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Botulinum toxin in parkinsonism: The when, how, and which for botulinum toxin injections

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ABSTRACT

The aim of this article is to provide a review of the use of injections of botulinum toxin in the management of selected symptoms and signs of Parkinson's disease and other forms of parkinsonism. Sialorrhea is defined as inability to control oral secretions, resulting in excessive saliva in the oropharynx. There is a high level of evidence for the treatment of sialorrhea in parkinsonism with injections of different forms of botulinum toxin type A as well as botulinum toxin type B. Tremor can be improved by the use of botulinum toxin injections but improved tremor control often leads to concomitant motor weakness, limiting its use. Levodopa induced dyskinesias are difficult to treat with botulinum toxin injections because of their variable frequency and direction. Apraxia of eyelid opening, a sign more commonly seen in progressive supranuclear palsy and other tauopathies, often improves after botulinum toxin injections. Recent data suggest that regardless of the underlying mechanism, pain in parkinsonism can be alleviated by botulinum toxin injections. Finally, freezing of gait, camptocormia and Pisa syndrome in parkinsonism almost invariably fail to respond to botulinum toxin injections.

1. Introduction

The mainstay of the treatment of Parkinson's disease (PD) and other parkinsonian syndromes is pharmacological management of dopamine and other neurotransmitters. Surgical procedures such as deep brain stimulation may provide help to a relatively small proportion of patients with PD who fail to improve with best medical treatment. There are patients who remain with symptoms and signs non-responsive to these therapeutic options. In a few of these instances injections of botulinum toxin (BoNT) may be beneficial. The list of symptoms and signs in different parkinsonian disorders reported to be amenable to treatment with BoNT is long and includes sialorrhea, freezing of gait, overactive bladder, dystonia, apraxia of eyelid opening, levodopa-induced dyskinesias, limb and jaw tremor, camptocormia, intestinal constipation, and pain. One recently published retrospective chart review of a busy Canadian movement disorders clinic identified no more than 160 patients with parkinsonism with clinical features treated with injections of BoNT in the period from 1995 to 2014. Out of these individuals, 117 had PD, 36 received the diagnosis of atypical parkinsonism and the etiology was not identified in seven patients (Bruno et al., 2016). According to the criteria of evidence based medicine there are Class I studies only for sialorrhea and freezing of gait and open-label studies for overactive bladder. Unfortunately for the other parkinsonian symptoms and signs previously listed, there are just case reports that render it difficult to understand the actual role of injections of BoNT injections in their management. The aim of this article is to provide a critical personal review of the use of BoNT to treat selected symptoms and signs in PD and other parkinsonian syndromes. The article is based on personal experience of the author as well as a review of the published literature in English using the following search words: botulinum toxin, parkinsonism, sialorrhea, drooling, dyskinesia, tremor, dystonia, levodopa-induced dyskinesia, apraxia of the eyelid opening, overactive bladder, pain, camptocormia, other postural deformities, freezing of gait, and pain. The subject was reviewed in Toxicon in the past (Jankovic, 2009).

2. Sialorrhea

Sialorrhea is defined as the inability to control oral secretions, resulting in excessive saliva in the oropharynx. Unlike what

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common sense indicates, the pathogenesis of drooling in PD does not involve excessive production of saliva but rather impairment of swallowing. The flexion of head adds further difficulty in the clearance of saliva. The frequency of sialorrhea is reported to range from 31% to 86% of patients with PD (Barone et al., 2009; Chou et al., 2007). The discrepancy of the numbers depends on the method used to assess the accumulation of saliva as well as the characteristics of the studied population. Regarding the latter, as expected the prevalence is greater in patients with dysphagia (86%) in comparison with those without swallowing impairment (44%) (Chou et al., 2007). Interestingly, drooling is seen in very early stage of the disease when patients list it as one of the most disabling non-motor findings of PD (Khoo et al., 2013). Despite its frequency and related disability, there are few proven efficacious treatments for sialorrhea in parkinsonism. Potential treatments for this condition include anticholinergics (sublingual atropine, ipratoprium bromide spray, and glycopyrrolate), adrenergic receptor agonists (clonidine and modafinil) and non-pharmacological approaches such as chewing gum, behavioral modification, speech therapy, surgery and even radiotherapy of the salivary glands (Chou et al., 2007). Unfortunately, only ipratoprium bromide spray and glycopyrrolate underwent clinical trials of good quality that led to the conclusion that the former is investigational and the latter possibly useful for the management of sialorrhea (Seppi et al., 2011). There is, therefore, the need for alternative and more efficacious treatments for this condition.

