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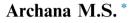
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REVIEW ARTICLE

Toxin yet not toxic: Botulinum toxin in dentistry

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Abstract   Paracelsus contrasted poisons from nonpoisons, stating that "All things are poisons, and there is nothing that is harmless; the dose alone decides that something is a poison". Living organisms, such as plants, animals, and microorganisms, constitute a huge source of pharmaceutically useful medicines and toxins. Depending on their source, toxins can be categorized as phytotoxins, mycotoxins, or zootoxins, which include venoms and bacterial toxins. Any toxin can be harmful or beneficial. Within the last 100 years, the perception of botulinum neurotoxin (BTX) has evolved from that of a poison to a versatile clinical agent with various uses. BTX plays a key role in the management of many orofacial and dental disorders. Its indications are rapidly expanding, with ongoing trials for further applications. However, despite its clinical use, what BTX specifically does in each condition is still not clear. The main aim of this review is to describe some of the unclear aspects of this potentially useful agent, with a focus on the current research in dentistry.

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1. Introduction

Botulinum neurotoxin (BTX) is a neurotoxic protein produced by the Gram-positive, rod-shaped, spore-forming, and strictly anaerobic bacterium *Clostridium botulinum* and, rarely, by *Clostridium butyricum* and *Clostridium baratii*, commonly found on plants and in soil, water, and animal intestinal tracts. Although once considered lethal, BTX is now used as a therapeutic drug. BTX exhibits transient, nondestructive, dose-dependent, and localized actions, with minimal systemic side effects (Marchese et al., 2008), underlying its wide use in various orofacial and dental disorders. The exact mechanism of action, dosage, and delivery procedure of BTX are very important. In addition to conditions for which BTX is currently used as a therapeutic agent, evidence supports the expansion of its indications in dentistry. The purpose of this review is to provide insights into the current indications of BTX, highlight its expanding use, and review recent advances in the use of BTX in dentistry.

2. Sites and modes of action of BTX

Modes of action of BTX are summarized in Table 1 (Muthane and Panikar, 2003). BTX induces muscle weakness by inhibiting transmission of alpha motorneurons at the neuromuscular junction. Release of acetylcholine (ACh) is mediated by the assembly of synaptic fusion complexes—a set of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins, including synaptobrevin, synaptosomal-associated protein (SNAP), and syntaxin. Seven BTX serotypes have been identified. BTX types B, D, F, and G cleave synaptobrevin; types A, C, and E cleave SNAP-25; and type C cleaves syntaxin (Kant et al., 2009; Davis, 1993).

2.1. Forms of BTX

Commercially available various forms of BTX are summarized in Table 2 (Rao et al., 2011). Forms of BTX range in weight

Table 1 Action of botulinum toxin.

Absorption via the GI tract or through tissue

↓

Reaches the lymphatic channels and the blood stream

↓

Circulates in the blood until it reaches cholinergic synapses

↓

Binds with the help of binding domain

↓

Cholinergic neuronal cell membrane at nerve terminal

↓

Enters neuron by endocytosis

↓ light chain of the toxin

Crosses the membrane of the endocytic vesicle

↓

Enters cytoplasm of the pre synaptic terminal

↓ cleaves to sites on SNARE proteins

Prevents assembly of synaptic fusion complex

↓

Blocks docking, fusion and acetylcholine release

Table 2 Forms of botulinum toxin.

Type A –	BOTOX
	DYSPORT
	XEOMIN
Type B –	MYOBLOC
	NEUROBLOC

from 300 to 900 kD, with the pure toxin, including both light and heavy chains, typically weighing about 150 kD (Muthane and Panikar, 2003). Crude toxin is purified and diluted with human serum albumin. Each vial of 100 units (U) is reconstituted with preservative-free normal saline (1–5 ml) immediately before use. BTX begins to act within 24–48 h of administration, peaking at 2–3 weeks and maintaining its efficacy for about 3–4 months (Muthane and Panikar, 2003). Secondary nonresponsiveness could be encountered due to the production of neutralizing antibodies. To overcome this effect, newer toxins with higher activity levels are being engineered. Antibody production could be prevented by avoiding repeated injections and keeping the dose as low as possible (Nigam and Nigam, 2010).

2.2. Injection procedure

The BTX dose should be tailored to the severity of the condition. Toxin is injected with a 1- to 1.5-inch, 25- to 30-gauge needle, with electromyography (EMG) monitoring. Subsequent injections can be given according to the response after 3 months.

3. Adverse effects

Side effects of BTX use (Table 3) are generally transient, but could last up to several months after administration.

