Toxicon 67 (2013) 81–86

Contents lists available at SciVerse ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

Clinical utility of different botulinum neurotoxin preparations

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ARTICLE INFO

Article history:
Received 19 June 2012
Received in revised form 27 November 2012
Accepted 29 November 2012
Available online 30 January 2013

Keywords:
OnabotulinumtoxinA
AbobotulinumtoxinA
IncobotulinumtoxinA
RimabotulinumtoxinB
Chemodenervation
Evidenced-based review

ABSTRACT

Comparative literature assessing the relative safety and efficacy of different BoNT products is limited. The quantity and quality of data vary by preparation and indication. Clinicians seeking data relevant to the care of patients with specific conditions may find only reports about small numbers of patients with varying symptoms. While a literature search for "botulinum neurotoxins" will yield a large number of publications; only a fraction of these meet criteria for an academic evidence-based review. Patients may have been treated with a different BoNT formulation than that with which the physician is familiar, or there may be little or no clinical data on the use of a specific BoNT product for the proposed intervention. This paper is an introduction to a series of papers (which follow) in which an expert panel reviewed the BoNT clinical trial literature in order to provide evidence-based recommendations regarding the clinical use and efficacy of available BoNT preparations for four major therapeutic areas: movement disorders, spasticity, urology, and secretory disorders. Expert opinion is also included to address practical issues where more evidence and further research is needed.

1. Introduction

Botulinum neurotoxin (BoNT), produced by *Clostridium botulinum*, is a potent natural poison that blocks normal synaptic release of neurotransmitter at the muscle end plate and causes muscle relaxation. Historic steps in the discovery and characterization of BoNT span centuries (Table 1). The first practical application to human therapeutics occurred during the 1970s, when ophthalmologist Alan Scott, seeking an alternative to surgical correction of strabismus, injected BoNT into the extraocular muscles in primate and human subjects (Erbguth, 2008; Schantz and Johnson, 1992; Scott, 1981; Scott et al., 1973). These pioneering studies established BoNT as the first microbial protein to be administered by injection for the treatment of human disease (Schantz and Johnson, 1992); they were the foundation for a body of research evaluating BoNT as a treatment for disorders characterized by excessive muscle tone. In contemporary medicine, the therapeutic injection of BoNT is performed in many clinical settings by an expanding population of clinicians. Several different BoNT preparations are available and provide potential alternative treatment options.

2. Botulinum neurotoxin therapeutics and the need for practical guidance

There are seven serotypes (A–G) of BoNT, all of which block the exocytosis of acetylcholine into the neuromuscular junction, but only type A and type B are available for clinical use. These preparations are broadly utilized: In the

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http://dx.doi.org/10.1016/j.toxicon.2012.11.024

Table 1
Major historic steps in the discovery and development of botulinum neurotoxin. Adapted from Erbguth (2008).

