriately (Lim et al., 2011). In particular, passive-monitoring EMG guidance has been recommended in conditions characterized by sustained muscle contractions, such as cervical dystonia. Active-monitoring EMG guidance may instead be useful when patients can voluntarily activate the target muscle, as occurs in limb dystonia (Lim et al., 2011). In adult patients with spasticity, guidance (e.g. EMG/electrical stimulation or ultrasonography) has been recommended as standard practice for deep-seated, small muscles, while palpation with no instrumental guidance is commonly used when injecting BoNT-A into large, superficial muscles (Wissel et al., 2009). The importance of guidance during BoNT-A injection in adults with spasticity is being increasingly recognized in clinical practice. Ultrasonography, in particular, not only contributes to accurate BoNT-A injection, by allowing the needle to be positioned precisely in the target muscle, but can also be used to investigate other potential underlying causes of a lack of BoNT-A response in these patients, such as the development of changes in the muscle (fibrosis) (Picelli et al., 2012). The routine use of ultrasonography to guide BoNT-A injections in children with cerebral palsy has been reported in the literature (Sheean et al., 2010; Olver et al., 2010). In particular, studies on children with cerebral palsy have reported a correlation between the effectiveness of BoNT-A-induced selective neuromuscular blocking and the accuracy of injections guided by ultrasonography (Py et al., 2009;

Kaishou et al., 2009; Kwon et al., 2010), which allows rapid identification of the muscle, precise needle positioning and real-time adjustment of the injection procedure in these patients (Sheean et al., 2010).

Although rehabilitation has been reported to improve BoNT-A-injection-based clinical interventions, allowing the dose of subsequent injections to be reduced or the time between injections to be increased (Novak et al., 2010; Heinen et al., 2010; Wissel et al., 2009; Sheean et al., 2010; Olver et al., 2010; Fehlings et al., 2010; Love et al., 2010), the optimal adjunctive interventions in the BoNT-A management of neurological patients remain a matter of debate. In this survey, 78% of the physicians prescribed, when appropriate, rehabilitation procedures (such as electrical stimulation, casting, splinting, taping and physical therapy) after BoNT-A injection. According to the international consensus, physical therapy and EMG biofeedback are recommended as adjunctive interventions to BoNT-A in patients with cervical dystonia (Novak et al., 2010). In such cases, physical therapy may include cervical flexibility and strengthening exercises, soft tissue mobilization and myofascial elongation maneuvers, axial strengthening and stretching exercises, and balance and posture retraining combined with biofeedback to teach patients how to actively control their dystonic neck muscle contractions (Novak et al., 2010). As regards patients with limb dystonia, evidence suggests that electrical stimulation to the injected muscles enhances the effect of BoNT-A (Olver et al., 2010; Picelli et al., 2011). The European consensus table on the use on BoNT-A in adult spasticity recommends that a multidisciplinary team undertake spasticity management since optimal treatment involves physical therapy in conjunction with intermittent pharmacological treatment (Wissel et al., 2009). In particular, electrical stimulation of the injected muscles after BoNT-A injection, as well as the use of casting, splinting or taping, reportedly enhance the effect of BoNT-A in adults with spasticity (Olver et al., 2010; Picelli et al., 2011; Smania et al., 2010; Carda et al., 2011; Baricich et al., 2008; Reiter et al., 1998; Carda et al., 2005; Farina et al., 2008; Yaşar et al., 2010). Moreover, physical therapy protocols, including strengthening, stretching and mobilization exercises, have been recommended as adjunctive interventions to BoNT-A in such patients (Sheean et al., 2010; Olver et al., 2010). As regards children with cerebral palsy, not only are serial casting and prolonged stretching recommended for the management of fixed contractures and muscle lengthening after BoNT-A injections, but also muscle strengthening and targeted motor training are suggested as essential adjunctive interventions to improve motor function (Fehlings et al., 2010; Love et al., 2010).

This survey undoubtedly has certain limitations, which should be highlighted. First, we did not involve all the neurology and neurorehabilitation units in our country, and it is possible that the relatively small population size may have hindered the evaluation of other aspects that deserve attention. Second, we focused on the most common neurorehabilitation applications of BoNT-A, namely dystonia, adult spasticity and cerebral palsy. It would be interesting to investigate other applications of BoNT-A, such as autonomic disorders, in more depth. Future studies should take these aspects into account, comparing the results obtained in Italy with those available on the routine use of BoNT-A across Europe.

In conclusion, the results of this survey indicate that the application of BoNT-A treatment in patients with neurological disorders varies considerably and is far from standardized. This overview may help to achieve a more widespread consensus on the use of BoNT-A, particularly as regards the assessment, treatment and injection procedures involved.

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References

Albanese A (2011). Terminology for preparations of botulinum neurotoxins: what a difference a name makes. JAMA 305:89-90.

