

Case Report

Low-Dose Oral Therapy of Pyridostigmine for the Treatment of Severe Side Effects from *Botulinum* Toxin Injection

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Abstract

Botulinum toxin is a potent neurotoxin that causes flaccid paralysis of muscles by blocking the release of acetylcholine at the neuromuscular junction, thus preventing muscle contraction. Injecting the toxin is a cosmetic procedure used to relax the underlying facial muscles which results in a smoothing effect on the overlying skin. The procedure is not uncommon and where available is used serially over time. The side effects of the injection typically are mild and well-tolerated. However, neck muscle injection patients may develop dysphagia, dysphonia, dystonia or even airway compromise. Treatment of these complications historically has been supportive until the effects of the injection subside. Another treatment option reported is the use of pyridostigmine, a cholinesterase inhibitor. Pyridostigmine functions through a reversible inhibition of acetylcholinesterase (AChE) which prevents acetylcholine (ACh) degradation at the neuromuscular junction, promoting muscle contraction. This treatment has not been standardized but to this point cases have mostly described using 60 mg orally as a maintenance dose until the side effect resolves.

A 37-year-old healthy female with no past medical history presented with a chief complaint of a 4-day history of difficulty swallowing. The patient was unable to swallow water since the onset of symptoms and had only worsened over time. Her only notable history was a series of *botulinum* toxin (Botox) injections received one week prior, a total of 300 units into her bilateral forehead, masseters and anterior neck per usual protocol. The patient was found to be protecting her airway and her physical exam was unremarkable. After labs, imaging and consultations were completed the patient was diagnosed with a muscular paralysis side effect of Botox injections and started on oral pyridostigmine at 30 mg three times daily starting dose which was used until symptoms cleared. She continued the 30 mg. The patient had improved significantly

following treatment with pyridostigmine at her 1-month follow-up visit.

Rare sequelae of Botox injections can be life-threatening without treatment. Reversing the method of nerve conduction toxicity using a reversible acetylcholinesterase inhibitor can improve Botox's side effects. The oral maintenance dose, however, is not standardized. This case supports the use of a much lower dose in an average-sized adult.

Keywords: *Botulinum* Toxin; Cosmetic Procedure; Dysphagia

Abbreviations

AChE: Acetylcholinesterase; Botox: *Botulinum* Toxin; CBC: Complete Blood Count CMP: Comprehensive Metabolic Panel; CT: Computerized Tomography; ENT: Ear, Nose and Throat; ED: Emergency Department; PCP: Primary Care Provider

Introduction

Botulinum toxin (Botox; Allergan, Inc, Irvine, CA) is an extremely potent neurotoxin produced naturally by *Clostridium Botulinum*, an anaerobic gram-positive spore forming bacteria [1]. *Botulinum* toxin causes flaccid paralysis of muscles by blocking the release

of acetylcholine at the neuromuscular junction, thus preventing muscle contraction [1,2]. It is these properties that make it a popular cosmetic procedure as relaxation of underlying facial muscles causes a smoothing effect on the overlying skin [3]. Though this procedure is well tolerated there remain risks of treatment that are often inherent to its paralytic effect on musculature depending on the extent of toxin infiltration. Minor and short-lived side effects include headache, as there is an initial muscle contraction phase prior to the flaccid paralysis phase and injection site complications such as bleeding or infection [4]. Accidental paralysis of adjacent unintended muscles is technique dependent but may lead to cosmetic and functional complications such as diplopia, paradoxical worsening of wrinkles or post-injection ectropion. More severely, as neck muscles are prone to diffusion, patients may develop dysphagia, dysphonia, dystonia or even airway compromise [4]. Historically, treatment of all of these side effects, from minor to severe, has been symptom-driven supportive care while waiting for the effect of the *botulinum* toxin to subside over weeks to months.

