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CASE REPORT

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Fatal Case of BOTOX®-Related Anaphylaxis?

ABSTRACT: Anaphylactic drug reactions are rare and often serious events. The Botulinum toxin A, marketed as BOTOX®, was recently approved by the Food and Drug Administration for cervical dystonia and glabellar wrinkles, after its approved use and success with blepharospasm, strabismus, and disorders of the 7th cranial nerve. It has been well received due to its efficacy in improving facial lines. This case report documents the first death associated with a Botox-lidocaine mixture given to a woman for chronic neck and back pain. Based on the medical records, autopsy, and laboratory findings, the cause of death was determined to be anaphylaxis to the Botox-lidocaine mixture. The history, indications, off-label uses and possible future applications of Botox are reviewed as well as the uses and complications of lidocaine. Although the anaphylaxis cannot be definitively proven to be due to Botox alone, this case warns of an adverse reaction related to Botox, a drug that is rapidly expanding in range of use as well as increased usage.

KEYWORDS: forensic medicine, pathology, toxicology, botulinum toxin, anaphylaxis, lidocaine, cervical dystonia, adverse drug reaction, serum tryptase

Adverse drug reactions (ADRs) have been experienced with virtually all therapeutic drugs. Immune-mediated hypersensitivity reactions represent a small percentage of these reactions. The signs and symptoms of hypersensitivity reactions are most often rashes, fever, cytopenias, vasculitis and anaphylaxis (1). Prior to marketing a new drug, clinical trials are implemented to detect these ADRs; however, rare types of ADRs and those with long-time to onset are often difficult to predict (2). Botox is a relatively new drug that was been approved by the Food and Drug Administration (FDA) in 1989 for treatment of blepharospasm, strabismus, and disorders of the 7th cranial nerve. In 2002, it was approved for the treatment of cervical dystonia and glabellar wrinkles (3), and most recently in 2004, approved for treatment of severe primary axillary hyperhidrosis (4). However, it is often used for "off-label" applications, often with success, and with no significant adverse consequences. To date, no systemic complications associated with Botox injections have been documented, according to the American Society for Aesthetic Plastic Surgery (5,6). Deaths involving Botox injections have not been reported (Search of death certificates involving Botox, personal communication, US Consumer Product Safety Commission, 7). The most common side effects are local numbness, swelling, bruising, or a burning sensation during injection. Lidocaine is used to diminish these side effects and has few adverse reactions (8), however, there are occasional reports of minor allergic reactions and even anaphylaxis. This case represents the first Botox-related anaphylaxis and death reported in the literature.

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Case History

A 43 year-old woman with a history of chronic pain, muscle spasm, and rigidity of the upper and lower back and neck, specifically located to the bilateral upper trapeziuses, levator scapulae and rhomboid muscles, presented at a rehabilitation medicine clinic for repeat Botox injections. Approximately 14 months prior to her death, she was evaluated at the clinic for her symptoms and was injected with Botox, which proved to be beneficial. She had dramatic improvement within three months, which lasted for approximately seven months. However, she stated that relief due to the injection had subsided over the last several months, that the bilateral neck pain had returned and was worsening, and thus she returned for repeat Botox injections. Her current medications were Methadone (10 mg, two to three times a day), Robaxin (750 mg, twice a day), and Oxycodone (5 mg, one to two times a day). Other medical history and review of systems were noncontributory.

A physical exam at this time demonstrated rigidity over the upper trapeziuses, levator scapulae and rhomboid muscles bilaterally, with the right side more affected than the left. Compression of the distinct trigger areas reproduced pain.

A preparation of Botox was used by mixing preservative-free Lidocaine 1% and Botox: 100 units diluted in 5 cc Lidocaine were prepared in two different syringes for a dilution of 20 u/cc. Five trigger points were injected on the right shoulder girdle: three in the upper trapezius, one over the levator scapulae and one over the rhomboid. Aspiration was carried out prior to the injection, to exclude penetration of vasculature. Each injection was 1 cc, and guided electromyographically.

Upon injection of 1 cc over the mid-belly of the upper trapezius, the patient described a sensation in the tip of the nose and a taste in the mouth which rapidly resolved. No complaints were associated with the other four sites. Upon completion of all 100 units, the patient described feeling dizzy and anxious, as well as weakness in the right side of the body. With assistance, the patient was transferred

to the exam table, whereupon she had a vaso-vagal reaction and lost consciousness. This was followed by generalized seizure activity and bladder incontinence. Cardiopulmonary resuscitation was initiated and the patient was transferred emergently to the local hospital. Emergency medical services documented ventricular fibrillation. The patient was intubated, administered epinephrine, and cardioshocked, but nonetheless expired in the emergency department.

