CASE REPORT

Dysphagia as a Side Effect of Botulinum Toxin Injection

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Summary

Dysphagia is a known adverse effect of botulinum toxin injection into the cervical region for dystonia. We present an unusual case of dysphagia arising from injection into the orbicularis oculi muscle, which has hitherto not been described. We postulate that her dysphagia was caused by distant side effects of botulinum toxin due to repeated injections. We recommend that clinicians should restrict the frequency of injections to as few life-time doses of the toxin as possible for adequate management of spasm. The practice of re-injecting patients routinely every three months, or at the first return of mild spasms should be discouraged.

Key Words: Dysphagia, Botulinum toxin

Introduction

Botulinum A Toxin (BOTOX® Allergan, USA; Dysport® Proton Products Limited, UK) has been used since 1983 in the treatment of strabismus and blepharospasm [1]. It has become the initial treatment of choice for the management of essential blepharospasm, hemifacial spasm and other craniocervical dystonias. The most common complications of this treatment are related to acute local effects of its neuromuscular blockade. Local side effects include ptosis, facial numbness, diplopia and ectropion. Distant effects include pruritis, dysphagia, nausea and a flu-like syndrome. Here we present an unusual but known side effect of this treatment. A review of the literature is also presented.

Case Report

A 64-year-old Chinese woman presented with bilateral blepharospasms to a neurologist in private practice. She received three courses of botulinum toxin injections (BOTOX®, Allergan Pharmaceuticals, USA) to bilateral orbicularis oculi as therapy for her blepharospasms. Her first course of BOTOX® injections 60 Units per eye produced partial response. A week later, a second course of BOTOX® of 60 Units per eye was given with no response. Ten days later, a third course of BOTOX® of 80 Units per eye was given.

About one month after her last injection, she began to experience progressive dysphagia. She had difficulty in swallowing solid food and had a sensation of food being stuck at her throat. On examination, she also had bilateral ptosis. The pupils were equal in size and reactive to light. There were no cerebellar signs. Cranial nerves examination revealed loss of sensation in the first and second divisions of the fifth cranial nerve bilaterally. Neurological examination of the central and peripheral nervous system was otherwise unremarkable.

Oesophagogastroduodenoscopy was performed and did not reveal any abnormality in the oesophagus. Normal larynx and vocal cords were confirmed on nasoendoscopy by an otolaryngologist. Computed tomography of the brain was normal. After exclusion

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of these possible structural causes of dysphagia, her symptom was attributed to the action of botulinum toxin. She received enteral nutritional support in the form of naso-gastric tube feeding and her dysphagia started to improve two months later. Similar improvement in her bilateral ptosis was also noted at the same time.

Discussion

Botulinum toxin is a dreaded biological toxin elaborated by *clostridium botulinum*. The action of this toxin is to cause paralysis of both voluntary and involuntary muscles. The ophthalmologist, Alan Scott, started the practice of injecting botulinum into eye muscles to treat strabismus in 1980. This was followed by extensive clinical research in the use of this neurotoxin in a variety of disorders characterised by muscle overactivity and subsequently led to the US Food and Drug Administration's approval for the use of this neurotoxin in strabismus, blepharospasm and hemifacial spasm. Its main action is at the terminal nerve endings of the myoneural junction and it prevents release of acetylcholine from vesicles thus causing chemical denervation.

It has now many other clinical indications. Amongst these other indications include focal dystonias, such as cervical dystonia (spasmodic torticollis), spasmodic dysphonia and spasm affecting limbs. In the field of gastroenterology, it has been used to treat achalasia, sphincter of Oddi dysfunction and chronic anal fissures. Detrusor-sphincter dyssynergia has also been treated with this neurotoxin. Dermatologic indications include the treatment of dynamic and hyperkinetic facial lines and furrows. Glabellar furrows of the forehead (frown lines) and lateral canthal rhytids (crow's feet) can be aesthetically treated by botulinum toxin injection. Tension headache and migraine have also been shown to respond to this treatment. It is also used in the treatment of patients with palmar or axillary hyperhidrosis.

