

Delayed Hypersensitivity Reaction to OnabotulinumtoxinA

Peter A. LeWitt, MD, MMedSc^{1,2,*}

Of the millions of botulinum toxin treatments administered annually, the vast majority has been safe and well tolerated. When adverse effects do occur, most are predictable consequences of either the muscle-weakening effects of botulinum toxin or the manner of injection. The safety of botulinum has been established in the extensive reporting and meta-analysis of adverse events over almost three decades since the drug's FDA approval in the U.S.^{1–3} Several publications have documented rare occurrences of sudden or sub-acute adverse effects that appear to be immunologically-mediated (and in several instances, strongly suggestive of anaphylactic reactions).^{4–7} In some reports, localized swelling reactions developed immediately or within a few hours after injections with botulinum toxin-type A. Among the more severe reactions, outcomes including circulatory and respiratory compromise and even death⁷ have occurred. For most of these cases, the co-administration of other medications has confounded the interpretation of causation. In the current report, severe cervical swelling that developed several hours after injection of onabotulinumtoxinA implicates a reaction attributable solely to the neurotoxin.

Case Report

A 63 year-old healthy woman with dystonic head tremor underwent selective denervation treatment with onabotulinumtoxinA. On five occasions several years earlier, she received small periorbital doses of onabotulinumtoxinA for facial wrinkles without adverse effects. There was no past history of unexplained swelling or allergic reactions other than from contact with latex. She had no recent immunization or initiation of medication. Her family history was unremarkable.

One hundred units of onabotulinumtoxinA (Botox®; lot # C4356C3, expiration date: October, 2019) was administered by EMG guidance and divided equally into right and left cervical

muscles (five sites each side). The drug was diluted into 2 ml of 0.9% saline; no local anesthetic was used topically or by injection. There were no immediate adverse effects. However, within a few hours post-injection, the patient started to experience marked swelling and dull aching of the lower neck. The severity of bilateral swelling continued to increase over the next day, raising concern for compromised swallowing or breathing (although neither problem occurred). The lower neck, face, and mouth were mildly reddened. Around the neck, there was no subcutaneous bleeding or tenderness. Also lacking were flushing, conjunctivitis, rhinorrhea, itching, dyspnea, wheezing, gastro-intestinal symptoms, faintness, or taste change. Examination did not reveal rash, hives, oral swelling, or adenopathy.

The patient received intravenous methylprednisolone 40 mg and diphenhydramine 50 mg. Within two hours, her neck swelling was diminished. Oral prednisone (20 mg daily) was continued for 5 days. Though most of her neck swelling was resolved within 24 hours, residual swelling was evident 9 days later. At that time, head tremor was diminished and the injected neck muscles were mildly weak.

Discussion

As in the current case, rare idiosyncratic responses to botulinum toxin have involved prominent swelling and other features suggestive of anaphylactoid reactions.⁸ However, interpreting the prior reports of similar outcomes has been confounded by co-administration of other medications, including lidocaine,^{5,7} prilocaine,⁷ and fentanyl together with midazolam.⁶ The only reported case of an immediate severe (and ultimately fatal) anaphylaxis after onabotulinumtoxinA injection⁵ was associated with the unapproved practice of reconstituting the freeze-dried neurotoxin using 1% lidocaine solution. Our experience, similar to another case in which severe leg edema developed several hours after onabotulinumtoxinA injection,⁴ suggests that the neurotoxin product alone can initiate an anaphylactoid reaction.

¹Department of Neurology, Henry Ford Hospital, West Bloomfield, MI, USA; ²Wayne State University School of Medicine, West Bloomfield, MI, USA

*Correspondence to: Peter A. LeWitt MD, MMedSc, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, Michigan 48322, USA; E-mail: plewitt1@hfhs.org

Keywords: anaphylaxis, botulinum toxin, hypersensitivity, onabotulinumtoxinA.

Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 23 October 2017; revised 7 December 2017; accepted 7 December 2017.

