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Invited Review Paper
Therapeutics

Clinical use of botulinum toxins in oral and maxillofacial surgery

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Botulinum toxin (BTX) is a bacterial toxin that could be used as a medicine. Clinical applications of BTX have been expanding over the last 30 years and novel applications reported. Its mechanism of inhibiting acetylcholine release at neuromuscular junctions following local injection is unique for the treatment of facial wrinkles. Other dose-dependent anti-neuroinflammatory effects and vascular modulating properties have extended its spectrum of applications. Conditions such as temporomandibular joint disorders, sialorrhea, headache and neuropathic facial pain, muscle movement disorders, and facial nerve palsy could also be treated with this drug. Further applications of BTX are likely to be developed. This paper reviews the established and emerging applications of BTX in the field of oral and maxillofacial surgery. An overview of the pharmacology, toxicity and preparations of the agent is given.

Keywords: botulinum; clinical use.

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Purified botulinum toxin (BTX) was the first bacterial toxin used as a medicine. Since its introduction into clinical use, over 30 years ago, it has become a versatile drug in various fields of medicine. The clinical applications of BTX have been expanding and novel applications developed.

BTX is widely used in cosmetic applications for the treatment of facial wrinkles after local injection, but conditions such as temporomandibular joint disorders, sialorrhea, headache and neuropathic facial pain, muscle movement disorders, and facial nerve palsy could be treated with this drug. Many other indications are under investigation, and further applications for BTX are likely to be developed[220]. In the maxillofacial region, most studies on the use of BTX are of low quality (noncomparative, non-randomized trials), but the overall results were promising.

In this review, established and emerging applications of BTX in the field of oral and maxillofacial surgery are discussed. Emphasis is placed on the mechanism of action and outcome of treatment in different clinical situations. An overview of the pharmacology, toxicity and different preparations of the agent is given.

History

The idea of a possible therapeutic use for botulinum toxin (BTX) was first developed by the German physician and poet Justinus Kerner (1786–1862); he called it 'sausage poison'. In 1870, Muller, another German physician, coined the name botulism. The Latin form is *botulus*, which means sausage[66].

In 1897, Emile van Ermengem investigated an epidemic of botulism in Ellezelles, Belgium, after the consumption of raw ham. He isolated the bacteria from the ham and produced the disease in laboratory animals by injecting the toxin produced by the organism[41].

BTX was developed as a biological weapon by many countries in the twentieth century[50]. Although many countries stopped research related to biological weaponry after signing the Biological and Toxin Weapons Convention, purification of BTX for medical use continued[222].

A therapeutic use for botulinum toxin type-A (BTX-A) was first studied in primates by Scott et al in 1973[187]. In the late 1970s, the toxin was introduced as a therapeutic agent for the treatment of strabismus[186]. Since then, its therapeutic applications have expanded into many

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different fields, often with innovative treatments and surprising results.

BTX was first used for treating facial wrinkles and aging skin in 1988, but its widespread cosmetic use did not occur until the mid-1990s[148]. There was much speculation about the storage, dilution, delivery methods and treatment doses. In maxillofacial surgical practice, Niamtu reported on the cosmetic use of BTX for facial rhytids and dynamic lines in 1999 and 2000[147,149]. During the mid- and late-1990s, BTX was used for lateral canthal lines (crow's feet), platysmal banding, orbicularis oris injection, masseter muscle injection and the treatment of temporomandibular disorders (TMDs). Later, there were many attempts to use BTX for different clinical situations in oral and maxillofacial surgery.

Bacteriology

Clostridium species bacteria are sporulating, obligate anaerobic, Gram-positive bacilli. The spores of *C. botulinum* are ubiquitous, distributed widely in soil and marine sediments worldwide and often found in the intestinal tract of domestic grazing animals[199,206].

Under appropriate environmental or laboratory conditions, spores can germinate into vegetative cells that will produce toxin. *C. botulinum* grows and produces neurotoxin in the anaerobic conditions frequently encountered in the canning or preservation of foods[200,223].

Seven different strains of *Clostridium* have been described (designated A, B, C (1 and 2), D, E, F and G), and each produces a distinct neurotoxin identified by the corresponding letter of the bacterial strain producing it, so, there are 7 distinct neurotoxins (BTX-A, -B, -C, -D, -E, -F, -G)[100,216]. Humans can be affected by the toxins of 5 strains (A, B, E, F and G) and are not affected by the toxins of strains C and D[71,100]. All 7 toxins may potentially cause botulism in humans given a high enough exposure[140]. All 7 neurotoxins are structurally similar but immunologically distinct[92]. There is some serum cross-reactivity among the serotypes because they share some sequence homology with one another as well as with tetanus toxin[91].