Autopsy Findings

Autopsy revealed a slender female appearing her recorded age. The external examination was remarkable only for a resuscitative abrasion on the mid-anterior chest wall and intravenous catheters in the bilateral antecubital fossae. The internal examination demonstrated a small amount of soft tissue hemorrhage in the anterior mediastinum. The combined lung weight was 1350 g, and on cut sections throughout both lungs and tracheobronchial tree, there was exudation of pink-tan froth. The heart weighed 250 g. The neck organs appeared free of trauma and obstruction. The hypopharynx, larynx and trachea showed no evidence of grossly visible hemorrhage or edema. The most significant pathologic finding on histologic sections was marked intraalveolar hemorrhage and edema on the lung sections.

Toxicologic Analysis

Toxicology was performed on hospital blood and serum, postmortem blood, and bile. No volatiles were detected. The comprehensive drug screen revealed the presence of lidocaine in the hospital and postmortem blood specimens, which was further quantified in the postmortem blood as 1.1 μmg/L. Methadone was detected in the postmortem blood at 0.12 mg/L. Lastly, comprehensive drug testing of the bile indicated the presence of amitriptyline, lidocaine, methadone, and a methadone metabolite. Further testing on a premortem hospital serum specimen indicated a tryptase concentration of 37.6 μg/mL (reference range of 0.4–10.9 μg/mL) and an IgE concentration of 6.7 IU/mL (reference range 0.0–100.0 IU/mL), which supports the clinical scenario of anaphylaxis. Additional studies to determine the specificity of the IgE were not possible due to specimen depletion.

Discussion

Botox has been touted as an extremely safe drug for its approved uses, and because of its purported safety and appeal in cosmesis and pain reduction, it has become a widely used drug in a multitude of varied "off-label" uses. We present the first death due to anaphylactic shock in a patient who received a mixture of Botox and lidocaine injections.

Botulinum toxin is an extremely potent neurotoxin that prevents the release of acetylcholine at the neuromuscular junction, producing chemical denervation and paralysis of the muscles (9). The signs and symptoms of botulism were first described between 1817 and 1822 by the German physician Justinus Kerner, who noted that a "zoonotic" poison in smoked blood-sausages caused muscular and autonomic paralysis. Although he was not able to isolate the responsible agent, he did discuss in his monograph the possibilities of using the toxin as a remedy for certain diseases (10,11). In 1895, following a botulism outbreak after a funeral ceremony in a Belgian town, microbiologist Emile-Pierre van Ermengem found that the neurotoxin arose from an anaerobic bacillus, and named it "*bacillus botulinus*," after the Latin word *botulus* for "sausage" (10–13). Since this time, eight immunologically distinct toxins (A, B, C1, C2, D, E, F, and G) have been isolated from C. *botulinum*. With the exception of C2, all are neurotoxins with relatively little homology (12,14). The lethal dose is approximately 10^{-9} g/kg body weight, making it the most potent naturally occurring toxin (9,15). The seven serotypes differ in potency and duration of action (7). Serotypes A and B, which are antigenetically different, are the most commonly used in clinical practice, marketed in the United States as botulinum toxin type A (BTX-A; Botox, Allergan, Irvine, CA) and botulinum toxin type B (BTX-B; Myobloc; Elan, San Diego, CA). While the true lethal dose of Botox A for humans is not known, it is estimated to be 3000 units (7). The majority of the studies in the literature focus on Botox (type A), but studies on Myobloc (type B) are rapidly accruing (16).

Botulinum toxin was first used therapeutically for the treatment of strabismus in 1981 (17). After successful clinical studies, FDA approval came in 1989 for treatment of strabismus in addition to blepharospasm and hemifacial spasm. Incidental to the treatment of hemifacial spasm was the improvement of facial wrinkles (18), which introduced Botox to the field of dermatology. FDA approval for glabellar wrinkles and cervical dystonia came in 2002. Since its inception into the cosmetic industry, Botox injections have become the fastest-growing cosmetic procedure, with more than 1.6 million people receiving injections in 2001 alone, an increase of 46% over the previous year (3,5). Due to the success in treatment of cervical dystonia, Botox has been evaluated in "off-label" uses for other chronic pain syndromes such as migraine headaches, chronic low back pain, and myofascial pain (19–22). The pathway in which botulinum alleviates pain is not well understood, but many clinical trials are underway with encouraging results and FDA approval is anticipated. Other "off-label" uses include such varied entities as anal fissure, bruxism, and achalasia. Long-term effects have not been well established, but so far the consequences have been minimal (19–23).

