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Uncontrollable Distant Effects of Botulinum Neurotoxin Injections

JOSEPH SCHAMES, DMD; Y. DOV PRERO, BA, MED; DAVID SCHAMES, BA; MAYER SCHAMES, DDS; WILLIAM GABRIEL, DDS; AND ROBERT REED, DDS

ABSTRACT Some dentists propose administering botulinum neurotoxin injections to treat orofacial pain. The scientific literature has documented there are dangerous uncontrollable effects of long-distance traveling of botulinum neurotoxin from the injection site. These distant effects are not technique-specific, not predictable, and cannot be controlled by the amount of neurotoxin, nor by the site administered. These uncontrollable distant effects of "off-label" botulinum neurotoxin injections, at the very least, must be thoroughly disclosed to patients.

AUTHORS

Joseph Schames, DMD, is a director of the Craniofacial Pain/TMJ Clinic at White Memorial Medical Center in Los Angeles.

Y. Dov Prero, BA, MED, is a student at the University of California, Los Angeles, School of Dentistry, Class of 2011.

David Schames, BA, is a student at Loma Linda University, School of Dentistry, Class of 2012.

Mayer Schames, DDS, is a director of the Craniofacial Pain/TMJ Clinic at White Memorial Medical Center in Los Angeles.

William Gabriel, DDS, is an elected member of the American Academy of Oral and Maxillofacial Pathology.

Robert Reed, DDS, is a past president of the Kern County Dental Society. He is a member of the American Academy of Orofacial Pain.

Botulinum neurotoxin, BoNT, is a toxin produced by the anaerobic spore-forming bacterium *Clostridium botulinum*.[1] There are seven different types of toxins categorized as BoNT/A through BoNT/G. Ingesting BoNT contaminated food can cause an intoxication called botulism. Infant botulism occurs when the intestinal tract of infants are colonized by *C. botulinum*, which lead to infant intoxication. Wound botulism is the result of production of BoNT by *C. botulinum*.

Mechanism of Action of Botulinum Neurotoxin

Acetylcholine is a neurotransmitter responsible for communication of a signal from a neuron to a postsynaptic structure. In normal physiological transmission of a neuronal signal at a cholinergic synapse, vesicles storing acetylcholine fuse with the membrane and expel their contents to trigger the adjacent structure. Specific proteins embedded in the membrane of the neuron are essential for fusion of the vesicles. It is these proteins that are the target of BoNT. BoNT cleaves these proteins, inhibiting the fusion of the vesicle with the membrane. Specifically, BoNT/A and BoNT/E target SNAP-25 (Synaptosomal-Associated Protein of 25 kDa), one of the proteins that reside in the plasma membrane.[2] Thus, BoNT inhibits the signal from being transmitted to the adjacent structure.

Botulinum Neurotoxin Injections in Dentistry

BoNT injections are being advocated for use in the treatment of orofacial pain. Tan and Jankovic anecdotally reported their use of BoNT injections in the

masseter muscles to treat patients with bruxism.[3] An additional anecdotal report by Kwek et al. stated they have given BoNT injections to relax the sensitivity and pain caused by trigeminal neuralgia.[4]

Uncontrollable Distant Effects of Botulinum Neurotoxin Injections

There have been numerous cases of dysphagia (dysfunction in swallowing) associated with botulinum neurotoxin injections into the facial and cervical regions. Kwek et al. reported that a patient suffered dysphagia after receiving a BoNT injection in the orbicularis oculi.[4] Tan et al. treated 18 patients with BoNT injections for bruxism and one patient experienced dysphagia for an extended period of time.[3]

Rossi et al. even reported dysphagia caused from BoNT injections into the lower limbs and into the lumbar paraspinal muscles.[5] Significantly, there was no correlation between these distant effects and the dosage of the injection. Rossi et al. suggested that the mechanism of the transport of the neurotoxin could be through spinal motor neurons or systemic distribution via the blood circulation.

In addition, injections into the cervical region can have distant effects on the upper and lower limbs. Garner et al. found that after treatment of focal dystonia with BoNT injections there were increased jitter and blocking in six out of eight patients in distal sites such as in the areas of the extensor digitorum brevis and the tibialis anterior.[6]

Other distant effects of BoNT injections were reported by Ansved et al. where they observed muscle atrophy in the leg muscle even though the BoNT injection was performed in the cervical region.[7]

A recent groundbreaking study by Antonucci et al. has identified that there are long-distant effects of BoNT/A, the most commonly used form of BoNT.[8] They conclusively identified that BoNT does travel far from the injection site and proposed a potential mechanism for this migration. Their study performed on mice showed that BoNT in the injection site of the ipsalateral hippocampus produced the cleaved protein SNAP-25. Within three days, the same cleaved protein was detected on the contralateral side, implying the toxin had traveled. Considerably large quantities of cleaved SNAP-25 remained for up to 120 days. Similarly, toxin injected in the optic tectum was detected in the retina.

IT WAS SHOWN
that it was the toxin that traveled, and not just the cleaved protein.

It was shown that it was the toxin that traveled, and not just the cleaved protein. BoNT/A was injected, and the connection between the injection and distal site was then severed. BoNT/E, which is an agent that removes proteins that are cleaved by BoNT/A, was then administered. BoNT/A remains active for 120 days, while BoNT/E is no longer active after 21 days. After the BoNT/E wash had degraded, the concentration of cleaved SNAP-25 in the distal site still increased significantly. This proved that BoNT/A itself, and not its products traveled to the distal site and continued to cleave SNAP-25 proteins, allowing the increase in SNAP-25 to be detected. This study revealed for the first time that BoNT/A injected into a peripheral site traveled to central circuits, providing a mechanism by which the toxin can travel into the CNS after peripheral administration.

Conclusion

As of 2009, the American Dental Association has not taken an official position regarding the standard of care for a dentist administering BoNT injections to treat orofacial pain. Currently, state dental boards are determining whether this falls within the scope of the practice of dentistry. There have not been any randomized controlled trials for this type of treatment.

The scientific literature has documented there are dangerous uncontrollable effects of long-distance traveling of BoNT from the injection site. These distant effects are not technique specific, not predictable, and cannot be controlled by the amount of neurotoxin, nor by the site administered. These uncontrollable distant effects of "off-label" botulinum neurotoxin injections, at the very least, must be thoroughly disclosed to patients. ■■■■

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