4. Applications in dentistry (Table 4)

4.1. Pain disorders

BTX type A inhibits the calcium-dependent release of substance P in the embryonic dorsal root ganglia, producing an analgesic effect through peripheral inhibition of C and A delta fibers (Purkiss et al., 2000). Peripheral and central analgesic

Table 3 Side effects of botulinum toxin use.

Systemic side effects include anxiety, dizziness, drowsiness, headache, dry mouth and eyes, pharyngitis, dysphagia, facial pain, flu-like symptoms, inability to focus eyes, drooping eyelid or eyebrow, double/blurred vision, sensitivity to light indigestion, nausea, sweating, fever, chills, allergic reaction like rash, itching, dyspnoea, tightness of chest, edema of face, hoarseness of voice, respiratory infection, anaphylaxis, urticaria, erythema multiforme, pruritus, loss of bladder control, loss of strength, paralysis, seizures etc.
Locally, at the injection site side effects include pain, redness, tingling, bruising, swelling or tenderness, stiff or weak muscles at or near the site, bleeding etc.

Table 4 Current and expanding applications in oro-facial disorders.

1. Oro-facial pain conditions like trigeminal neuralgia, post-herpetic neuralgia, migraine, headache and myofacial pain dysfunction
2. Salivary gland disorders like sialorrhea, sialocele, Frey's syndrome etc.
3. Hypertrophy of masseter muscle
4. TMJ disorders like dislocation, bruxism, and oro-mandibular dystonia and arthritis
5. Trismus
6. Gummy smile
7. Disorders of the facial nerve i.e. Facial nerve palsy/paresis
8. Cancer therapy
9. Botulinum toxin as a carrier for oral vaccines
10. Preparation of oral cavity for microsurgical reconstruction
11. During dental implant, jaw and periodontal surgeries.
12. In wound healing
13. Treatment of hypertrophic scars

effects of BTX arise from the direct and indirect (retrograde transport) effects of the toxin on peripheral nociceptive neurons.

4.1.1. Trigeminal and postherpetic neuralgia

When used to treat intractable and idiopathic neuralgia, BTX type A acts by inhibiting the exocytosis of ACh and other neurotransmitters. This action could be analgesic if it prevents the release of neuropeptides from nociceptive nerve endings. BTX type A inhibits the release of norepinephrine and ATP from postganglionic sympathetic nerve endings, providing an analgesic effect and reducing central and peripheral sensitization. The appropriate dose of BTX for treating trigeminal neuralgia is 20–50 U, injected at the trigger zone or into the masseter muscle (Zuniga et al., 2008).

Recently, BTX type A has been used as an alternative treatment modality for refractory cases of postherpetic neuralgia (Emad et al., 2011). When provided intradermally at 15 U, BTX inhibits the release of formalin-induced glutamate, substance P, and calcitonin gene-related polypeptide (CGRP), with direct effects on sensory neurons and indirect effects on the central nervous system (CNS). Pain decreases to mild and tolerable levels within the first week of administration.

4.1.2. Headache and migraine

Headache may be due to abnormal excitation of the peripheral nociceptive afferent fibers, leading to central sensitization and an increase in pericranial muscle hardness and tenderness. Headache may also be due to enhanced responsiveness of the trigeminal nucleus caudalis neurons, leading to the generation of pain signals that decrease pain modulation involving serotonin and norepinephrine. Migraine is a neurovascular pain syndrome associated with sterile inflammation and vasodilatation, which activate the trigeminal afferents on the vessel wall and cause pain. In cluster headache, the ophthalmic branch of the trigeminal nerve relays a pain signal, leading to the release of substance P and CGRP, vasodilatation of the dural blood vessels, and neurogenic inflammation.

Four modes of action for BTX in migraine and headache have been proposed. (1) BTX may decrease muscle contractility by preventing ACh release from the presynaptic terminal. However, this theory does not explain why pain relief with BTX often occurs before muscle relaxation (Gobel et al., 2001). (2) BTX may inhibit the extrafusal muscle fibers and normalize excessive levels of muscle spindle activity (Rosales et al., 1996; Gobel et al., 2001). Excessive release of ACh at the neuromuscular junction leads to abnormally high levels of end-plate activity, resulting in extrafusal muscle contraction. BTX inhibits transmission of neurotransmitters at the gamma motorneurons in the muscle spindle and decreases muscle activity. (3) BTX may enter the CNS, modulating pain by inhibiting the release of substance P from the trigeminal nerve endings and activating the expression of substance P in the raphe nuclei. The BTX-mediated inhibition of SNAP-25 blocks neurotransmitter exocytosis, leading to a decreased pain through the colocalization of vasoactive intestinal peptide and neuropeptide Y with ACh in the parasympathetic neurons. Further contributing to the analgesic effect is the decompression of afferent nociceptive neurons, which leads to a decrease in excitatory metabolite levels secondary to muscle relaxation (Weigand and Wellhoner, 1977). (4) BTX may reduce parasympathetic outflow, leading to analgesia. For this reason, BTX use is indicated in cases of chronic headache (Goadsby and Edvinsson, 1994).