Once injected, Botox irreversibly binds to the neuromuscular junction of the presynaptic neuron and prevents acetylcholine release, thereby producing muscle paralysis. This may take a period of two weeks to be complete. Muscular function, due to new sprout formation as well as endplate recovery, takes approximately 3 to 6 months (24,25).

Contraindications to the use of Botox include pregnancy, active nursing, pre-existing neuromuscular diseases (such as myasthenia gravis and Eaton-Lambert syndrome), and certain medications (aminoglycosides, penicillamine, quinine, and calcium channel blockers) (9,26–28). In this case report, the patient did not have any of the above contraindications.

Botox-related systemic adverse complications or generalized anaphylaxis have not been reported (6,9). The usual complications of Botox injections are either procedure-related, drug effects, or idiosyncratic reactions (24). The injection itself may be painful, or cause ecchymoses or swelling. Accidental spillover to adjacent muscles causing undesired paralysis in those areas can also occur, and are related to technique and dosage (9). Idiosyncratic reactions are varied and reports include blurry vision, a metallic taste, and persistent facial rash (29–31). Rare incidental deaths have been reported—in one case, dysphagia with consequent aspiration pneumonia developed and led to death. Other rare reports include Botox administration in patients with pre-existing cardiovascular disease who experienced arrhythmia and myocardial infarction, some with fatal outcomes (32).

One of the non-life-threatening complications of Botox injections that concerns clinicians is the development of immunologic resistance to the drug (9,14,16,33). This is associated with higher dose per treatment, high cumulative dose, treatment more often than

every 8–12 weeks, or the use of booster doses (7,14). This may require an alternative treatment with botulinum type B (Myobloc), which is effective since type A and B are antigenetically different, and they differ in their mechanisms of action. On a molecular level, they bind to different receptors on the neuronal cells. Type A cleaves the SNAP 25 protein while type B targets and cleaves the SNARE protein synaptobrevin (16).

Botox is supplied in a single vial as a lyophilized sterile vacuum-dried form without a preservative (34) that requires reconstitution prior to injection. The recommended diluent is normal saline (32,34). In this case, the Botox was reconstituted in 1% preservative-free Lidocaine. IgE mediated allergic reactions to lidocaine are uncommon, but have been documented (8,35,36). Cases of severe anaphylaxis and death are exceedingly rare, but again, is documented in the medical literature (37–41).

Postmortem assessment included toxicological analysis. Lidocaine was detected at low therapeutic concentration in postmortem blood, as well in the hospital specimen. Botox is not expected to be present in the peripheral blood at measurable concentrations following intramuscular injection at the recommended doses (21). Currently, there is no standardized method to measure Botox in humans (34). Other medications known to be taken by the patient were present at therapeutic concentrations.

Generally, the diagnosis of anaphylaxis is a clinical one, and at autopsy, may be manifested by marked laryngeal edema or pulmonary edema. However, there may be few to no findings. Premortem and postmortem serum tryptase and IgE elevation can support the clinical diagnosis of anaphylaxis (42–44). Upon mast cell activation in anaphylaxis, degranulation occurs and mast cell enzymes are released. Although histamine is the major effector, it degrades too quickly for evaluation, and is not specific for mast cells. Tryptase, on the other hand, has a longer half-life and is found exclusively in mast cells (45,46). In this case, hospital blood demonstrated a serum tryptase of 37.6 μg/L by fluorescence immunoassay, a marked elevation above the upper limit of 10.9 μg/L. Elevated IgE concentrations do not necessarily indicate anaphylaxis, but does signify pre-sensitization. In this case, IgE concentrations were not elevated significantly, which does not exclude the diagnosis of anaphylaxis since certain drugs and diagnostic agents can directly trigger mast cell histamine release in the absence of IgE antibody (23).

Conclusion

The yearly incidence of anaphylaxis in the US is approximately 30 per 100,000 (47). The annual international incidence of deaths from anaphylaxis is approximately 154 per 1 million hospitalized patients (48). Anaphylaxis occurs most commonly with insect stings, food allergies, drugs and contrast media. The possibility of anaphylaxis is an unpredictable event, and there is no specific prevention other than to prevent exposure to substances that elicit hypersensitivity if that has been previously demonstrated. The symptoms of urticaria, laryngeal edema, and cardiovascular collapse can occur quite suddenly and become life-threatening within minutes due to the release of mast cell chemical mediators (49). While lidocaine has been rarely reported to cause anaphylaxis and death, Botox has not. It cannot be definitively determined which drug played a greater role in the patient's allergic response, given that she had a previous sensitization with the same mixture of Botox and lidocaine 14 months prior to her death. However, despite the reported safety of both drugs, all drugs deserve preparation and emergent response with epinephrine and intravenous support for untoward events.

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