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REVIEW ARTICLE

Xeomin®: an innovative new botulinum toxin type A

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Botulinum toxin type A (BoNT/A) is a well-established treatment for conditions characterized by muscle and autonomic nerve terminal overactivity, such as cervical dystonia and blepharospasm, and hyperhidrosis, respectively. BoNT/A is not digested in the gastrointestinal tract as it forms a complex with several proteins that protect and stabilize the neurotoxin. However, the pure neurotoxin is solely responsible for the therapeutic effect, and the complexing proteins have been shown to exhibit immunostimulating activity. The complexing proteins are not required for the stabilization of the neurotoxin in a formulation; the complexing proteins immediately dissociate from the neurotoxin at a physiologic pH, so they do not influence the spread of the neurotoxin. Xeomin® is the only botulinum toxin that is free from complexing proteins and is stable at room temperature for a period of 4 years. When injected directly into muscles, Xeomin® inhibits local neuromuscular cholinergic transmission, causing focal weakness. It binds to motor nerve terminal pre-synaptic receptors, is internalized via receptor-mediated endocytosis and then selectively cleaves a protein called SNAP-25. This is one of several so-called 'SNARE' proteins involved in exocytosis. Cleavage of SNAP-25 inhibits the secretion of acetylcholine causing the paralysis of the muscle. The clinical effects begin 24–72 h after injection, peak at approximately 4–6 weeks and are sustained for several months.

Introduction

Botulinum toxin type A (BoNT/A) is a poison usually found in decaying food that is produced by the anaerobic bacterium *Clostridium botulinum*. In 1895, van Ermengem isolated the spore-forming bacterium from salted pork meat and post-mortem tissue of botulism victims [10]. About 50 years after this, Schantz succeeded in preparing the toxin complex in a crystalline form, but it wasn't until the 1970s that it was found that the crystalline complex of BoNT/A could be used to treat dystonias, and this led to the development of a clinical formulation of the toxin.

Today, BoNT/A is used to treat conditions characterized by muscle overactivity, such as dystonia and blepharospasm [9], and overactivity of cholinergic autonomic nerve terminals, such as hyperhidrosis.

This paper provides an overview of the key features of BoNT/A which facilitate its use in the relief of a variety of conditions characterized by muscle overactivity and examine the novel clinical features of a new formulation, Xeomin®.

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Xeomin®: a new BoNT/A formulation

Xeomin® is a new, highly purified, freeze-dried formulation of BoNT/A that lacks the complexing proteins associated with the native toxin. In contrast, complexing proteins are present in other commercially available preparations. Xeomin® became commercially available in Germany in June 2005 for the treatment of spasmodic torticollis and blepharospasm.

Therapeutic value of BoNT/A

When injected directly into muscles, botulinum neurotoxin (BoNT; all types) produces its therapeutic effect by inhibiting local neuromuscular cholinergic transmission, causing focal weakness sensitivity. The process involves BoNT binding to motor nerve terminal presynaptic receptors, being internalized via receptor-mediated endocytosis and then selectively cleaving a protein called SNAP-25 (Fig. 1). This is a 'SNARE' protein and is involved with other SNARE proteins in exocytosis, capturing vesicles and then fusing them with

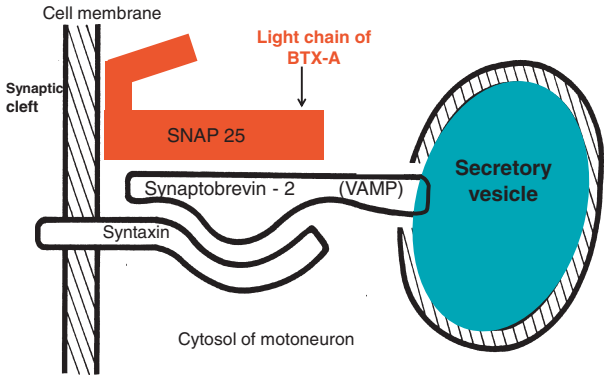

Figure 1 Mechanism of action of botulinum toxin type A.

the nerve terminal membrane to release the contents – in this case the neurotransmitter acetylcholine – into the synaptic cleft. By blocking the action of SNAP-25, BoNT/A inhibits the release of acetylcholine from the nerve terminal. The complexity of this mechanism, which is common for all BoNT/A products, may account for the relatively slow onset of 7 days [6].

Like other BoNT/A formulations, Xeomin® exerts its therapeutic effect by inhibiting local neuromuscular cholinergic transmission. The clinical effect of Xeomin® begins to appear within a couple of days of injection, peaks at approximately 4–6 weeks and is sustained for several months.

Role of complexing proteins

Although proteins are usually digested in the gastrointestinal tract and not resorbed, the botulinum neurotoxin is orally toxic. This is because the bacterium *Clostridium botulinum* produces several proteins that form a complex with the neurotoxin. These complexing proteins protect against the harsh conditions of the gastrointestinal tract, particularly the stomach, and stabilize the neurotoxin. The complex is only stable under acidic pH and readily dissociates under physiologic conditions [3] to liberate the pure neurotoxin, which is solely responsible for the therapeutic effect.