A 37-year old female presented with dysphagia and hoarseness that improved rapidly following treatment with low dose pyridostigmine Pyridostigmine (Mestinon; Valeant Pharmaceuticals International, Aliso Viejo, CA), allowing her to return to normal life earlier than she would have with supportive care alone.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Case Report

Investigations

A 37-year-old otherwise healthy female with no past medical history presented with a chief complaint of difficulty swallowing. The patient described a 4-day history of dysphagia as well as hoarseness, dizziness, headache and neck tightness. The patient was unable to swallow water since the onset of symptoms and had only worsened over time, prompting her presentation to the emergency room. The patient had never had symptoms like this in the past and the patient had no sick contacts. She denied blurred vision, shortness of breath, weakness, numbness, tingling, head trauma, syncope, fever, cough or other associated symptoms. The patient's only notable history was a series of *botulinum* toxin injections received one week prior, a total of 300 units into her bilateral forehead, masseters and anterior neck per usual protocol. She had received Botox in these very locations many times in the past without experiencing symptoms like she presented with.

Diagnosis

In the Emergency Department (ED), the patient was normotensive and afebrile. Her body mass index was 24.8. The patient was found to be protecting her airway and her physical exam was unremarkable. Laboratory evaluation including Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP) and urinalysis, were unremarkable. Computerized Tomography (CT scan) of her head was negative for significant arterial stenosis, intracerebral hemorrhage or infarct. Incidental partially empty sella and transverse dural sinuses were noted. Ear, Nose and Throat (ENT) was consulted in the ED and recommended speech-language pathology evaluation. The patient was tolerating a nectar-thickened diet as recommended and because of this improvement in oral intake, the patient was eager to return home. However, though she was tolerating her modified diet, she was still requiring significant effort to speak, eat and drink. A diagnosis by exclusion was made that her condition was muscular paralysis sequelae of Botox injections. Based on her continued symptoms, extensive conversation was held regarding the risks and benefits of starting pyridostigmine as case studies have shown benefit from temporary utilization of this medication to allow for safe eating and drinking.

Treatment

The patient was started on IV pyridostigmine 0.1 mg/kg with significant and rapid improvement of her symptoms while inpatient and was able to be discharged on the same day. The patient was counseled that her symptoms were expected to last approximately 3 months given the usual effects of Botox injections and she followed up consistently as an outpatient.

Follow-up

She was started on a conservative regimen of pyridostigmine 30mg three times daily and encouraged to titrate to effect under guidance by her Primary Care Provider (PCP) as an outpatient. The patient had improved significantly following treatment with

the 30 mg. pyridostigmine at her 1 month follow up visit with no reported side effects and continued compliance with the medication regimen.

