Botulinum Toxin: Cosmetic and Adjunctive Applications in Oral and Maxillofacial Region

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Abstract
Botulinum toxin is, also, called as “miracle poison,” and is one of the most poisonous biological substances known. (Münchau A. and Bhatia K.P., 2000) It is commercially available as purified exotoxin of anaerobic bacteria, Clostridium botulinum. Botulinum is a neurotoxin produced by the bacterium Clostridium botulinum, an aerobic, gram-positive, spore-forming rod commonly found on plants, water, in soil and the intestinal tracts of animals. The therapeutic use of botulinum toxin was discovered in the 1970s and has since been used in broad range of medical problems. Botulinum toxin is used in primary care setting to treat conditions such as allergic rhinitis, hyperhidrosis, lichen simplex chronicus, migraine, myo-fascial pain syndrome and certain task-specific idiopathic focal dystonias (eg. Writer’s cramp) more specific to cosmetic improvement of the face. Here we are presenting a short review on Botulinum toxin for a cosmetic purpose and their associated applications to the Maxillofacial region.

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1. Introduction

Botulism has been recognized since the early 19th century, and there was speculation about what caused the condition. In 1822 it was suggested that a “fatty acid” in sausages was the culprit, and this led to the term botulism (botulus being the Latin word for sausage). (Kerner J., 1817) In 1897, van Ermengen related botulism to a bacterial toxin. (van Ermengen E., 1897) The discovery that botulinum toxin blocks neuromuscular transmission and thereby causes weakness laid the foundation for its development as a therapeutic tool. (Burgen A.S.V. et al., 1949) In 1981, the ophthalmologist Alan Scott pioneered treatment with botulinum toxin when he used it to treat strabismus. (Scott A.B., 1981) He paved the way for clinical research in many specialties.
2. Discussion

2.1: Mechanism of action

Strains of C. Botulinum elaborates eight antigenically distinguishable exotoxins (A, B, C₁, C₂, D, E, F, and G). Type A is the most potent among them followed by types B and F toxin. Types A, B, and E are commonly associated with systemic botulism in humans. (Ellenhorn M.J. and Barceloux D.G., 1988) All eight serotypes have similar structure and molecular weight, consisting of a heavy (H) chain and a light (L) chain joined by a disulphide bond. (Dolly J.O., 1997) They all interfere with neural transmission by blocking the release of acetylcholine (Figure 1), which is the principal neurotransmitter at the neuromuscular junction. This inhibition occurs as a neurotoxin cleaves SNAP-25 (synaptosomal protein of 25 kDa), a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. (BOTOX, 1989) When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. (Figure 2) In addition, the muscle may go into atrophy, axonal sprouting or, extra-junctional acetylcholine receptors may develop. There is evidence that re-innervation of the muscle may occur, thus, slowly reversing muscle denervation produced by BOTOX. (BOTOX, 1989)

2.2: Preparations:

Serotype A is the only one commercially available for clinical use, although experience is emerging with serotypes B, C, and F. There are two preparations exists: Dysport, which is most widely used in the United Kingdom, and BOTOX, which is used in the United States and elsewhere. Unfortunately, there has been much confusion over the doses and units of potency of the two preparations.

a. BOTOX Cosmetic (Allergan, Irvine, Calif): This was the first commercially available types in United States. Its safety is well established. The drawback is that once the contents of a vial are dissolved, the reconstituted product loses its potency.

b. Dysport (Ipsen pharmaceuticals): One unit of BOTOX has a potency that is approximately equal to 4 unit of Dysport.

c. Xeomin: It is the third botulinum toxin type A licensed in UK. It is an innovative formulation, in which complexing proteins have been removed by an extensive purification process from the botulinum toxin complex. Xeomin contains the pure 150 kD neurotoxin.

d. Neorobloc (Myobloc): It is the registered trademark of Solstice Neurosciences Inc, San Francisco, California. It is a type B neurotoxin complex which became available in UK in 2001. There is a limited experience in the use of this toxin, and the product does not currently have approval for cosmetic use anywhere in the world.

e. Myobloc (Elan): Myobloc has a shelf life of more than 12 months. This is important in terms of patient scheduling. However, larger volumes of Myobloc may be needed to obtain effects similar to Botox. According to a report, 1 nanogram of toxin contains approximately 20 U of BTX-A, or, 1 U of BTX-A is equal to approximately 0.05 nanogram of the toxin. (Botox, 1998)

2.3: Reconstitution and Storage:

BOTOX is stored in a freezer at or, below -5°C. The package insert recommends reconstitution using sterile saline without preservative; 0.9% sodium chloride is preferred diluents. Some researchers suggest that reconstitution with sterile saline solution with preservative 0.9% benzyl alcohol reduces microbial contamination and provides a weak local anesthetic effect. Once reconstituted, Botox is kept refrigerated at 2-8°C. The reconstituted Botox should be used within 4 hours. Only one study found no loss of activity at 6 hours but a 44% loss after 12 hours and a 70% loss with refreezing at 1-2 weeks. (Ranoux D. et al., 2002)

2.4: Routes of Administration:

