

## A New Therapeutic Indication of Botulinum Toxins: Sialorrhea

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*Acta Neurol Taiwan 2006;15:151-153*

Botulinum toxins (BoNT), especially the serotype A (BoNT/A), have already been known to be a promising treatment for neuromuscular disorders, and have revolutionized the therapy of dystonias, spasm, and spasticity<sup>(1)</sup>. The mechanism underlying the effect of BoNT in these conditions is the inhibition of acetylcholine (ACh) release at the neuromuscular junction<sup>(2)</sup>. Following local injection into the muscles, the toxin will enter the cholinergic nerve terminals via endocytosis, interact with the intracellular SNARE proteins, impede the fusion of synaptic vesicles with the presynaptic membrane, and inhibit the release of ACh<sup>(3)</sup>. Cholinergic parasympathetic and postganglionic sympathetic nerve synapses should be also amenable to the action of BoNT. In this perspective, BoNT could be a new way in treating a variety of autonomic hypersecretory disorders<sup>(4)</sup>. The emerging articles in recent years have quickly expanding the use of BoNT in new field of movement disorders, in sudomotor glandular dysfunction, and in pain syndromes. The studies of the efficacy in treating tics, tremor, myoclonic jerks and stuttering have showed satisfactory results<sup>(5)</sup>. There is a class I evidence for the efficacy of BoNT in axillary hyperhidrosis and a class II evidence for the palmar hyperhidrosis and gustatory sweating. There was increasing number of open pilot studies with small groups of patients describing the new applications of BoNT in hyperlacrimation, nasal hypersecretion and excessive drooling<sup>(6)</sup>.

There are seven serotypes of BoNT known alphabetically as types A to G. Of these serotypes, only A and B are available as commercial preparations<sup>(7)</sup>. Type C

and F have been used in human only on the experimental basis. The Botox<sup>®</sup> is one kind of serotype A BoNT, and the first commercial product to be used clinically. It is the most popular preparation in Taiwan and many countries throughout the world. The other commodity of serotype A BoNT (Dysport<sup>®</sup>) was later introduced in Europe and launched in Taiwan since 2001. Another product of serotype B BoNT with brand name as Myobloc<sup>®</sup>/Neurobloc<sup>®</sup> became available in 2000 in the United States, but not yet in Taiwan. Although all these 3 products have already been used clinically for a long time with the same mechanism of inhibiting ACh release, it should be kept in mind that they execute the clinical effect at different unit doses with different dilution preparations that may vary up to several orders of magnitude to have clinical comparability, and to avoid the side effect<sup>(8)</sup>.

Sialorrhea is a common symptom in many neurodegenerative diseases, such as the motor neuron disease and Parkinson's disease. Approximately 70% of patients with Parkinson's disease and 20% with bulbar amyotrophic lateral sclerosis suffered from excessive drooling<sup>(9)</sup>. Sialorrhea poses social embracement and significant risk of choking with aspiration and pneumonia. Pharmacotherapy is limited by insufficient efficacy and adverse effects. Surgical treatment like denervation of the parotid gland<sup>(10)</sup>, salivary duct ligation<sup>(11)</sup>, and bilateral excision of the sublingual salivary glands<sup>(12)</sup>, might risk irreversible adverse effects. Over the past few years, more than 10 studies reported the effectiveness of BoNT, including Botox<sup>®</sup>, Dysport<sup>®</sup>, and Myobloc<sup>®</sup>, in

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reducing the sialorrhoea in Parkinson's disease, parkinsonism, and cerebral palsy<sup>(13-18)</sup>. Although most of the literatures were open-label studies with relatively small groups of patients, the majority of patients experienced substantial beneficial responses with the duration varying from 7 weeks to 7 months after injection of parotid glands or parotid and submandibular glands combined. These studies did not report any significant adverse events including local pain, local infection of the salivary glands, dry mouth, deterioration of dysphagia, weakness of mouth closing and opening, hematoma, and injury of the facial nerve. However, detail information on the incidence of such side effects is currently not available.

In this issue, Su et al.<sup>(19)</sup>, analyzed the efficacy of Botox<sup>®</sup> in reducing drooling in 10 patients with Parkinson's disease, 4 patients with dementia with lewy bodies, and 1 patient with multiple system atrophy. The authors injected a total of 40-unit dose of Botox<sup>®</sup> into bilateral parotid and submandibular glands. They used the subjective assessment of "Drooling Score", and objective evaluation of measuring saliva production with dental rods to validate the improvement after treatment. They documented mean onset of Botox<sup>®</sup> effect was  $5.4 \pm 2.7$  days, and mean duration of responsiveness was  $16.3 \pm 5.7$  weeks. Except for 2 patients, one with Parkinson's disease and 1 with dementia, all patients reported more than 50% improvement. Although these results were in concert with the reports in the literature, the authors emphasized that low dose Botox of 40 units do not cause severe adverse effects, even in those associated with existing moderate dysphagia. However, it should be noted that Winterholler et al.<sup>(20)</sup>, described marked deterioration of dysphagia in ALS patients. Many studies used ultrasound guidance to target the parotid and/or submandibular glands. The authors injected these glands with blind technique and obtained comparable clinical effects.

Encouraging results from recent few controlled studies involving more than 30 patients have show that BoNT has the potential to replace the pharmacological therapy and surgical techniques in treating the sialorrhoea, and should at least be considered as a promising alterna-

tive<sup>(16-18)</sup>. We, of course, need further formal clinical trials of well-designed, double-blind, placebo-controlled, crossed-over studies with large patient group to optimize the dosage, to find the best mode of application, to clarify the duration of BoNT action, and to document the side effects in detail

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