Discussion

C. botulinum produces eight antigenically distinguishable exotoxins (A, B, C1, C2, D, E, F, G) [1]. Serotypes share a similar biochemical structure which consists of a heavy chain and light chain connected by disulfide bonds [1]. Once injected intramuscularly, all serotypes selectively target cholinergic neurons by binding to specific high-affinity receptors, leading to the inhibition of neurotransmitter release and inducing flaccid paralysis in muscles [1]. This complex undergoes endocytosis and cleavage of disulfide linkages between the heavy and light chains and the freed light chain hinders fusion of acetylcholine vesicles to the cell membrane thereby preventing exocytosis [1]. This decreases the neurotransmitter release at the neuromuscular junction and induces localized muscle relaxation by preventing contraction, which is beneficial in both therapeutic and cosmetic applications. [2] While all serotypes exhibit this action, A, B and E are frequently associated with systemic botulism in humans. Systemic botulism is characterized by descending flaccid paralysis starting with bulbar signs (diplopia, mydriasis, dysphagia) and potentially culminating in respiratory failure if left untreated [5]. Type A produces the most potent effect and is common in cosmetic treatment and is commonly used as a treatment for wrinkles [4]. Wrinkles are characterized by dermal atrophy due to continuous contraction of facial muscles. Static wrinkles, visible at rest and dynamic wrinkles, evident during muscle contraction, represent distinct manifestations of facial aging [4]. By paralyzing key underlying musculature, Botox reduces the appearance of dynamic wrinkles resulting in cosmetic improvements. Inherent iatrogenic risks of Botox injections include minor symptoms such as headaches or bruising which resolve on their own and more severely may mimic symptoms of systemic botulism [3]. Although *botulinum* toxin may result in minor headaches it paradoxically is also being used for the treatment of migraines to great effect [6]. Other therapeutic uses include relaxation in dystonic and spastic disorders such as strabismus or focal dystonias as well as emerging roles in achalasia and anal fissure management. There is also increasing clinical applications for treatment of hypersecretory disorders such as hyperhidrosis, hypersalivation, pyralism or gustatory sweating [1]. Even though *botulinum* toxin is often well-tolerated and promising in an ever-growing range of treatment applications caution should be exercised as there remains significant risks for toxicity. Systemic botulism as a side effect of *botulinum* toxin administration has been observed in case reports, one such report being a pyloric botox injection for gastroparesis [7]. Depending on the location of the injections during cosmetic applications, as neck muscles are prone to diffusion even across fascial planes, *botulinum* toxin may penetrate more deeply than intended resulting in dysphagia and possible airway compromise as seen in our patient [4]. Treatment of side effects has historically relied on supporting the patient's airway and nutrition intake while the *botulinum* toxin clears over time, a problematic solution due to its long duration of action (up to 3 months) [1]. Although *botulinum* antitoxin is a treatment option, it is neither readily available nor effective once severe symptoms have declared themselves [8]. To reduce the length of time a patient with severe *botulinum* toxicity experiences symptoms, other treatment options are constantly being considered. One medication that has been considered for this application is pyridostigmine, a cholinesterase inhibitor, with a paucity of case reports supporting its use in systemic *botulism* [8]. Pyridostigmine operates through a reversible inhibition of Acetylcholinesterase (AChE) which prevents ACh degradation at the neuromuscular junction, increasing neurotransmitter availability and promoting muscle contraction [9]. Pyridostigmine is primarily used in the treatment of myasthenia gravis, increasing ACh availability for unaffected ACh receptors [9]. Treatment is not currently standardized for use in severe symptoms from cosmetic *botulinum* toxin and further study should be performed. Off-label use of pyridostigmine has been suggested to be helpful in the treatment of both the systemic and local side effects of *botulinum* toxin injections. As reported by Young the oral maintenance dose is 60 mg of pyridostigmine t.i.d. Our case suggests 30 mg may be a useful starting dose [8]. This may reduce potential pyridostigmine side effects while effectively treating the Botox complications.

Conclusion

Botulinum toxin is a potent yet versatile neurotoxin for a wide range of clinical applications. Although it is well tolerated, application of *botulinum* toxin may result in severe symptoms such as dysphagia or airway compromise which may lead to significant morbidity. To this point supportive care has been the mainstay of treatment, though it is suboptimal due to the long duration of botulinum toxin's effect (up to 3 months). Our case report joins the literature in support of pyridostigmine use for severe side effects of cosmetic *botulinum* toxin administration to decrease the morbidity and increase quality of life in those suffering from *botulinum* toxicity. Our case also, suggests that a lower starting dose of 30 mg three times daily of pyridostigmine may be a safe and effective starting dose. The reason a lower dose was found successful in our patient is undefined, but could reflect several variables including methods of injection, body mass index and unique patient characteristics. Conclusions that

can be drawn from our case alone are limited given the evidential quality inherent in case reports due to limited sample size and challenges with controlling bias. However, future higher-power prospective studies are encouraged to further examine the dose-response relationship of pyridostigmine and its role in the reversal of cosmetic *botulinum* toxicity.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Data Availability

Data Availability Statement: All data generated or analyzed in this study are included in this article. Access to data is possible with permission from the responsible author.

Consent for Publication

Informed consent was obtained from the patient for publication of this case report and is stated in the manuscript.

Author's Contribution

Writing the initial draft of the manuscript: BS, BB, OQ

Conceptualization and supervision: BS, RS, SJC

Medical management of the case: BS, OQ

Revising the manuscript critically and literature review: BS, BB, RS, SJC

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