The complexing proteins are not required for the stabilization of BoNT/A in clinical formulations. However, Xeomin® is the only botulinum toxin that is free from complexing proteins (i.e. it consists of only the neurotoxin) and is stable at room temperature for a period of 4 years [4].

Adverse reactions associated with the use of BoNT/A depend on the spread of the neurotoxin from the injected muscle, and it was initially thought possible that the complexing proteins might prevent or reduce the diffusion of the pure neurotoxin. However, studies have not revealed any apparent differences between Xeomin® and the commercially available preparation Botox® in terms of diffusion characteristics into adjacent muscles in clinical studies [11]. Moreover, direct comparisons between Xeomin® and a BoNT/A formulation containing complexing proteins did not reveal the emergence of paralysis in adjacent muscles after injection of Xeomin® in the extensor digitorum brevis muscle in clinical studies amongst healthy volunteers [5,11].

Immunogenicity and the complexing proteins

Patients treated with the complex containing products can develop neutralizing antibodies against the neurotoxin and then do no longer respond to the therapy (secondary non-responder). Some of the complexing proteins associated with BoNT/A and retained in other commercially available preparations are haemagglutinins, and whilst these proteins have no therapeutic effect nor are they required to stabilize the neurotoxin in a commercial formulation, they have the potential to exhibit immunostimulating activity i.e. they act as adjuvants.

Immunization studies have shown that haemagglutinins can enhance the antibody titre against the neurotoxin or other proteins, which could lead to antibody generation and therapy failure. For example, Lee *et al.* [7] found that in mice immunized with botulinum toxoids of BoNT/B with and without associated haemagglutinins, the antibody titre against the neurotoxin was markedly higher when haemagglutinins were present. Moreover, the concentrations of interleukin-6 and interferon were also increased in the presence of haemagglutinins.

With Xeomin®, the generation of antibodies in animal studies has not yet been observed [2,6]. No head-to-head clinical studies have been carried out to compare Xeomin® with the complexing protein containing products.

Conclusions

Botulinum toxin is a food poison; therefore, it is a orally toxic protein. The neurotoxin is produced as part of a high molecular weight complex consisting of a number of other proteins that include haemagglutinin molecules. Whilst these complexing proteins have no therapeutic effect and are not required to stabilize the molecule in commercial preparations, they have the potential to act as adjuvants stimulating the production of antibodies to the neurotoxin. The presence of such antibodies has been associated with therapy failure.

Xeomin® is the first commercially available BoNT/A preparation free from the complexing proteins associated with the neurotoxin. The formulation is

highly stable at room temperatures, and has an *in vivo* diffusion profile comparable with that of preparations retaining the complexing proteins. Clinical studies support the efficacy of Xeomin® compared with other BoNT/A preparations [1,5,6,8,11]. These characteristics make Xeomin® a real alternative to current BoNT/A preparations.

Conflicts of interest

J.F. is an employee of Merz Pharmaceuticals GmbH.

References

1. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. *Neurology* 2005; **64:** 1949–1951.
2. Blumel J, Frevert J, Schwaier A. Comparative antigenicity of three preparations of botulinum neurotoxin type A in the rabbit. *Neurotox Res* 2006; **9:** 238 (abstract).
3. Eisele KH, Taylor HV. Dissociation of the 900 kDa neurotoxin complex from *C. botulinum* under physiological conditions. *Toxicon* 2008; **51:** 10.
4. Grein S, Mander GJ, Taylor HV. Xeomin® is stable without refrigeration: complexing proteins are not required for stability of botulinum toxin type A preparations. *Toxicon* 2008; **51:** 13 (Abstract #36 and associated poster).
5. Jost WH, Kohl A, Brinkmann S, Comes G. Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (BOTOX) in healthy volunteers. *J Neural Transm* 2005; **112:** 905–913.
6. Jost WH, Blumel J, Grafe S. Botulinum neurotoxin type A free of complexing proteins (Xeomin®) in focal dystonia. *Drugs* 2007; **67:** 669–683.
7. Lee JC, Yokota K, Arimitsu H, *et al*. Production of antineurotoxin antibody is enhanced by two subcomponents, HA1 and HA3b, of Clostridium botulinum type B 16S toxin-haemagglutinin. *Microbiology* 2005; **151:** 3739–3747.
8. Roggenkämper P, Jost WH, Bihari K, Comes G, Grafe S, for the NT 201 Blepharospasm Study Team. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. *J Neural Transm* 2006; **113:** 303–312.
9. Simpson DM, Blitzer A, Brashear A, *et al*. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; **70:** 1699–1706.
10. Van Ermengem E. Uber einen neuen anaëroben bacillus une seine beziehungen zum botulismus. *Z Hyg Infektionskr* 1897; **26:** 1–56 (republished as: A new anaerobic bacillus and its relation to botulism. Rev Infect Dis 1979; 1: 701–719).
11. Wohlfarth K, Muller C, Sassin I, *et al*. Neurophysiological double-blind trial of a botulinum neurotoxin type a free of complexing proteins. *Clin Neuropharmacol* 2007; **30:** 86–94.

