

Prolonged Effect of Botulinum Toxin- A Treatment in Patients with Myasthenia Gravis

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Abstract

Purpose: To report the unexpectedly prolonged effect of botulinum toxin A (BTX) injection in patients with myasthenia gravis.

Methods: Retrospective review of presenting history, clinical findings and treatment of two cases.

Results: Two patients with myasthenia gravis underwent a single BTX injections for gustatory epiphora (case 1) and hemifacial spasm (case 2). The effect of the treatment lasted 18 months and at least 8 months respectively.

Conclusion: We report the prolonged effect of BTX in two patients with myasthenia gravis. To our knowledge, the prolonged and distant effect of BTX in myasthenia gravis has not been specifically addressed in the literature. We postulate that this prolonged effect may be due to the presence of autoantibodies in patients with myasthenia gravis.

Introduction

Botulinum toxin A (BTX) injection is a recognised treatment for facial dystonias including blepharospasm, hemifacial spasm, aberrant facial nerve regeneration (AFR), strabismus and for therapeutic ptosis [1,2] Its effect usually lasts 3 to 4 months. We report two cases where BTX was used in patients with myasthenia gravis (MG) and in both cases there was an unexpectedly prolonged effect.

Case 1

A 63 year old woman was referred complaining of gustatory epiphora that had developed alongside AFR following a right lower motor neurone seventh nerve palsy due to a closed head injury 10 years previously. She was also diagnosed with ocular MG seven years prior to presentation causing a variable ptosis and diplopia. Anti-acetylcholine receptor (anti-AchR) antibodies were negative but single-nerve fibre electromyography (SFEMG) of facial muscles was positive at that time. Her myasthenia was controlled on Pyridostigmine (60-180mg/day).

On examination she had right aberrant facial nerve regeneration with gustatory epiphora ("crocodile tears"). She had a negative fluorescein dye retention test and her nasolacrimal system was patent on syringing. Weak orbicularis strength was also noted.

The patient underwent a routine BTX injection (7.5units, Botox[®]) to the orbital lobe of the right lacrimal gland through a transcutaneous approach. She developed a right ptosis one week after the injection which resolved within two weeks. At the two month visit there was a 90% subjective improvement in her epiphora. The effect of the botulinum toxin injection persisted for 18 months following treatment before her gustatory epiphora returned.

Case 2

A 56 year old man presented with a 9 month history of difficulty keeping his left eye open. Clinical examination showed variable active contraction of the left orbicularis oculi. He was presumed to have left hemifacial spasm and treated with BTX injections into the left orbital orbicularis oculi (5 x 15 units, Dysport[®]). He developed a complete left ptosis with global reduction of left eye movements 3 days after the procedure. He was referred for a second opinion when in addition to the above signs he was found to have mild right inferior rectus weakness,

right upper lid twitches on vertical saccadic movement and marked right orbicularis oculi weakness. SFEMG on the right orbicularis oculi showed abnormal jitter suggesting a defect of neuromuscular transmission. Anti-AchR antibodies were negative.

A clinical diagnosis of ocular MG was made supported by the SFEMG result. The left ptosis persisted for 8 months before slowly but incompletely resolving. Left eye movements improved but remained variably reduced. He had persistent intermittent double vision and left partial ptosis. A trial of anti-cholinesterase treatment provided some benefit. The patient declined systemic immunosuppression treatment.

Discussion

We report the prolonged effect of BTX in two patients with MG. These are the only two patients in our practice with MG that have received BTX. The effect lasted 18 months and at least 8 months, respectively. To our knowledge, the prolonged and distant effect of BTX in MG has not been specifically addressed in the literature. We postulate that this prolonged effect may be due to the presence of auto antibodies in patients with MG.

The potential for a therapeutic use for BTX was first recognised by Justinus Kerner who in 1817 provided the earliest account of food borne botulism. He correctly recognized that the toxin paralyzed skeletal muscles and parasympathetic function, and proposed that BTX could be used as a therapeutic agent [3]. It was not until the 1981 report of BTX injections into eye muscles to correct strabismus that the therapeutic potential of this agent was fully recognized [4].

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BTX rapidly and strongly binds to presynaptic cholinergic nerve terminals resulting in a reduction in the output of acetylcholine (ACh). Blockade of ACh release at the neuromuscular junction (NMJ) induces the formation of an extensive network of nerve terminal sprouts. These newly formed sprouts release ACh, forming a functional synapse. They are felt to have a role in the functional recovery of the original terminal. Typically at 3 months, there is functional recovery of the original paralysed nerve terminal with elimination of these sprouts [5].

The effect of BTX for the treatment of gustatory epiphora (crocodile tears) following AFR has been shown to last between 3-5 months [6,7] In patients with blepharospasm its effect lasts between 2 to 4 months [8]. Bentley et al. [9] used BTX, either alone or combined with surgery, in patients with MG and variable strabismus. Its effect in the toxin only group lasted between 6-12 months. However, Hara et al. [10] also used BTX in a patient with MG and blepharospasm with a 3-month effect.

In case 2, muscles not directly treated by injections became profoundly and persistently weakened. Such spread would theoretically occur if insufficient functioning NMJs limit local uptake of BTX, allowing greater spread. It is perhaps this theoretical phenomenon that raises concern about potential systemic effects of BTX injection, unmasking or worsening MG and other disorders of the neuromuscular junction [11]. Lower doses with greater concentrations have therefore been recommended to minimise such potential distant effects [12].

Patients with MG have circulating anti-AchR antibodies which cause structural and functional damage to the post synaptic AchR at the NMJ [13]. If the newly formed sprouts are affected in the same way they will be unable to form effective synaptic activity. This may delay the functional recovery of the original nerve terminal. Hence the effect of the BTX will last longer.

A negative serum anti-AchR antibody assay does not imply the absence of circulating antibodies. In fact, serological tests suggest the presence of varied antibodies to numerous muscle proteins involved in neuromuscular signalling [13]. As with both patients in our series, only 50-70% of patients with ocular MG have detectable antibodies using currently available commercial assays.

BTX injection appears to have a prolonged effect in some patients with MG. We feel it is important to counsel patients regarding this. Lower doses may minimise any such undesirable effect.

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