The rationale for the use of BoNT injections of the salivary glands to treat drooling is based on the blocking of cholinergic transmission that underlies the secretion of saliva. An important issue that needs to be taken into account when designing the strategy to use BoNT injections to manage sialorrhea is to understand that the majority of saliva is secreted by the parotid and submandibular glands. There have been several well-designed trials assessing the role of BoNT injections into the parotid and submandibular glands to treat sialorrhea in PD. Seven studies, of which two were placebo controlled, assessed the use of Onabotulinumtoxin A in drooling in PD. The dosage for the parotid and submandibular glands were, respectively, 5–50U and 5U. The data show that the active drug is significantly more efficacious than placebo and the effect lasted from one to four months. Moreover, the treatment was well tolerated with few and mild side effects (dryness of mouth and dysphagia). Three trials, two of which were placebo controlled, replicated these findings with Abobotulinumtoxin A. The dosage for each parotid gland ranged from 75 to 146U and each submandibular gland was injected with 78U (Srivanitchapoom et al., 2014). Because of its greater affinity for autonomic terminals, it was expected that Rimabotulinumtoxin B could be more efficacious than the type A toxins. In fact, in studies of treatment of cervical dystonia with toxin type A and type B, dry mouth was more commonly seen in the latter group (Pappert et al., 2008). However, five studies of this BoNT (three of them were placebo controlled) found results similar to those reported for BoNT A: better response than placebo, resulting in improvement of drooling for up to four months, with a few patients also developing dysphagia and dryness of mouth. In these trials the dosage per parotid gland was 500–2000U and each submandibular gland received 250U (Srivanitchapoom et al., 2014). One more recent report describes the open label long term experience of BoNT injections in the management of drooling in 33 PD patients and 32 individuals with amyotrophic lateral sclerosis. The authors performed ultrasound guided injections either of Abobotulinumtoxin A (250U) in 136 sessions or Rimabotulinumtoxin B (2500U) in 181 sessions. There was 'clearcut' benefit in 89% of sessions without any difference between the two types of BoNT. The average benefit lasted 87 days and side effects were reported solely in 8.9% of sessions (Petracca et al., 2015). Based on these results, the MDS Evidence Based group concluded that injections of both BoNT A and B are an efficacious and clinically useful treatment for sialorrhea in PD carrying an acceptable risk with specialized monitoring (Seppi et al., 2011). There are, however, unsettled issues that require further studies to be solved: number of injection sites; parotid versus submandibular gland injections; blind versus ultrasound guided injections; and type A or type B toxin (Dogu et al., 2004).

3. Hyperkinesias

Bradykinesia is the hallmark of all parkinsonian syndromes. Nevertheless, a proportion of patients with parkinsonism may develop hyperkinesias either spontaneously as part of the underlying disease or because of use of pharmacological agents, particularly dopaminergic drugs.

3.1. Tremor

Tremor is the most common spontaneous hyperkinesia associated with parkinsonism, in particular PD. Because it is often a tremor at rest that improves or even disappears with action, it does not cause marked disability in the majority of individuals. It is true though that a few patients with PD have re-emergent tremor, tremor at rest that re-emerges after a variable delay while maintaining a posture tremor. This particular tremor may lead to functional disability (Jankovic et al., 1999). There have been a few open label studies of the use of BoNT injections to treat parkinsonian tremor refractory to conventional treatments. For hand tremor, there are reports showing that OnabotulinumtoxinA, 15U into the extensor compartment and 50–100U for the flexor compartment, improves parkinsonian tremor but at the expense of disabling weakness (Sheffield and Jankovic, 2007). This result mimics the experience of most experts in the field leading to the conclusion that the role of BoNT injections in the management of parkinsonian hand tremor is very limited. Although there are no published data supporting this, clinicians treating tremor with BoNT injections currently avoid injecting the forearm extensor muscles to prevent development of finger weakness. There is one description of a series of PD patients with jaw tremor treated with injections of 30–100U of AbobotulinumtoxinA per masseter. The authors reported that the injections were efficacious and without side effects (Schneider et al., 2006).

3.2. Levodopa-induced dyskinesias

It is estimated that for every year of exposure to levodopa, 10% of PD patients develop dyskinesias. In fact, a recent study showed that they are the clinical feature best correlated with the pathological findings of PD at autopsy (Adler et al., 2014). The most common dyskinesias occur during the *on* period, ie, when the patients are under the effect of levodopa. Typically, these dyskinesias are mobile and have a choreo-dystonic nature. A few patients with *on* dyskinesias and the majority of subjects with *off* dyskinesias have dystonia or stereotypies that have a predictable phenomenology. Their management involves changes of levodopa administration, use of other drugs such as amantadine, and, in selected patients, surgery. Exceptionally, when they fail to respond to these options, they can be treated with BoNT injections. This applies in particular when the phenomenology involves blepharospasm, jaw closing dystonia, and other predictable phenomena (Gupta and Visvanathan, 2016; Pacchetti et al., 1995). Because of the fluctuating and unpredictable phenomenology, treatment of levodopa-induced cervical dystonia with BoNT injections has been reported to have an unfavorable risk-benefit ratio (Espay et al., 2011). This is the opposite of

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