Botulinum Toxin in the Treatment of Neurological Disorders of the Autonomic Nervous System

Markus Naumann, MD; Wolfgang H. Jost, MD; Klaus V. Toyka, MD

Botulinum neurotoxin A (BoNT/A) has become a valuable tool in the treatment of neurological disorders associated with increased muscle tone and has revolutionized the treatment of dystonia and focal spasticity. It acts at cholinergic nerve terminals by cleaving SNAP-25, a protein involved in the fusion of synaptic vesicles with the presynaptic membrane.1 Cholinergic autonomic parasympathetic and postganglionic sympathetic nerve synapses are also amenable to treatment with botulinum toxin.

Within the last few years, an increasing number of articles have been published focusing on new applications for BoNT/A. This short review gives an overview on recent indications of BoNT/A in the treatment of disorders of the autonomic nervous system and an outlook on possible future application.

TREATMENT OF AUTONOMIC DISORDERS

In view of the restricted action on the cholinergic system, potential indications for BoNT/A in disorders of the autonomic nervous system include diseases associated with sudomotor or secretomotor hyperactivity, neurogenic urinary bladder dysfunctions, and some gastrointestinal disorders, as well as uncommon dysfunctions of the pelvic floor involving smooth and striated muscles.

SUDOMOTOR AND SECRETOMOTOR HYPERACTIVITY

Neurogenic hyperactivity of secretory glands results in hyperhidrosis, hypersalivation, or increased tearing. The synaptic nerve endings of cholinergic neurons supplying eccrine sweat glands, salivary glands, and lacrimal glands are the target of BoNT/A.

Focal, segmental, or generalized hyperhidrosis may result from lesions at various levels of the central nervous system, such as cortical, subcortical, and spinal cord diseases, and may also be associated with some polyneuropathies. The most frequent form of hyperhidrosis, however, is essential (idiopathic) focal hyperhidrosis of the palms, axillae, or feet, affecting up to 0.5% of the population. Its pathogenesis is unknown, but a central mechanism has been suggested that may be located in the hypothalamus. Medical treatment of pathologic hyperhidrosis is often unsatisfactory, and surgical procedures, eg, sympathectomy, may involve considerable risks. Intradermal injection of BoNT/A has proved highly effective in abolishing focal sweating in essential hyperhidrosis. A number of prospective studies and one double-blind trial,2,3 conducted in more than 75 patients within the last 2 years, have uniformly shown a marked reduction of sweat secretion in the injected area and an improvement of quality of life. A total dose of up to 50 MU of Botox (or 300 MU of Dysport), evenly distributed over one palm or one axilla at multiple sites, is sufficient to control sweating. While the treatment is generally regarded as safe and simple, pain during the injection is the main complaint. In contrast to the neuromuscular system, there is a surprisingly long-lasting effect of BoNT/A in sudomotor fibers ranging from 6 to 12 months. Botulinum neurotoxin A may soon become the therapy of choice for focal hyperhidrosis that otherwise does not respond
to current procedures and may eventually replace sympathectomy. It may also be very effective in treating Ross syndrome, a rare condition that is characterized by a progressive anhidrosis due to degeneration of sudomotor fibers associated with areas of compensatory hyperhidrosis.3

A special variant of focal hyperhidrosis is gustatory sweating (Frey syndrome), which manifests as pathological sweat secretion on the cheek during eating. It is frequently observed after parotidectomy but may also occur with diabetes or after sympathectomy. It is based on aberrant sprouting of parasympathetic nerve endings originally supplying the parotid gland to the preauricular sweat glands. Various open studies on more than 100 patients5,6 have shown the efficacy of BoNT/A injections in abolishing gustatory sweating. Doses of intradermal injections ranged from 5 to 100 MU of Botox (20-250 MU of Dysport) administered at multiple sites over the affected areas. So far, it is unclear why the effect of BoNT/A in this syndrome has been lasting up to 3 years in some patients.

Increased tearing during eating is well known as the crocodile tears syndrome that is observed after facial nerve lesions with aberrant sprouting of autonomic parasympathetic fibers to the lacrimal gland. Although such pathological tearing is uncommon, it may be a very disabling disorder for which no adequate treatment is available. Botulinum neurotoxin A has turned out to be a simple and highly effective treatment option for pathological hyperlacrimation. Presently, its use is only documented by anecdotal case reports showing sufficient control of hyperlacrimation with no major adverse effects at very low doses (3 MU of Botox or 20 MU of Dysport, respectively, per lacrimal gland).7

Hypersalivation is only rarely the result of primarily increased salivary production but may more commonly be a serious secondary problem of dysphagia in neuromuscular diseases with predominant pharyngeal involvement or after brainstem lesions have occurred. Systemic anticholinergics are frequently not tolerated by the patients. Botulinum neurotoxin A seems to be a promising tool in reducing salivary gland secretion, as recently shown in an animal model,8 but clinical studies are lacking so far. Prospective efficacy and safety studies are required for hypersalivation and pathological tearing in order to evaluate the role of these potentially valuable indications.

