Aesthetics
The monthly journal for medical aesthetic professionals
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Emerging aspects in Botulinum Toxin use

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Abstract

With an established number of licensed medical indications, Botulinum Toxin type A (BoNT-A) is also globally acknowledged to effectively refine many of the senescent changes which occur in the ageing face. BoNT-A is widely considered to be an effective first line therapy to eradicate dynamic lines, as well as an adjunctive treatment for a number of aesthetic rejuvenation strategies in softening more established rhytides. The exceptional popularity of the products for aesthetic use and the new potential applications currently under investigation remain unabated. Such demand reinforces the importance of continuous educational updates for the medical practitioner to provide valuable information on the evolving aesthetic and medical modalities, ensuring an optimal understanding of the uses of the product, and safe treatment outcomes for the patient.

Key words: Botulinum Toxin type A, emerging indications, delivery devices, pharmacology, dermatology, pain

Introduction

In this article, we will examine the currently available literature surrounding the emerging indications for Botulinum Toxin type A (BoNT-A), as well as recent pharmacological developments. BoNT remains one of the most extensively researched drugs to date[1,2] and a very popular treatment for patients. A recent annual survey by the American Society of Plastic Surgeons indicates that there were over over 6 million aesthetic treatments with BoNT-A alone during 2013[3], reinforcing to the practitioner the importance in maintaining an awareness of current developments. Clinicians should therefore continue to develop their clinical knowledge and practice to ultimately deliver an enhanced aesthetic result.

The history of BoNT in medicine is well known. Initially isolated from an outbreak of food poisoning, the causative organism Clostridium botulinum soon became of intense interest due to the exceptional potency of the neurotoxin produced **(Fig. 1)**. Following the isolation of BoNT, clinical trials and the path to product registration were followed, both in the United States with the product Oculinum (eventually Botox) and Europe as the product Dysport. Since then, the molecule has been isolated and characterized **(Fig. 2)**, but there are still unknown aspects about the mode of action that are elusive and not yet fully determined. For example, why does the activity of the molecule persist for many months when normally, any foreign proteins in the body are rapidly identified and eliminated? Recent evidence indicates that the common phenomenon of phosphorylation may play a role, although this may also significantly reduce enzymatic activity.[4]

Currently there are a number of BoNT-A products available worldwide, with regional products and others in development **(Fig 3)** – a recent number emerging from South Korea in particular.

The pharmacology of BoNT-A, when used in aesthetic treatments and for medical indications, has been the subject of considerable discussion in recent years. Attempts have been made, based on pseudo-scientific arguments, to distinguish certain products from the others. However, the arguments used were identified as incorrect some years ago.[5] Originally, these arguments related to the existence of the so-called BoNT complex, a natural formation of the active neurotoxin, produced by the bacteria, that serves to protect the neurotoxin element in the natural environment. The neurotoxin molecule is naturally protected by a family of related proteins. However, unlike certain claims, these accessory proteins were found to dissociate from the neurotoxin molecule during reconstitution of the products in the vial.[6] Apparent product differences relating to, typically, the size of the BoNT-A complex were therefore inaccurate and misleading. Additional features of BoNT-A pharmacology are defined by the injection itself and what occurs subsequently. Diffusion refers to the BoNT complex moving from an area of high concentration to an area of low concentration during the binding to receptors, whereas Spread refers to the physical movement of the product once injected, which may be caused by factors such as dilution volume, needle gauge and injector.[6]

The pharmacodynamics of BoNT-A, in particular its uptake into the neuromuscular junction (NMJ), is of clinical importance. Recent reports indicate a rapid uptake with no residual BoNT-A in the injected muscle within 20 minutes. Thus questioning post injection protocols currently being promoted.

The main areas to consider in the use of BoNT represent:

1. Toxin effects on muscles,
2. Effects on glands,
3. Pain relief,
4. Dermatological uses and
5. Methods of delivery.

1. BoNT effect on muscles

The specific target for BoNT is the NMJ, where the nerve synapse connects to the muscle systems. This is a highly complex, universal connection within the body and much about how the NMJ functions is still a subject of investigation.[7] In particular, the existence and role of the neurotransmitters involved in overall signaling processes continues to be an area of discovery.[8]

The specific anatomical distribution of the NMJ within a muscle is of critical importance in understanding the effects of BoNT-A on muscle dynamics. Unlike other muscles in the body, facial muscle fibres have single or multiple NMJ's which determine the ability to control very fine and intricate muscle movements.[9-11] However, apart from limited studies to date, we have little information on these target sites in the majority of other facial muscles, even though knowledge of the gross anatomy of these muscles, with respect to use of BoNT-A, has recently been described.[12] A more detailed understanding of the effects of BoNT-A on facial muscle activity with respect to dose, action and recovery, through the use of electromyography, is also being gained.[13,14]

Detailed understanding is essential in optimization of the dose-effect relationship for BoNT-A, in order to gain the best aesthetic results for the patient, with minimal doses. Facial aging is a universal process that affects many different aspects of size, shape, volume and function.[15] However, in addition to ageing effects on muscle size and strength, there is one additional effect that has been overlooked until now – the ageing of NMJs.[16] With clear evidence of such ageing processes,