Methods of BTX administration currently used include a fixed-site approach, following the pain, direct injection into the tender muscles, and a combination of these methods. Glabellar injections can provide complete relief. Other injection sites include the suboccipital region, where higher or lower doses are necessary for the posterior or anterior (e.g., frontal and temporal) regions, respectively. Doses of BTX used for headache and migraine range from 10 to 150 U, with clinical improvement within the first 2 weeks of injection, maximum benefit at about 6 weeks, and efficaciousness for 3 months. For cluster headache, commons doses are 24–150 U of BTX type A or the equivalent BTX type B (1200 U) (Winner, 2003).

4.1.3. Myofacial pain dysfunction syndrome (MPDS)

A complex pain syndrome with an unclear etiology, MPDS is associated with pain and tenderness of the muscles, especially those involved in mastication, and with trigger points/bands. Injection of 50 U of BTX type A is a simple and effective means to reduce the muscle hyperactivity of MPDS, by blocking ACh release from the neuromuscular junction (Nixford et al., 2002). Although this mechanism of BTX has been studied extensively, the results have been inconclusive owing to the unclear etiology. For example, EMG studies of MPDS patients have not consistently shown muscle hyperactivity. Other studies reported myositis as the underlying cause of pain in MPDS; however, myositis cannot be treated by BTX as the toxin does not have anti-inflammatory activity. Furthermore, the presence of trigger points in MPDS has not been confirmed. Overall, insufficient prospective randomized controlled studies have been performed to prove the effectiveness of BTX use in MPDS. Until recently, BTX has only been used as a temporary therapy to alleviate pain and dysfunction in the disorder (Fallah and Currimbhoy, 2012; Laskin, 2012).

4.2. Disorders of the salivary glands

BTX has been used in the treatment of disorders of the salivary glands, such as sialorrhea, sialocele, and Frey's syndrome. When used in the treatment of hypersalivation (sialorrhea), BTX acts on the cholinergic nerve endings, causing proteolysis of SNAP-25, chemical denervation, and loss of neuronal activity. BTX is injected intraglandularly, mainly to the parotid gland, at a dose that depends on the condition. Common dose ranges are 10–100 U of Botox or 20–300 U of Dysport (Fuster Torres et al., 2007). Sialocele is an accumulation of saliva surrounded by a tissue reaction, which develops as a postoperative complication after parotidectomy. When used for this condition, BTX type A acts by blocking ACh release from the secretomotor parasympathetic autonomic nerve. Doses of 50–70 U are given percutaneously in the parotid region (Chow and Kwok, 2003). Another common complication of parotidectomy, Frey's syndrome is characterized by facial hyperhidrosis in the preauricular region initiated by a gustatory stimulus. The mode of action of BTX type A in Frey's syndrome involves inhibition of ACh release at the nerve endings and in the muscles, and blockade of the motor end plates. At the autonomic level, sweat secretion is blocked in glands that depend on ACh release for their activation. BTX is typically administered at 30 U, and its efficacy lasts 6–15 months. Repeated administration decreases the symptom severity, reduces the extent of the affected area, and increases the time to relapse (Diaz et al., 2008).

4.3. Masseter muscle hypertrophy

Injection of BTX type A is a minimally invasive treatment modality for massetric hypertrophy, defined as the asymptomatic enlargement of one or both masseter muscles. The masseter muscle is injected with 100 U of BTX type A in 2 ml of sterile saline. The only limitation of this therapy is recurrence after 6 months, when the procedure must be repeated (Bas et al., 2010).

4.4. Temporomandibular disorders (TMDs)

TMDs are a group of nonodontogenic facial pain disorders associated with the temporomandibular joint (TMJ) or associated muscles.

4.4.1. TMJ dislocation

Dislocation of the TMJ is caused by excessive forward movement of the condyle beyond the articular eminence, with complete separation of the articular surfaces and positional fixation. By inhibiting ACh release at the neuromuscular junction and weakening the lateral pterygoid muscles via chemodenervation, BTX type A causes an imbalance between the muscles used for opening and closing the jaw. These effects of BTX limit mouth opening and help to prevent dislocation (Fu et al., 2010), with effects lasting 2–4 months. The BTX dose for this purpose is 25–50 U, injected percutaneously into each lateral pterygoid muscle.

