The use of intra-detrusor onabotulinumtoxinA in patients with myasthenia gravis

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Abstract

The use of intra-detrusor onabotulinumtoxinA (Botox®) in patients with myasthenia gravis has not been reported, and little evidence exists to substantiate a complete contraindication of Botox use in this population. Here, we present two cases of comorbid overactive bladder (OAB) and myasthenia gravis successfully treated with intra-detrusor Botox.

Introduction

Intra-detrusor onabotulinumtoxinA (Botox®) is commonly used in the treatment of patients with both neurogenic detrusor overactivity and idiopathic overactive bladder (OAB) who have failed anticholinergic therapy. This biologic toxin works by binding to receptors on presynaptic motor neurons and preventing release of acetylcholine into the neuromuscular junction.[1] When injected into the detrusor muscle, partial chemical denervation of the muscle occurs, manifesting as local muscle paralysis.

Given the mechanism of action of Botox, the product monograph warns that "extreme caution" should be exercised when administering this drug to patients with neuromuscular junction disorders. The most common of such conditions is myasthenia gravis (MG), an autoimmune disorder in which an antibody-mediated, T-cell-dependent process targets acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction.[2] This presents as weakening of the voluntary (skeletal) muscles of the body. The condition can deteriorate and can eventually lead to respiratory failure.[3]

The use of intra-detrusor Botox in patients with MG has not been reported and there is a paucity of evidence to support an absolute contraindication to its use in this population. Further, it is a clinical challenge to withhold life-altering treatment from patients with OAB and MG when there is no clear evidence of morbidity. We report two cases in which Botox was successfully used without complication in patients with comorbid OAB and MG.

Case reports

Our first case is a 70-year-old woman with urinary urgency, frequency, and mixed incontinence who was referred to our multidisciplinary bladder clinic after failing two anticholinergic medications due to side effects of dry mouth and dry eyes. At the time of initial referral in 2008, she did not have a diagnosis of MG. She was treated with intra-detrusor injection of Botox 200 units in October 2008, with significant improvement in her OAB symptoms (as documented in a validated OAB patient-reported outcome tool) and quality of life. She went on to have three subsequent treatments with 200 units in Oct. 2009, Oct. 2010, and July 2011. It should be noted that Botox was used in this patient prior to Health Canada approval for idiopathic OAB. It was used off-label in some refractory OAB patients at a dose of 200 units, as this reflected our clinical practice in neurogenic patients.

She was diagnosed with MG by a neurologist in the fall of 2011. Her main symptoms included daytime fatigue, profound sweating, episodic swallowing difficulties, and bilateral ptosis. Her treatment consisted of prednisone 15 mg, mestinon, and IVIG 150 mg monthly divided in two doses. She wished to continue with her Botox treatments, as her symptoms, reported by a standardized OAB tool, had increased to severe while off of Botox. After consulting her neurologist, permission was given to go ahead with a reduced dose of 100 units of intra-detrusor Botox. She went on to have 100 units injected in Oct. 2013 with excellent effect. There was no worsening of her neurologic symptoms or progression of her MG on followup. She went on to have a further 100 units July 2014, again with no neurologic deterioration.

Our second case is an 80-year-old woman referred in January of 2013 with poorly controlled OAB and a Grade

3 cystocele. Her primary urinary bother was that of nocturia every two hours with severe nighttime urgency and a very poor quality of life. She had previously been diagnosed with MG and followed by a neurologist. She was taking mestinon, an acetylcholinesterase inhibitor, for control of her MG symptoms, which precluded the use of anticholinergic medications. Her MG symptoms were mild, manifesting only as bilateral ptosis.

She was started on mirabegron (Myrbetric®) 50 mg daily and a pessary was fitted for her cystocele. Mutichannel urodynamics confirmed terminal detrusor overactivity at reduced bladder volumes. Her symptoms were not well-controlled on Myrbetriq and she subsequently requested Botox therapy. After consulting her neurologist, permission was given to proceed with Botox treatment at a dose of 100 units. In April 2015, she received her first treatment. She reported no worsening of her neurological status at her one-month followup. Her nocturia improved to once every four hours and led to a significant improvement in her quality of life. We plan to continue with Botox injections for ongoing symptom control.

Discussion

The medical literature is sparse when reporting the use of Botox in patients with MG. Most of the available experience is reported in the use of Botox for cosmetic indications and in those with dystonia. One case study describes a 49-year-old woman with both MG and cervical dystonia.[4] The individual was treated for her dystonia using Botox, with no observed flare in her MG symptoms. Her MG did not progress following the Botox treatment. Another study reports treatment of dystonia with Botox in an individual with comorbid MG.[5] The treatment was successful and, using EMG guidance and small dosage, the individual was safely treated without any side effects or generalized weakness. This was partially achieved through use of a more concentrated solution than usual to prevent spreading of the Botox to other muscle areas.

Other research suggests that pre-existing conditions, such as MG, may increase the potency of Botox-type drugs, causing adverse effects, such as muscle weakness.[6] However, it is also suggested that this can be corrected for by dose adjustment. A similar suggestion is made in a case study that reports MG symptoms worsening post-Botox administration for the treatment of dystonia.[7] The case study concludes that individuals with underlying neuromuscular conditions can develop more generalized weakness after Botox treatment and that caution should be used when administering Botox to these individuals, even in small doses.

We have presented two cases of comorbid OAB and MG that have successfully been treated with intra-detrusor Botox. Both patients were treated after careful consultation with their neurologist. We have also limited the dosage to 100 units in order to minimize the heightened theoretical risk of systemic side effects in the setting of MG. This report highlights the lack of evidence to support the practice of withholding Botox from all patients with MG.

Competing interests: Dr. Baverstock has served as an Advisory Board member for Allergan, Astellas, and Pfizer; a member of the Speakers' Bureau for Allergan, AMS, Astellas, and Pfizer; received payment/grants/honoraria from Allergan, AMS, Astellas, and Pfizer; and has participated in clinical trials for Allergan, Astellas, and Pfizer. The remaining authors declare no competing financial or personal interests.

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