Baricich A, Carda S, Bertoni M, et al (2008). A single-blinded, randomized pilot study of botulinum toxin type A combined with non-pharmacological treatment for spastic foot. J Rehabil Med 40:870-872.

Carda S, Molteni F (2005). Taping versus electrical stimulation after botulinum toxin type A injection for wrist and finger spasticity. A case-control study. Clin Rehabil 19:621-626.

Carda S, Invernizzi M, Baricich A, et al (2011). Casting, taping or stretching after botulinum toxin type A for spastic equinus foot: a single-blind randomized trial on adult stroke patients. Clin Rehabil 25:1119-1127.

Esquenazi A, Novak I, Sheean G, et al (2010). International consensus statement for the use of botulinum toxin treatment in adults and children with neurological impairments - introduction. Eur J Neurol 17 Suppl 2:1-8.

Farina S, Migliorini C, Gandolfi M, et al (2008). Combined effects of botulinum toxin and casting treatments on lower limb spasticity after stroke. Funct Neurol 23:87-91.

Fehlings D, Novak I, Berweck S, et al (2010). Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement. Eur J Neurol 17 Suppl 2:38-56.

Heinen F, Desloovere K, Schroeder AS, et al (2010). The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy. Eur J Paediatr Neurol 14:45-66.

Kaishou Xu, Tiebin Yan, Jianning Mai (2009). A randomized controlled trial to compare two botulinum toxin injection techniques on the functional improvement of the leg of children with cerebral palsy. Clin Rehabil 23:800-811.

Kwon JY, Hwang JH, Kim JS (2010). Botulinum toxin A injection into calf muscles for treatment of spastic equinus in cerebral palsy: a controlled trial comparing sonography and electric stimulation-guided injection techniques: a preliminary report. Am J Phys Med Rehabil 89:279-286.

Lim EC, Seet RC (2010). Use of botulinum toxin in the neurology clinic. Nat Rev Neurol 6:624-636.

Lim EC, Quek AM, Seet RC (2011). Accurate targeting of botulinum toxin injections: how to and why. Parkinsonism Relat Disord 17 Suppl 1:S34-39.

Love SC, Novak I, Kentish M, et al (2010). Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. Eur J Neurol 17 Suppl 2:9-37.

Naumann M, So Y, Argoff CE, et al (2008). Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 70:1707-1714.

Novak I, Campbell L, Boyce M, et al (2010). Botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck: international consensus statement. Eur J Neurol 17 Suppl 2:94-108.

Olver J, Esquenazi A, Fung VS, et al (2010). Botulinum toxin assessment, intervention and aftercare for lower limb disorders of movement and muscle tone in adults: international consensus statement. Eur J Neurol 17 Suppl 2:57-73.

Picelli A, Smania N, Storti I, et al (2011). Immediate versus delayed electrical stimulation boosts botulinum toxin effect: a pilot study. Mov Disord 26:1784-1785.

Picelli A, Bonetti P, Fontana C, et al (2012). Is spastic muscle echo intensity related to the response to botulinum toxin type A in patients with stroke? A cohort study. Arch Phys Med Rehabil 93:1253-1258.

Py AG, Zein Addeen G, Perrier Y, et al (2009). Evaluation of the effectiveness of botulinum toxin injections in the lower limb muscles of children with cerebral palsy. Preliminary prospective study of the advantages of ultrasound guidance. Ann Phys Rehabil Med 52:215-223.

Reiter F, Danni M, Lagalla G, et al (1998). Low-dose botulinum toxin with ankle taping for the treatment of spastic equinovarus foot after stroke. Arch Phys Med Rehabil 79:532-535.

Sheean G, Lannin NA, Turner-Stokes L, et al (2010). Botulinum toxin assessment, intervention and after-care for upper limb hypertonicity in adults: international consensus statement. Eur J Neurol 17 Suppl 2:74-93.

Simon O, Yelnik AP (2010). Managing spasticity with drugs. Eur J Phys Rehabil Med 46:401-410.

Smania N, Picelli A, Munari D, et al (2010). Rehabilitation procedures in the management of spasticity. Eur J Phys Rehabil Med 46:423-438.

Ward AB, Molenaers G, Colosimo C, Berardelli A (2006) Clinical value of botulinum toxin in neurological indications. Eur J Neurol 13 Suppl 4:20-26.

Wissel J, Ward AB, Erztgaard P, et al (2009). European consensus table on the use of botulinum toxin type A in adult spasticity. J Rehabil Med 41:13-25.

Yaşar E, Tok F, Safaz I, et al (2010). The efficacy of serial casting after botulinum toxin type A injection in improving equinovarus deformity in patients with chronic stroke. Brain Inj 24:736-739.