4.4.2. Bruxism

Observed in individuals while awake or asleep, bruxism is an involuntary disorder manifested by jaw clenching, tooth gnashing, and grinding. For bruxism treatment, BTX type A is injected into the masseter muscle at 60 U per side. A dose range of 25–100 U elicits a good response for up to 3–4 months (Tan and Jankovic, 2000).

4.4.3. Oromandibular dystonia

These involuntary spasms of the masticatory, lingual, and pharyngeal muscles result in distortions of the oral position and function. Modes of action of BTX type A in oromandibular dystonia include local chemodenervation of the motor end plates and central intracortical inhibition, which normalizes the distorted primary motor cortex projection. Which muscle is injected depends on the form of dystonia, with the bilateral masseter muscles being injected for jaw-closure dystonia, lateral pterygoids with the anterior belly of the omohyoid muscle for jaw-opening dystonia, and tongue muscles for lingual dystonia. The recommended dose of BTX is 30 U per side (Tintner and Jankovic, 2002).

4.4.4. Arthritis.
This inflammatory joint disease manifests as joint pain and dysfunction, with joint contractures and muscle atrophy in advanced stages. The pain in chronic arthritis is amplified by neuropeptide release in the periphery. BTX type B inhibits neuropeptide release, thereby altering the nociceptor function and reducing pain and neurogenic inflammation. BTX also causes chemodenervation of the articular pain fibers (Anderson et al., 2010).

4.5. Trismus

Trismus is defined as a motor disturbance of the trigeminal nerve, especially spasm of the masticatory muscles, with difficulty in opening the mouth. In this disorder, BTX type A acts at the synaptic terminal of the cholinergic lower motorneuron and causes flaccid paralysis due to blockade of neuroexocytosis at the lower motorneuron terminal presynaptically (Andrade and Brucki, 1994). The recommended dose of BTX for trismus is 25 U injected into each masseter muscle and 10 U into the temporalis muscle.

4.6. Gummy smile

Gummy smile is defined as the display of excessive gingival tissue in the maxilla upon smiling, caused by hyperfunctional muscles of the upper lip. Treatment with BTX type A provides effective, minimally invasive, and temporary improvement (for 3–6 months) of gummy smile (Polo, 2005). BTX acts by cleaving SNAP-25, which blocks ACh release from motorneurons and enables repolarization of the postsynaptic terminal, resulting in partial chemodenervation and blockade of muscular contraction. Muscles are injected close to the nasalis or orbicularis oculi, with some muscle fibers intermeshing the levator labii superioris, levator labii superioris alaeque nasi, levator anguli oris, and zygomaticus major and minor. The ideal dose of BTX is about 2.5 U per side at the levator labii superiori and zygomaticus sites, and 1.25 U per side at the orbicularis oculi sites.

4.7. Facial nerve palsy/paresis

Facial palsy refers to both incomplete loss (paresis) and complete loss (paralysis) of facial nerve function. Unilateral palsy affects the balance between the right and left sides of the face, causing asymmetry. Injection of BTX type A into the contralateral lower facial muscles weakens these muscles and restores facial symmetry. BTX acts at the neuromuscular junction by inhibiting the release of ACh and preventing muscle contraction. A dose of 10–80 U of BTX in saline is given intramuscularly, with the precise dose being tailored to each patient and monitored by EMG. On average, the effect begins within 6 days and lasts 7–24 weeks. BTX can be re-administered, depending on the response. A minor and self-limiting side effect of the treatment is drooling of saliva (Sadiq et al., 2012).

4.8. Cancer therapy

Adjunctive treatment with BTX type A can be used to potentiate the tumor response to chemo- or radiotherapy, by opening the vascular bed. Local administration of the toxin promotes tumor perfusion and oxygenation, and modulates the vasoreactivity of vessels. BTX potentiates with the release of noradrenalin, a vasomodulator that maintains sympathetic vascular tone through activation of the vascular smooth muscle adrenoceptors, in arterioles co-opted by the surrounding tumor. Greatest effects are seen when BTX is injected 3 days before beginning anticancer treatment (Ansiaux et al., 2006).