Published online 9 March 2018 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12575

The current product information for onabotulinumtoxinA mentions the risk for various hypersensitivity reactions, including anaphylaxis, though little detail is provided.⁹

Each vial of 100 units of onabotulinumtoxinA is combined with 0.5 mg of human albumin. Hence, it is plausible that the albumin component might be a trigger or adjuvant for a hypersensitivity reaction. Compared to albumin, the quantity of botulinum toxin is far less, though sufficient for initiating immunological responses that include the generation of neutralizing antibodies and the clinical outcome of blocked denervation effect.¹⁰ In some instances, patients experiencing hypersensitivity reactions (including ours) had past exposure to the drug, though in two cases, they occurred following its initial use.^{5,6}

The hypersensitivity reaction we observed (localized tissue swelling and redness around the face and neck) does not constitute the full spectrum of what anaphylaxis can be, though a conspicuous cutaneous reaction generally is a prominent feature.⁸ In some instances, an anaphylactic reaction can present a challenge for its recognition, especially when subtle or developing sub-acutely. In these circumstances, certain laboratory tests can be useful both for enhancing diagnostic suspicion and for excluding disorders that mimic anaphylaxis.⁸

The several reported instances of hypersensitivity reactions should alert practitioners to be aware that administration of a foreign proteinlike botulinum toxin can result in an adverse reaction requiring rapid recognition and intensive management. In particular, hypersensitivity reactions following injections into cervical muscles (one of the most common uses of botulinum toxin) may pose a threat for breathing and swallowing if not promptly treated.

Author Roles

The author solely conceived and executed the writing of this paper. The patient described was under his care.

Disclosures

Ethical Compliance Statement: The author confirms that the approval of an institutional review board was not required for this work, and that he has read the Journal's position on issues involved in ethical publication; he affirms that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: No specific funding was received for this work and the author declares that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months: In the past year, the author reports no stock ownership in medically related fields, intellectual property rights, expert testimony, partnerships, contracts, or royalties. He has been a compensated consultant or advisory board member for Acorda Therapeutics, Adamas Pharmaceuticals, Biogen Inc., Bukwang Pharmaceutical Co., Cavion Pharma, Chrono Therapeutics, Intec Pharma, Merz Pharmaceuticals, NeuroDerm Ltd, Pfizer Inc., Prexton Therapeutics, Revance Therapeutics, Sage Therapeutics, SynAgile Corporation, Titan Pharmaceuticals, USWorldMeds LLC, and Voyager Therapeutics, and has served as a speaker for Acadia Pharmaceuticals, Lundbeck, and USWorldMeds LLC. He receives compensation for services as editor-in-chief of CLINICAL NEUROPHARMACOLOGY. Clinical trial support includes Acorda Therapeutics, Biotie Therapies, Intec Pharma, Lundbeck, The Michael J. Fox Foundation for Parkinson's Research, NeuroDerm Ltd., The Parkinson Study Group, Roche Pharmaceuticals, Sunovion Pharmaceuticals, and USWorldMeds.

References

1. Coté TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administrations in therapeutic and cosmetic cases. *J Am Acad Dermatol* 2005;53:407–415.
2. Naumann M, Jankovic J. Safety of botulinum toxin type A – a systematic review and meta-analysis. *Curr Med Res Opin* 2004;20:981–990.
3. Albavera-Hernandez C, Rodriguez JM, Idrovo AJ. Safety of botulinum toxin type A among children with spasticity secondary to cerebral palsy: a systematic review of randomized clinical trials. *Clin Rehabil* 2009;23:394–407.
4. LeWitt PA, Trosch RM. Idiosyncratic adverse reactions to intramuscular botulinum toxin type A injection. *Mov Disord* 1997;12:1064–1067.
5. Li M, Goldberger BA, Hopkins C. Fatal case of BOTOX®-related anaphylaxis? *J Forensic Sci* 2005;50:169–172.
6. Aggarwal A, Kaul V, Kaur G, et al. A new facial expression to botox!. *Am J Emerg Med* 2014;32:290e5–290e6.
7. Moon IJ, Chang SE, Kim SD. First case of anaphylaxis after botulinum toxin type A injection. *Clin Exptl Derm* 2017;42:760–762.
8. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol* 2015;115:341–384.
9. Botox® (onabotulinumtoxinA) Full Prescribing Information (FDA Label). Allergan, Inc.: Irvine, California, revised 1/20/2016.
10. Benecke R. Clinical relevance of botulinum toxin immunogenicity. *BioDrugs* 2012;26:e1–e9.