

Pyridostigmine for Reversal of Severe Sequelae From Botulinum Toxin Injection

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Summary: Objective. Botulinum toxin is used to treat a wide range of dystonias in the head and neck. Occasionally, patients receiving laryngeal botulinum toxin experience severe dysphagia, dyspnea, or even distant and autonomic symptoms. Rarely, these patients may require hospitalization with possible intubation and placement of nasogastric tubes. Botulinum antitoxin is not readily available and ineffective once symptoms have progressed, so patients must wait until the toxin wears off over weeks to months. Pyridostigmine prevents the breakdown of acetylcholine at the neuromuscular junction, thus making more neurotransmitter available for the muscles.

Study Design. A retrospective case study of patients receiving botulinum toxin for dystonia in the head and neck from 1998 to 2012 who experienced adverse effects that were successfully treated with pyridostigmine.

Methods. Twenty cases were selected and reviewed to demonstrate how pyridostigmine was used to modulate severe dysphagia, breathiness, dyspnea, and some distant/autonomic symptoms.

Results. Pyridostigmine was well tolerated and resulted in significant symptom improvement. Only one significant adverse effect, bradycardia, occurred in a patient with severe cardiac disease.

Conclusions. Given the safety and efficacy of this medication, pyridostigmine should be considered to modulate severe sequelae of botulinum toxin in select patients when conservative management is deemed insufficient. Also, physicians should be aware that patient complaints of symptoms at distant sites and temporally delayed from the injection may be a result of the botulinum toxin and relieved with pyridostigmine.

Key Words: Botulinum toxin–Adverse reactions–Reversal of botulinum toxin–Botox–Pyridostigmine.

INTRODUCTION

Botulinum toxin (Botox; Allergan, Inc, Irvine, CA) has become standard of care for treating laryngeal dystonias such as adductor spasmodic dysphonia (ADSD) and abductor spasmodic dysphonia (ABSD).^{1–3} It has also been used for decades to treat a myriad of neurologic and cosmetic conditions.^{4–7} Throughout that time, the evidence has shown it to be an effective treatment with minimal adverse events and side effects that are generally tolerated by most patients.^{8–10} Despite its safety record, botulinum toxin carries a small risk of severe adverse sequelae.^{11–13} These effects may result from local or systemic spread days to weeks after the injection and can include such varied symptoms as dysphonia, dysphagia, difficulty breathing, and muscle weakness, and autonomic symptoms.¹⁴

Pyridostigmine (Mestinon; Valeant Pharmaceuticals International, Aliso Viejo, CA) is a reversible acetylcholinesterase inhibitor approved by the Federal Drug Administration for treatment of myasthenia gravis.¹⁵ It is also used off label for the emergency reversal of nondepolarizing neuromuscular junction blockers in anesthesia.^{16,17} Based on this, it was hypothesized that it may also function to reverse some of the neuromuscular junction blocks induced by botulinum toxin. The following are cases at our institution of patients who had severe reactions to

botulinum toxin therapy, each of which experienced significant symptom reduction after treatment with pyridostigmine.

MATERIALS AND METHODS

A retrospective case review was conducted of patients treated by the senior author between 1998 and 2012. The study was approved by the Institutional Review Board of the Medical University of South Carolina. Greater than 20 patients have been treated with pyridostigmine. Table 1 is a brief summary of all the patients for whom there was adequate documentation. The first six cases will be detailed to highlight the range of presentation for botulinum toxin side effects and the potential benefit of pyridostigmine in patients not responding to conservative management.

Case 1

A 55-year-old man with ADSD had a long history of successful botulinum toxin injections which he had received at 2-month intervals for years. In early 2008, his voice began to change and an abductor component became noticeable. To address this, his injection was changed from bilateral thyroarytenoid (TA) injections to unilateral TA and posterior cricoarytenoid (PCA) injections. His first injection of 5.0 U in the right PCA and 1.8 U in the right TA was well tolerated and voice was excellent. He presented for a repeat injection 2 months later.

On day 0 he received the following doses of botulinum toxin: 1.8 U in the left TA and 5.0 U in the left PCA. He tolerated the procedure well and did not complain of unusual side effects immediately afterward. Forty-four days later he was admitted to our emergency department with inspiratory stridor, choking, and insomnia. A thorough history revealed that these symptoms had begun 1 week postinjection with mild dysphagia and a choking sensation. He experienced this throughout the day and it also interfered with his sleep. Gradually, the symptoms

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TABLE 1.
Summary of Patient Receiving Pyridostigmine for Adverse Symptoms Resulting From Botulinum Toxin Injection

Patient	Age	Condition Being Treated	Total BTX Dose (U)	Patient Complaint	Time to Report of Symptoms	Pyridostigmine Dose	Outcome	Time to Maximal Improvement	Side Effects of Pyridostigmine
1	55	ADSD	6.8	Stridor, choking	44 days	2 mg IV	Relief of symptoms	Immediate	None reported
2	68	Tardive dyskinesia	90	Dysphagia	1–6 days	60 mg tid	Relief of symptoms	10 days	None reported
3	77	Cricopharyngeal achalasia	20	Dyspnea	38 days	60 mg tid	Relief of symptoms	Immediate	Bradycardia
4	56	ADSD	14.5	Dyspnea, weakness	14 days; 60 days	60 mg tid	Relief of symptoms	24–48 hrs	None reported
5	78	ADSD; writer's cramp	85	Stridor, syncope, orthostasis	2 days	300 mg $\times$ 2; then 60 mg tid	Relief of symptoms	Within 24 hrs	None reported
6	38	ADSD	9.5	Dysphagia, choking, vomiting	4 days	60 mg tid	Relief of symptoms	Within 24 hrs	None reported
7	76	Tremor	4	Dysphagia	6 days	60 mg tid	Relief of symptoms	8 days	None reported
8	36	ABSD	10	Noisy inhalation when singing	10 days	60 mg tid	Relief of symptoms	2–3 days	ABSD Sx returned
9	62	ADSD	10	Breathiness	28 days	60 mg tid	Relief of symptoms	2 weeks	None reported
10	59	ADSD/ABSD	4.75	Breathiness	21 days	60 mg tid	Relief of symptoms	Immediate	None reported
11	42	ADSD	9.5	Vocal fatigue; Dysphagia	14 days	60 mg tid	Relief of symptoms	Over 5 days	None reported
12	72	ADSD	3.6	Vocal spasticity; lower pitch speech	7 days	60 mg tid	Spastic component resolved	Gradual over 7 days	None reported
13	64	ADSD	0.6	Breathiness	32 days	60 mg tid	Relief of symptoms	Gradual over 2 weeks	None reported
14	54	ADSD	1.25	Dysphonia, pitch change	30 days	60 mg tid	Stronger voice	Over 5 days	None reported
15	78	Tremor	3.75	Dysphonia, weak voice	21 days	60 mg tid	Louder voice	Over 2 weeks	Tremor more prominent
16	58	ADSD	6.5	Breathiness	26 days	60 mg tid	Relief of symptoms	Over 10 days	None reported
17	77	Tremor	7.5	Severe breathiness	7 days	60 mg tid	Relief of symptoms	Over 1 week	Tremor returned
18	73	Tremor	3.2	Aphonia	10 days	60 mg tid	Return of voice	5 days	None reported
19	61	ADSD	12	Breathiness; pain with phonation	14 days	60 mg tid	Stronger, easier voice	Over 5 days	None reported
20	42	ADSD	9.5	Breathiness, dysphagia	10 days	60 mg tid	Mild improvement	5 days	None reported

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