HISTORY OF BOTULINUM TOXIN AND FIRST CLINICAL USE		
JUSTINUS KERNER	1820	TOXIN
EMILE van ERMENGEM	1895	ORGANISM
KEMPNER	1897	ANTITOXIN
IVAN HALL	1916	EPIDEMIOLOGY
SOMMER (USA)	1926	PURIFIED
BIOLOGY DEPT. PORTON (UK)	1940	UK ARMY
EDWARD SCHANTZ (USA)	1944	US ARMY
CARL LAMANNA	1946	CRYSTALLINE TOXIN
DUFF	1957	IMPROVED PROCESS
MRE (UK)	1951	UK DEFENCE
UNIV. WISCONSIN	1974	FOOD RESEARCH
ALAN SCOTT & ED SCHANTZ	1968	INVESTIGATIONS OF USE IN MAN
OCULINUM INC		STARTED LATE 1970'S
CENTRE FOR APPLIED MICROBIOLOGY & RESEARCH	1982	FIRST UK TOXIN IN MAN
OCULINUM INC	1989	FIRST OCULINUM® APPROVAL
PORTON PRODUCTS	1990	FIRST DYSPORT® APPROVAL (UK)

Figure 1

there is a likelihood that BoNT-A may produce different responses, perhaps less pronounced, in the older patient. Indeed, one of the BoNT-A products has a qualification within the Summary of Product Characteristics (SmPC) that there is a different response between patients over 50 years of age and under that age: efficacy is less for patients over 50 years old and lower in men than women.[17]

2. Glandular effects

The effects of BoNT-A on hyperhidrosis are well documented, with over 160 publications covering nearly 20 years of use.[18] The products have widespread acceptability for treatment of the condition, wherever occurring on the body, in both paediatric and adult applications,[19] despite only being approved for axillary hyperhidrosis. BoNT-A is also used to treat gustatory sweating (Frey's Syndrome). Additional recent applications include the use for treatment of salivary glands for control of drooling by reduction of hypersecretion. This continues to be a well-studied area,[20-24] although a recent Cochrane Review found insufficient evidence to inform clinicians clearly about clinical interventions using BoNT for drooling in children with cerebral palsy.[21] There is generally no consensus which glands should be injected and studies looking at both the parotid and submandibular glands have been carried out.[22, 25-27] BoNT-A has also been reported to be useful in correcting the exaggerated appearance of the submandibular gland following a neck lift.[28] A novel application receiving attention in modern clinical trials is the treatment of benign prostatic hypertrophy (hyperplasia).[29-31] Additional benefits for such a condition, over and above the normal radiation or drug therapies, will always be of considerable clinical value to patients. In this case, a reduction in prostate volume and measurements related to prostate effects have been reported.[30]

3. Pain relief

The use of BoNT for the relief of pain has been studied in many different conditions.[32] To date, only the prophylactic treatment of migraines has been approved by the licensing authorities for one of the products. Nevertheless, use of BoNT for routine treatment of many pain conditions has found a widespread, off-label usage.[33-36] There is little doubt that further, detailed clinical trials, yet to be performed, will bring established use of BoNT in these types of pain conditions. There are close links between certain aspects of the pain indications under investigation following treatment with BoNT, and a number of painful dermatological conditions, as discussed below.

4. Dermatological uses

The dermatological potential for BoNT-A has recently been investigated with early findings in support of treating symptoms associated with rosacea, certain types of psoriasis, facial inflammatory diseases and acne. OnabotulinumtoxinA has been used experimentally to treat erythema and flushing in rosacea and been shown to demonstrate, through the neurogenic component, an ability to actively address vascular dysfunction and inflammation, with potential to reduce hyper seborrhea. Dayan and colleagues[37] conducted a two-year survey comprising a small number of subjects (13) presenting with rosacea. The authors utilised an intralesional microdroplet injection technique (0.05ml) of onabotulinumtoxinA, which was 100 units in a dilution of 7ml. Multiple injections were performed intradermally, which gave a dose on average from 8-12 units per affected side. Subjects were reviewed at three weeks and again at three months with a visible reduction in erythema reported, with the authors measuring outcomes on the basis of before and after photography, as well as verbal feedback. Some subjects experienced longevity of results beyond three months. The findings indicate a decrease in persistent as well as intermittent flushing, as well as reduced erythema and inflammation. A range of painful facial conditions, often involving inflammation, have also been studied. These include notalgia paresthetica,[38-40] refractory erythromelalgia,[41] and hidradenitis suppurativa.[42] Other developments include additional knowledge on the effect of BoNT-A on fibroblasts – showing a positive effect with collagen production.[43] This data, and others, indicate the potential role of BoNT-A to affect the growth of fibroblasts. Recent work has indicated that BoNT-A is a competitor for the fibroblast growth factor (FGF) receptor,[3,44] adding further weight to direct effects to reduce scar formation and improve wound healing. The ability to modulate scar tissue has been investigated further in an in-vivo animal study to show a reduction in capsule formation around a silicone implant.[45,46]