The most common complications of treatment with botulinum toxin are related to acute local effects resulting from chemodenervation. This effect of chemodenervation on adjacent muscle groups is responsible for many of its acute local side effects. For injection into the orbital muscles, the common local effect is weakening of the levator muscle resulting in ptosis, and the corneal consequences of lagopthalmos 1. The latter includes keratitis, dry eyes, blurred vision and hypersecretion epiphora. Less common local effects include facial numbness, diplopia, and ectropion.

Our patient had the commonly encountered problem of bilateral ptosis that occurs when botulinum toxin is injected into the orbicularis oculi muscles. In one study, the most common side effect in patients with blepharospasm treated with botulinum toxin injections was ptosis (44.4%). Her bilateral ptosis subsided about 3 months after the injections; this correlates with the finding that the mean duration of effect of the toxin is 13.4 weeks. Intense diffuse acetylcholinesterase staining has shown denervation of the orbicularis oculi muscle fibers 4 to 16 weeks following botulinum toxin injection. This duration of effect is temporally related to collateral axonal sprouting and the development of new myoneural junctions [2].

Apart from the above local effects, some distant effects are being observed with increasing frequency. These include pruritus, dysphagia, nausea and a flu-like syndrome[1]. Most significant, however, are the rare reports of generalised weakness and the documentation of electromyography abnormalities distant to the site of toxin injection. This severe side effect has been reported after injections for both blepharospasm and torticollis [1]. In patients with cervical dystonia treated with these injections, the most common side effect was dysphagia which has been reported to occur in up to one third of patients [2]. This is however a self-limiting adverse effect. Dysphagia can occur acutely (less than five days after toxin injection) or at a later onset. The effects are due to diffusion of toxin into tissues and its binding to recognition sites on the outside of cholinergic nerve terminals. Cholinergic nerve terminals are also found at neuromuscular junctions of skeletal muscles and along the autonomic nervous system. The resulting inefficient neuromuscular transmission in autonomic neurons is less specific than in skeletal muscles because of the dynamic interplay between the cholinergic and adrenergic components. Cholinergic blockade of the autonomic nervous system include nausea, vomiting, dysphagia, intestinal cramps, hypotension, pupillary dilatation, and may possibly also contribute to dysphagia and reduced bladder sphincter control.

Our patient had dysphagia as an adverse effect of botulinum toxin injection into orbital muscles. This is a common adverse effect for injection into the cervical muscles rather than the orbital muscles. A review of

the anatomy around the orbicularis oculi reveals that immediately below the muscle is a loose areolar connective tissue layer, the post-orbicular fascial plane that allows easy diffusion of fluid. Just posterior to this fascial plane is the orbital septum. It separates the eyelid from the orbital compartment and is a barrier to the posterior diffusion of botulinum toxin into the orbit. Accidental perforations of this septum during injections or in elderly patients, where the septum may be attenuated will result in higher likelihood of adverse complications such as ptosis. After injection, the toxin diffuses into the muscles and other tissues. It has been noted that the botulinum toxin diffuses to a distance of 30-45 mm from the site of initial injection [2]. Linear spread of toxin effect is greater within a single muscle than between adjacent muscles. Denervation was demonstrated to occur, regardless of anatomic barriers such as fascia and bone, at adjacent muscles, and to cross to the contralateral side. There have also been cases of paralysis of vocal cord contralateral to the injected sternomastoid[3]. Its effect diminishes with increasing distance from the injection site, but spread to nearby muscles is possible, particularly when high volumes are injected [4].

In a retrospective analysis of patients who had injections in cervical regions, it was noted that limiting the dose administered to the sternocleidomastoid muscle to 100 IU could substantially reduce the incidence of dysphagia [4]. In our patient, we postulate that her dysphagia could be caused by repeated injections with botulinum toxin. This hypothesis is supported by another case report akin to our current report. Schnider et al reported a patient who experienced biliary hypomotility three weeks after receiving botulinum toxin A at 120mU on three separate occasions for blepharospasm [5].

In conclusion, to reduce the risk of adverse effects, we would recommend that patients receive as few life-time doses of toxin as possible, consistent with adequate management of their spasm. The practice of re-injecting patients routinely every three months, or at the first return of mild spasms should be discouraged.

References

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