1700s	First documented endemic outbreaks of food-borne botulism (termed "sausage poisoning" in Europe)
1817–1822	Justinus Kerner and botulinum toxin: Preliminary animal experiments, systematic descriptions of clinical effects; theoretic considerations of possible therapeutic use
1895–1897	Emile Pierre van Ermengem: Discovery of neurotoxin-producing pathogen *Clostridium botulinum*
1910	J. Leuchs: Discovery of second botulinum toxin serotype (type B)
1920–1930	H. Sommer: Purification of botulinum toxin
1946	C. Lamanna and J. Duff: Techniques of toxin concentration and crystallization
1949	A. Burgen: Description of toxin effect on acetylcholine release at neuromuscular junction
1970s	Description of wound and infant botulism
1941–1972	Edward Schantz: Production of toxin at Fort Detrick (US)
1968	Contact between Alan Scott and Edward Schantz; search for therapeutic agents (e.g., botulinum toxin) to relax eye muscles
1973	Alan Scott: Publication of animal experiments using injections of botulinum toxin into eye muscles
1977–1980	Alan Scott: Treatment of strabismus patients with botulinum toxin; first publications of application in humans
1981–1988	Development of type A toxin preparation in the UK; later renamed Dysport®
1989	Alan Scott's type A toxin preparation approved by FDA as Oculinum in the US; later renamed Botox®
1989	Mark Hallett et al., show reproducible benefit for botulinum toxin injections in patients with hand dystonia (Cohen et al., 1989)
1989	Oculinum, Inc. receives FDA approval to market botulinum toxin type A in the United States as an orphan drug to treat strabismus, blepharospasm, and hemifacial spasm associated with dystonia in patients 12 years of age and older
1990	Dysport approved in the UK for blepharospasm and hemifacial spasm
1990s	Discovery of molecular action of botulinum toxin (Schiavo, Montecucco, Dolly)
2000	The FDA approves Botox® (botulinum toxin type A) for the treatment of abnormal head position and neck pain associated with cervical dystonia The FDA also approves Myobloc® (botulinum toxin type B) to reduce the severity of abnormal head position and neck pain associated with cervical dystonia Myobloc® is the US trade name for BoNT-B (Neurobloc® in Europe)
2002	FDA approves Botox® Cosmetic (botulinum toxin type A) for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity
2004	FDA approves Botox® (botulinum toxin type A) for the treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents
2005	Approval of Xeomin® (botulinum toxin type A) in Germany for blepharospasm and cervical dystonia
2008	FDA issues "Early Communication, Ongoing Safety Review of Botox®" and Botox® Cosmetic (botulinum toxin type A) and Myobloc® (botulinum toxin type B)
2009	FDA issues new established names for botulinum toxin products
2009	FDA approves Dysport® (abobotulinumtoxinA) for: Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity
2009	FDA issues "Update of Safety Review of onabotulinumtoxinA (marketed as Botox/Botox® Cosmetic), abobotulinumtoxinA (marketed as Dysport®) and rimabotulinumtoxinB (marketed as Myobloc®)"
2010	FDA approves Botox® (onabotulinumtoxinA) for treatment of upper limb spasticity in adult patients to decrease severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), and finger flexors (flexor digitorum profundus and flexor digitorum sublimis)
2010	FDA approves Xeomin® (incobotulinumtoxinA) to decrease severity of abnormal head position and neck pain in adults with cervical dystonia and to treat blepharospasm in patients previously treated with onabotulinumtoxinA (Botox®)
2010	FDA approves Botox® (onabotulinumtoxinA) for prophylaxis of headaches in adult patients with chronic migraine
2011	FDA approves Botox® (onabotulinumtoxinA) for the treatment of urinary incontinence due to detrusor overactivity associated with a neurogenic condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication
2011	FDA approves Xeomin® (incobotulinumtoxinA) for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity

United States, 17 million treatments with one commercial botulinum product have been reported since 1994, and in the United Kingdom, over 1 million first-time exposures are now reported annually for facial cosmesis (Poulter, 2011; Singer, 2009). Clinical indications for BoNT treatment have expanded considerably since the first preparation was used for this purpose nearly two decades ago. BoNT is now considered first-line therapy for patients with certain movement disorders, including blepharospasm and cervical and focal limb dystonias. BoNT injection is also an established treatment option for spasticity in the setting of traumatic brain injury, cerebral palsy, and post-cerebrovascular accident. Additionally, BoNT therapy has been shown to be effective for improving hyperactivity of the detrusor muscle of the bladder, for conditions characterized by hypersecretion (such as hyperhidrosis and sialorrhea), for the prevention of chronic migraine, and for the treatment of facial lines. Its use remains exploratory for chronic pain management and a variety of gastrointestinal conditions. Clinical trials, case reports, and basic science investigations are continually published. A simple database search for publications of any type since 1990 with "botulinum" in the title returns over 14,000 citations; limiting the query to guidelines, meta-analyses, or clinical trials of any design returns over 1000 publications, and of these, approximately 800 appeared in the most recent decade (based on query results from pubmed.gov on November, 2011).