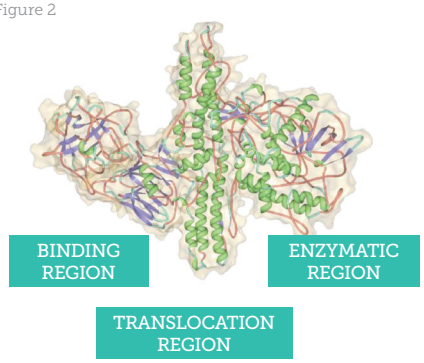
5. Methods of Delivery

Several areas need to be considered in delivering the treatment of BoNT-A:

I. No-needle techniques
II. Pain on injection
III. Accuracy of dosage
IV. No-needle injections

Studies to inject BoNT-A using several delivery devices have looked at the ability to drive the product through the epidermis and dermis.

Figure 2



This can be readily achieved with the electrical technique of iontophoresis.[47-51] However, pressure delivery using the Dermojet has also been evaluated and is a technique to deliver the product into different areas, for example, for treating palmar hyperhidrosis. However there is no control over depth of injection and the toxin may be delivered deeper than required, resulting in adverse consequences. More recent research is looking at techniques to modulate the skin barrier and allow penetration of BoNT through the dermis. Here, formulation of the BoNT using various carriers is a key area. The US-based company Revance has completed limited Phase 3 testing of a topical BoNT-A gel. This would allow treatment of conditions such as hyperhidrosis and wrinkles due to superficial muscles – typically Crow's feet, without a needle to puncture the skin. The company is one of around four in the world examining the potential for topical application of BoNT, but the doses required are known to be much higher than used for injection, and the effects are limited to the more superficial facial muscles; not the stronger and deeper muscles of the glabella complex.

II Pain

The volume of solution injected is directly related to the volume used for reconstitution of the product from the powder form, which is provided for each commercial product. Each manufacturer has specific recommendations for the volume of reconstitution of their product, based specifically upon the format used in the registration clinical trials. These can be different for each product. Many clinicians, however, have preferred volumes of reconstitution based on volumes of injection that they are used to. Therefore there is considerable variability between the injection techniques used – with regard to volume from the official recommendations. Trials have been carried out on different volumes of injection, with the same units being administered in each treatment, but the results have demonstrated either no difference in onset or duration of the effects obtained[52] or the opposite, contrary result.[53] Volume of injection has been reported as unlikely to have an effect over the standard range of product reconstitution volumes recommended.[54]

In one study, the volume of injection was found to be related to pain on injection, with a higher volume giving more pain. Unfortunately, there were insufficient patients in the study to conclude significance, but nevertheless a guide was established.[55]

Since the initial use of BoNT-A for aesthetic corrections, clinicians have often chosen to use a diluent containing a preservative (benzyl alcohol) instead of the diluent recommended by the manufacturers: unpreserved saline. To date, nothing has been published directly from the manufacturers when using preserved saline for their products but clinician-led studies are available,[56-58] and these indicate a reduction in pain on injection when using preserved saline.

There are two possible reasons for this. Firstly, normal (pharmacopoeial) 0.9% saline is incorrectly considered to be a physiological solution.[59] Therefore any change from this state, especially if the pH is nearer to neutrality, could improve the pain perception upon injection. But secondly, benzyl alcohol is also recognized to have a minor anesthetic effect when injected. The net effect is likely to be a combination of these and other factors.

MAIN BoNT-A PRODUCTS

Product™	Production Strain	Process	U/vial [Product specific]	Excipients (in vial)	
Dysport®	Hall	Fermentation Dialysis Chromatography	500 sU	HSA 125 ug	Lactose 2.5mg
Azzalure®	Hall	Fermentation Dialysis Chromatography	125 sU	HSA 125 ug	Lactose 2.5mg
Botox®	Allergan "hyper"	Fermentation Precipitation "Crystallisation"	100 B	HSA 500 ug	NaCl 0.9mg
Vistabel® & Vistabex®	Allergan "hyper"	Fermentation Precipitation "Crystallisation"	50 V	HSA 500 ug	NaCl 0.9mg
Xeomin®	Hall	[Unpublished]	100 X	HSA 1mg	Sucrose 5mg
Bocouture®	Hall	[Unpublished]	50 B	HSA 1mg	Sucrose 5mg

BoNT-A PRODUCTS FROM ASIA

Product™	Production Strain	Process	U/vial [Product specific]	Excipients (in vial)
BTXA	Hall	Crystallisation, dialysis	50/100 u	5 mg Gelatin 25 mg dextran 25 mg Sucrose
Meditoxin/Neuronox/Siax	Hall	unknown	50/100/200 u	0.5 mg HSA 0.9 mg NaCi
Botulax/Zentox/Regenox	CBFC26	Protamine sulphate DEAE sepharose chromatography	50/100/200 u	0.5 mg HSA 0.9 mg NaCi
Nabota	unknown	unknown	100 u	unkown

Figure 3