4.9. Carrier for oral vaccines

Recently, molecular biological techniques have been used to generate an expression product of BTX type A. While losing its neurotoxic effect, the expression product retains the abilities to escape the gut, reach the general circulation, and evoke an immune response. After the toxin is ingested, it traverses a portion of the gastrointestinal system and is transcytosed from the gut lumen to the general circulation. Circulating toxin binds to peripheral cholinergic nerve endings, is endocytosed, and acts as a metalloendoprotease to cleave essential polypeptides for exocytosis. The most important mechanism for the toxin to penetrate the gut cells is its specific binding to receptors on the mucosal side of polarized gut cells. Bound toxin is actively transported across cells and delivered intact and unmodified on the serosal side of the monolayer (Simpson et al., 1999).

4.10. Oral cavity reconstruction

In spite of good postoperative care, most oral cancer patients who are treated by tumor excision, neck dissection, and reconstruction will encounter complications, including infections, wound dehiscence, and fistula formation. These complications are caused by saliva stagnation due to reduced saliva clearance, limited capacity to swallow, and increased saliva production. Infiltration of BTX type A into the major salivary gland 4 days before surgery can help overcome these complications. Before injection, sialometry and sialography are performed, and gland markings are made. Then, 3–4 injections are given to each gland, with a total dose of 80–100 U of BTX. The peak effect is seen on days 5–8 after injection. Treatment results in a

50–70% reduction of salivary secretion (Corradino et al., 2012).

4.11. Dental implants, and jaw and oral surgery procedures

Failure of implant placement is mainly due to the lack of osseous integration, which could be due to excessive functional forces in patients with parafunctional habits. Treatment of maxillofacial (e.g., zygomatic and condylar) fractures requires multiple fixation sites and hardware to overcome the forces of masticatory musculature that prevent callus formation. Prophylactic injection of 100 U of BTX type A into the masseter muscle bilaterally 12–48 h before surgery could be beneficial in reducing these forces. In periodontal surgeries, BTX injection can reduce periodontal trauma due to excessive muscular function (Rao et al., 2011).

4.12. Wound healing

Healing of traumatic, surgical, or other wounds (e.g., fissures and ulcers) involves multiple processes (e.g., hemostasis, inflammation, tissue proliferation, and remodeling), disruption of which can lead to a chronic wound. Increases in metabolic activity and inflammation during the healing process induce muscle contraction around the wound edges. Recently, experimental treatment with BTX type A has been attempted for wound healing, based on the ability of BTX to eliminate dynamic tension on and around healing tissues. This chemoimmobilization can potentially improve healing and minimize scarring for optimal esthetics (Lebeda et al., 2012).

Cleft lip and palate repair is generally associated with distorted facial growth and retarded development of the midfacial region. Causes of these effects have been attributed to a tense cheiloplasty and excessive lifting of the soft tissue, which causes tension on the healing wound. Intraoperative injection of BTX type A into the medial and lateral portions of the orbicularis oris muscle has been shown to decrease muscle activity, thereby decreasing tension at the surgical wound and resulting in better healing. There has been an encouraging trend in support of using BTX in wound-healing paradigms, although additional studies are necessary to determine a standardized approach (Galárraga, 2009).

4.13. Hypertrophic scars

Increased deposition of collagen fibers and extracellular matrix can lead to hypertrophic scars. BTX type A influences the fibroblast cell cycle, causing decreased proliferation and increased apoptosis. These effects, in turn, lead to decreased expression of TGF-β1 protein. Injection with BTX type A decreases tension at the healing site to prevent scar formation. Studies of BTX use for hypertrophic scars have only been performed in vitro, but the results are encouraging for further in vivo studies to elucidate the mechanism and standardized procedure for BTX use in this context (Xiao and Qu, 2012).

5. Contraindications for BTX use

Contraindications and precautions for BTX use in dentistry are summarized in Table 5 (Muthane and Panikar, 2003).

6. Conclusions

As a group, the BTXs are the most potent of known neurotoxins. BTXs are clinically useful in the management of various dental and orofacial disorders involving the muscles and glands. BTX can be used as a helpful and minimally invasive treatment option to improve the quality of life of patients. As a versatile treatment option with a rapidly expanding list of uses, this toxin offers a reversible alternative to numerous aggressive procedures.

Conflict of interest

There is no actual or potential conflict of interest

Table 5 Contraindications/precautions for use of botulinum toxin.

1. Pregnant women and nursing mothers (not yet completely proved)
2. Use in children – could affect the nerve growth (not yet completely proved)
3. Neuromuscular disorders e.g. Myasthenia Gravis
4. Patients with impaired hemostasis
5. Cardiovascular disorders
6. Pre-existing infection at the injection site
7. Skin infections e.g. Eczeme, psoriasis
8. Individuals on aminoglycoside antibiotics, quinine, chloroquine, calcium channel blockers, aspirin
9. Emotionally disturbed individuals especially after the age of 65 years

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