Botox is most commonly administered intramuscularly. But sometimes it can, also, be administered intra-dermally and subcutaneously for the treatment of hyperhidrosis and blepharospasm respectively. In conditions with very localized muscle overactivity in delicate places such as Strabismus, the injections are usually guided by electromyography. Administration to children and relatively uncooperative patients requires general anaesthesia, which should be selected taking into consideration the special characteristics of the surgical procedure and the possible interactions of anaesthetic drugs and the toxin. (Muthane U.B. and Panikar J.N., 2003; Pullman S.L., 2005; Ravichandran E. et al., 2006)

2.5: Therapeutic Uses:

Botulinum toxins now play a very significant role in the management of a wide variety of medical conditions, especially strabismus and focal dystonias, hemi-facial spasm, and various spastic movement disorders. The lists of new indications were expanding day by day. (Table.1) The most important dento-facial applications include extra-capsular myogenic pain by masticatory muscle hypertonicity, trigeminal neuralgia, migraine,
Table 1: Botulinum Toxin: Cosmetic and Adjunctive Applications in Oral and Maxillofacial Region

<table>
<thead>
<tr>
<th>Disorders caused by overactivity of muscles for which treatment with botulinum toxin-A is established:</th>
<th>Disorders caused by overactivity of muscles for which treatment with botulinum toxin-A has been tried:</th>
</tr>
</thead>
</table>
Figure 1: Mechanism of action of Normal Neurotransmitter Release

(SNARE – Soluble-N-Ethylmaleilide-sensitive Attachment factor Receptor, SNAP-25 – Synaptosomal Protein of 25 kDa)

Figure 2: Mechanism of action on Exposure to Botulinum Toxin

mandibular spasms, neck pain, sialorrhea, gummy smile, elimination of bruxism, masseter hypertrophy, muscle hypertonicity after orthopaedic and orthognathic surgeries, patients with para-functional habits and oro-mandibular dystonia of varying etiologies, trismus and adaptation to rapid changes in vertical dimension associated with oral prosthesis. (Katz H., 2005; Rao L.B. et al., 2011)

2.6: Adverse Effects:

Injectons with botulinum toxin are generally well tolerated. After injection it diffuses in muscles and other tissues. Its effect diminishes with increasing distance from the injection site, but spread to nearby muscles is possible, particularly when high volumes are injected. Patients receiving injections into the neck muscles for torticollis may, therefore, develop dysphagia because of diffusion of the toxin into oro-pharynx. Other systemic side effects include an influenza-like illness and rarely brachial plexopathy which may be immune mediated. (Glanzman R.L. et al., 1990) No severe allergic reactions have been reported. Gall bladder dysfunction attributed to autonomic side effects of the toxin and a case of necrotizing fasciitis in an 80 year old immuno-suppressed woman with blepharospasm has been noted. (Schnider P. et al., 1993; Latimer P.R. et al., 1998) Botulinum Toxin is contraindicated in pregnancy and while breast feeding, known hypersensitivity to botulinum toxin, Infection at the injection site and urinary tract infection or, urinary retention. It is, also, contraindicated in patients with pre-existing motor neuron disease, myasthenia gravis, Eaton-Lambert syndrome, Neuropathies and psychological unstability. Careful monitoring should be done in children as it might alter cell functions such as Axonal growth. (Moore P., 1995; Harper M. et al., 1995) It is relatively contraindicated in patients who consumed those medications those decreases the neuromuscular transmission such as aminoglycosides,
penicillamine, quinine, chloroquine and hydroxychloroquine, calcium channel blockers and blood thinning agents.

2.7: Precautions:
There are some general and specific precautions for using BOTOX are present in which Epinephrine and other precautionary methods should be available to tackle anaphylactic reactions. Signs and symptoms of overdose are not apparent immediately post injection. In the event of an overdose an antitoxin may be administered. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration. In Specific precautions, the site of injection should be guided by standard guidelines used for electromyography, although actual site of injection will be finally determined by palpation. The dose should be lowered if there is evidence to suggest that this dose will result in excessive weakness of the target muscle, such as for patients whose target muscle is small. Any unusual or, allergic reactions to botulinum toxin type A or, any other type of botulinum toxin or, allergy to any other substances, such as foods, preservatives or, dyes. For Breast feeding, it is not known whether botulinum toxin type A passes into the breast milk. Although most medicines pass into breast milk in small amounts, many of them may be used safely while breastfeeding. Mothers who are taking this medicine and who wish to breast-feed should be explained about this fact.

Conclusion

The use of BOTOX has been revolutionized the treatment of various cosmetic and maxillofacial problems. A precise knowledge and understanding of the functional anatomy of the mimetic muscles is absolutely necessary to correctly use botulinum toxins in clinical practice. Adverse effects are usually mild and transient. The most common substantive complication is excessive or, unwanted weakness, dysphagia and diplopia may occur. Knowledge of the functional anatomy and experience with the procedure help injectors avoid complications. In future, the development of new potent toxins with increasing effectiveness and duration of effect will further aid this expanding and interesting field of chemo-denervation.

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