Structure and Toxicity

Toxins produced by clostridial bacteria are high-molecular-weight protein complexes that include 3 key proteins: a 150-kDa toxin, a non-toxin hemagglutinin protein, and a non-toxin non-hemagglutinin protein. The 150-kDa toxin is composed of a 100-kDa heavy chain and a 50-kDa light chain. Disulfide and noncovalent bonds link the heavy and light chains, and both chains are required for neurotoxicity[100].

BTX is the most toxic material known. It is 4 times more lethal in mice than tetanus toxin, 1×10^{10} more lethal than curare, and 100×10^{10} more lethal than sodium cyanide[33]. The estimated human dose (assuming a weight of 70 kg) of type A toxin lethal to 50% of an exposed population (the LD50) is estimated, based on animal studies, to be approximately 0.09–0.15 μg by intravenous administration, 0.7–0.9 μg by inhalation and 70 μg by oral administration[76,96,180,188]. Based on findings from primate studies, human LD50 for intramuscular BTX injection is estimated at 2500–3000 U for a 70-kg adult (35–40 U/kg).

Mechanism of Action

BTX is a protease that causes temporary chemical denervation of skeletal muscle by blocking the Ca^{+2}-mediated release of acetylcholine from nerve endings of alpha and gamma motor neurons (myoneural junction), producing a transient dose-dependent weakening of the muscle activity rendering it nonfunctional without systemic effects[23]. This inhibition of muscular contraction is believed to be followed by the sprouting of new axon terminals, which results in synaptic regeneration and the reestablishment of neuromuscular transmission[15].

The 7 neurotoxins have different specific toxicities,[87,113,151] different durations of persistence in nerve cells[49,74], and different potencies[5]. All BTX serotypes, ultimately, inhibit acetylcholine release.

The area of flaccidity produced may be larger than the area of muscle denervated as a result of postulated paralysis of gamma motor neurones, so the output of the muscle spindles is reduced leading to reduced muscular contraction at adjacent sites within the injected muscle[150]. Weakening of surrounding muscles not injected may also occur because of toxin diffusion. Animal studies have demonstrated that BTX-A diffuses across fascial planes to surrounding muscles[193].

Clinical effect occurs within approximately 3–7 days (typically seen after 1–3 days) after administration, followed by 1–2 weeks of maximum effect, which then levels off to a moderate plateau until full nerve recovery within 3–6 months (typically at approximately 3 months)[176].

Preparations

A number of BTX preparations have been approved in different countries. Currently, there are 6 different BTXs available on the market, 5 contain BTX-A (Botox, Dysport, Xeomin, Prosigne and PurTox) and the other contains BTX-B (Myoblocs/NeuroBlocs). Approval procedures are complex and vary between preparations and countries, but, in general, Botox has garnered the most approvals worldwide, followed by Dysport[220].

Treatment doses of BTX vary depending on the brand of toxin used. The dose given for any toxin refers only to that particular preparation and does not readily transfer to doses of other products, even if they are of the same toxin serotype. These ratios should be applied with extreme caution because different preparations may have different efficacy in different parts of the body[77].

BTX-A

Botox (Allergan Inc, USA): BTX-A (originally called 'Oculinum') was first used in humans in 1968 to treat strabismus[187]. In 1991, Allergan Inc. purchased several batches of this purified BTX-A, and the agent was given the name Botox[216].

Botox is the only available BTX product approved for cosmetic use in North America. It is specifically approved for the therapeutic treatment of strabismus, blepharospasm, cervical dystonia and axillary hyperhidrosis. There are reports of Botox specifically improving patient self-perception[35,37,38,69,90,124,126,127].

Each vial of Botox contains 5 ng (100 U) of air-dried toxin, with 1 unit (U) equal to the median amount necessary to kill 50% of female Swiss-Webster mice weighing 18–20 g each after intraperitoneal injection (LD50)[135,176,216]. Each vial contains 500 μg of albumin and 900 μg of sodium chloride[135].

Dysport (Ipsen Limited, UK) is another BTX-A product approved for cosmetic use, which is marketed and sold in many European countries as well as Russia, New Zealand, Mexico, Brazil, Argentina and Vietnam[35]. Each vial contains 12.5 ng (500 U) of air-dried toxin, 125 μg of albumin, and 2.5 mg of lactose[135]. Dysport comes from a different type A strain of bacteria than Botox and doses are not equivalent. Direct comparisons of Botox and Dysport in animal studies suggest that the equivalence doses are 1 U Botox to 2.5–5 U Dysport, though in humans, this conversion is largely an estimate[135].