Toxicon 54 (2009) 614–623

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

# Disease-oriented approach to botulinum toxin use

Joseph Jankovic*

*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, 6550 Fannin, Suite 1801, Houston, TX 77030, USA*

ARTICLE INFO

*Article history:*
Received 30 October 2008
Accepted 28 November 2008
Available online 6 December 2008

*Keywords:*
Blepharospasm
Botulinum toxin
Bruxism
Camptocormia
Constipation
Dystonia
Parkinson disease
Sialorrhea

ABSTRACT

Botulinum toxin (BoNT) has been used for over a quarter of century for the treatment of well over 100 different indications. Many of the symptoms for which BoNT has been found to be effective occur in a variety of neurological disorders. One neurodegenerative disorder in which BoNT has been used extensively to treat various symptoms is Parkinson's disease (PD). This review will highlight the following therapeutic applications of BoNT in conditions associated with PD: limb dystonia, blepharospasm and lid apraxia, bruxism, cervical dystonia (anterocollis), camptocormia, hand and jaw tremor, rigidity (painful shoulder), freezing of gait, sialorrhea, dysphagia (achalasia), seborrhea, hyperhidrosis, overactive bladder, and constipation.



## 1. Introduction

The application of botulinum toxin (BoNT) as a therapeutic modality has expanded markedly over the past quarter of century. Initially used by specialists in neurology (movement disorders) and ophthalmology (strabismus), BoNT has been subsequently used in nearly all specialties of medicine, including physiatry, orthopedics and sports medicine, otolaryngology, pediatrics, gastroenterology, urology, pain specialists, dermatology, and plastic surgery (Truong and Jost, 2006; Jankovic et al., 2008). In addition, neuroscientists and other basic scientists are using BoNT to study its mechanism of action, as a result of which our knowledge of BoNT as a molecule has increased exponentially.

There are several diseases in which troublesome symptoms, such as involuntary spasms or movements, hypesecretory or other autonomic dysfunctions, and other problems become amenable to BoNT treatment. Such disease-oriented application of BoNT has been successfully used in cerebral palsy and a variety of neurodegenerative disorders. Parkinson disease (PD), the second most common neurodegenerative disorder, has been selected for this review to illustrate how disease-related symptoms may be effectively relieved with BoNT. Manifested by dozens of motor and non-motor symptoms that can impair activities of daily living, PD can seriously impact the quality of life of those afflicted with this disease (Jankovic, 2008). While most of the motor symptoms, particularly the cardinal features of PD, such as tremor, bradykinesia, rigidity and gait difficulty, improve with dopaminergic and other therapeutic, including surgical, strategies, many troublesome symptoms do not respond to conventional treatments (Diamond and Jankovic, 2006). In this review, we will briefly describe the use of BoNT in the treatment of the following PD-related disorders: limb dystonia, blepharospasm and apraxia of eyelid opening, bruxism, cervical dystonia (anterocollis), camptocormia, hand and jaw tremor, rigidity (painful shoulder), freezing of gait, sialorrhea, dysphagia (achalasia), seborrhea, hyperhidrosis, overactive bladder, and constipation (Table 1) (Sheffield and Jankovic, 2007). We will use the generic term botulinum toxin or BoNT, but the brand names, such as Botox®, Dysport® and Xeomin®, all BoNT type A (BoNT/A)

* Tel.: +1 713 798 5998; fax: +1 713 798 6808.
*E-mail addresses:* josephj@bcm.edu, josephj@bcm.tmc.edu

0041-0101/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.toxicon.2008.11.013

**Table 1**
Botulinum toxin in the treatment of symptoms associated with Parkinson's disease.

| |
|---|
| Dystonia |
| • Blepharospasm – lid apraxia |
| • Bruxism |
| • Limb – striatal hand/foot, levodopa-related dystonia |
| • Cervical dystonia (anterocollis) |
| • Camptocormia |
| Tremor – hand, jaw |
| Rigidity (painful shoulder) |
| Freezing of gait |
| Sialorrhea |
| Dysphagia (achalasia) |
| Seborrhea |
| Hyperhidrosis |
| Overactive bladder |
| Constipation |

preparations, or Myobloc® (NeuroBloc®), a BoNT/B, will be identified whenever appropriate as properties and dosages are often unique to that product. While the intent of BoNT treatment is not only to improve the specific symptom but the patient's quality of life, it is important to point out that the overall outcome of BoNT treatment depends not only on selection of the appropriate target, preparation and dosage, but also on the injection technique, and many other factors (Lim and Seet, 2008).