URINARY BLADDER DYSFUNCTION

In the treatment of urological disorders, the use of BoNT/A has been studied primarily in detrusor sphincter dyssynergia. Detrusor sphincter dyssynergia is frequently seen in traumatic spinal cord injury or in multiple sclerosis based on a primarily neurogenic cause or that neurological involvement or after brainstem lesions have occurred. Systemic anticholinergics are frequently not tolerated by the patients. Botulinum neurotoxin A seems to be a promising tool in reducing salivary gland secretion, as recently shown in an animal model,8 but clinical studies are lacking so far. Prospective efficacy and safety studies are required for hypersalivation and pathological tearing in order to evaluate the role of these potentially valuable indications.

In this review, some autonomic disorders are included that are not primarily treated by neurologists but that may be based on a primarily neurogenic cause or that neurologists may be faced with in clinical practice. The excellent results of the study by Pasricha et al.10 in which BoNT/A was used for the treatment of achalasia, a disorder based on selective loss of inhibitory neurons in the myenteric plexus, have been replicated by several groups. Presently, injections of BoNT/A into the lower esophageal sphincter in this disorder can be recommended for multimorbid patients with complications following dilatation and with increased risk for other surgical therapies (myotomy). Insufficient relaxation of the upper esophageal sphincter, diffuse esophageal spasm, cricopharyngeal dystonia, sphincter Oddi dysfunction, and esophageal involvement in Chagas disease are other disorders that may also be amenable to BoNT/A treatment, but more studies are needed.

The efficacy of BoNT/A in the treatment of anal fissure has been demonstrated by several studies in which 5 to 20 MU of Botox or 20 to 80 MU of Dysport were injected into the external or internal anal sphincter. Studies published to date have included more than 200 patients and have demonstrated healing of the fissure in 70% to 90% of them.11 Surgery with the risk of permanent incontinence can thus be avoided. Other anal canal disorders, such as anismus, spasticity of the anal sphincter, and insufficient relaxation of the sphincter muscles with straining and defecation (paradoxical puborectalis syndrome), are also amenable to BoNT/A treatment. The use of BoNT/A for the treatment of constipation is restricted 58% and 88% using injections under urethroscopical or electromyographic guidance or using imaging techniques.9 The doses used are highly variable; some authors injected up to 140 U of Botox or 750 U of Dysport into the external and internal sphincter muscles at multiple sites. Future studies are needed to find the lowest effective dose in view of dose-dependent adverse effects, such as urinary incontinence, and in view of the cost of treatment. Since data supporting the use of BoNT/A for detrusor sphincter dyssynergia are incomplete, its routine use for this condition cannot be recommended at present. Therapy may be tried in patients with a high residual volume or in patients at high risk for reflux-induced renal damage, because the effect of BoNT/A is reversible and adverse effects are generally minimal. In potentially reversible spinal cord lesions, including those of acute severe spinal multiple sclerosis or isolated acute transverse myelitis, BoNT/A injection may become a valuable tool that will obviate the need for destructive surgical measures. There is a need for controlled studies using validated and reproducible outcome measures.

Injections of BoNT/A into the detrusor muscle may also be useful for the treatment of a hyperreflexic bladder. First studies with up to 30 injections into the detrusor muscle (2.5 MU of Botox injected per single site) show encouraging results. In some cases, endoscopically guided injections of the bladder apex may be sufficient to increase bladder capacity.

GASTROINTESTINAL AND OTHER RARE INDICATIONS

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to outlet constipation, while constipation in Parkinson disease, which is usually characterized by a slow transit, is not likely to respond favorably.

**CONCLUSIONS**

Botulinum neurotoxin A is of potential benefit in some autonomic disorders. However, it has not been formally approved for any of these indications. Larger studies have been performed only in patients with focal hyperhidrosis, including gustatory sweating, in a group of selected patients with detrusor sphincter dyssynergia, and in patients with achalasia or anal fissures. Possible indications based on single reports include pathological tearing (crocodile tears), hypersalivation, detrusor vesicourethral hyperactivity, chronic outlet constipation, and anismus. More research is needed to obtain a better insight into BoNT/A-induced morphological alterations in the injected tissues, the duration of action, the problem of neutralizing antibody formation, and possible long-term toxic effects.

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Reprints: Markus Naumann, MD, Neurologische Universitätsklinik der Bayerischen Julius-Maximilians-Universität, Josef-Schneider Strasse, 97080 Würzburg, Germany.