## 2. Dystonia

Dystonia, a syndrome characterized by sustained muscle contraction associated with twisting, repetitive, and patterned movements or abnormal postures, has been treated with BoNT for the past quarter of century (Jankovic, 2006b). One form of focal dystonia, blepharospasm, was the first indication for which BoNT was approved by the Food and Drug Administration (FDA) (Jankovic and Orman, 1987). Blepharospasm can occur as a form of focal primary dystonia, without an identifiable cause (idiopathic or essential blepharospasm), or it may be due to a variety of etiologies including PD (Hallett et al., 2008). Different forms of dystonia may be present in up to 60% of patients with PD, particularly those with early onset (Jankovic and Tintner, 2001). In addition, dystonia may occur as one of several motor complications of levodopa therapy (Jankovic and Stacy, 2007).

### 2.1. Blepharospasm and lid apraxia

Blepharospasm is an involuntary, forceful eye closure, considered to be a form of dystonia (Hallett et al., 2008). Blepharospasm usually occurs in more advanced stages of PD; when it occurs alone it rarely leads to PD (Soonawala et al., 1999). Although it may accompany PD, the presence of blepharospasm should raise the possibility of atypical parkinsonism, such as progressive supranuclear palsy, in which blepharospasm is more common (Azher and Jankovic, 2008). When seen in the setting of parkinsonism, blepharospasm is often associated with apraxia of eyelid opening. Attributed to a variety of possible mechanisms, such as focal dystonia, levator inhibition, abnormal contraction in the pretarsal orbicularis oculi, or eyelid freezing (analogous to freezing of gait, described below), the pathophysiology of lid apraxia is not well understood (Hallett et al., 2008; Elston, 1992; Krack and Marion, 1994).

The long-term experience with BoNT in the treatment of blepharospasm has provided evidence in support of the efficacy and safety of this treatment in patients with blepharospasm (Jankovic, 2004; Mejia et al., 2005; Kenney and Jankovic, 2008). Despite the extensive literature on BoNT in blepharospasm, an evidence-based review by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) concluded that there is only level B (probably effective) evidence for its efficacy, and recommended that "BoNT injection should be considered as a treatment option for blepharospasm" (Simpson et al., 2008). This study involved 300 patients with blepharospasm, 256 of whom completed the trial (Roggenkamper et al., 2006). The primary outcome was the change from baseline in the sum score of the Jankovic Rating Scale (JRS). The adjusted mean change in the JRS was −2.90 for the NT 201 and −2.67 for the Botox® group. The frequency of ptosis, the most common adverse effect, was 6.1% and 4.5%, respectively. When compared to Botox®, both products were found to be equally effective with no difference in adverse effects. The level B recommendation was supported by two Class II studies, both utilizing Botox® (Jankovic and Orman, 1987; Girlanda et al., 1996). One Class I study, which compared NT 201 (Xeomin®) with Botox® concluded that the two drugs are similar in their effects on blepharospasm (Roggenkamper et al., 2006). The likely reason for the lack of optimal evidence supporting BoNT use in blepharospasm is that the robust benefits observed in the initial open-label studies, coupled with the lack of alternative therapies, discouraged other and better controlled clinical trials.

Another Class I study, published after the above AAN report (Simpson et al., 2008), was a multicenter, clinical, fixed-dose, trial comparing Dysport® (40, 80, and 120 U/eye) with placebo (in a 3:1 randomization ratio) in 119 patients with blepharospasm, 85 of whom completed the 16-week study (Truong et al., 2008). There was a robust improvement in Dysport® arms compared to placebo in several measures. Overall, 80 U of Dysport® seemed to provide best balance between efficacy and adverse effects, such as ptosis, blurred vision, diplopia, tearing, and dry eyes. A Chinese formulation of BoNT/A, termed Prosigne, has been found in a double-blind, controlled, crossover trial to be similar in its safety and efficacy to Botox® when evaluated in 6 patients with blepharospasm and hemifacial spasm (Rieder et al., 2007). In addition to BoNT/A, BoNT/B has also been used successfully in the treatment of blepharospasm (and hemifacial spasm), although double-blind controlled studies in these disorders are lacking (Colosimo et al., 2003).

Several studies reported improvement in apraxia of eyelid opening, particularly if associated with or triggered