

Botulinum Toxin in Facial Rejuvenation

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Foreword, to the First Edition (2003) v

Appreciation vii

Introduction ix

- 1 Historical Background 1
- 2 Botulinum Toxin: Mode of Action and Serotypes 2
- 3 Clinical Indications and Use 8
- 4 Patient Preparation and Injection Skills 14
- 5 Patient Selection: The Art of Understanding Neuromodulation and Symmetry 25
- 6 The Art of Patient Selection and Short- and Long-Term Management 33
- 7 Contraindications and Complications 44
- 8 Management of Crow's Feet 55
- 9 Management of Forehead Wrinkles 64
- 10 Treatment of the Perioral Region, the Neck and Scars 78
- 11 Other Solutions 87

Index 107

Historical Background

The *Clostridium* family of bacteria, common to most environments, produces spores that, on germination, release some of the deadliest toxins known to mankind. *Clostridium Perfringens* contaminates wounds and caused the infamous gas gangrene of World War 1; *Clostridium botulinum* produces botulinum toxin (BTX)—a powerful neurotoxin.

Clostridium botulinum was first identified in 1897, in Belgium, by Professor Emile van Ermengenen, who was investigating fatal cases of food poisoning following the consumption of macerated ham. It was named after the disease it causes, botulism, a lethal form of food poisoning originally associated with sausage meat (botulus is Latin for sausage). In the same year, an antiserum for botulism was made.

There are seven known serotypes of BTX (A, B, C, D, E, F and G). Serotypes A, B and E cause the classic foodborne disease with a flaccid paralysis of motor and autonomic nerves. Type B was first discovered in 1910, and the isolation of type A began in the 1920s. During the Second World War, research continued into this potent neurotoxin as a possible agent ('agent X') for biological warfare. Most of this work was carried out at the chemical warfare laboratories of Fort Detrick, Maryland, and Porton Down in the United Kingdom. Porton Chemicals was bought by Ipsen Pharmaceuticals in 1989 and is the source of Dysport.

Dr Alan Scott, an ophthalmologist from the Smith-Kettlewell Eye Research Foundation, became interested in substances that caused transient muscular paralysis. He acquired BTX type A from Fort Detrick and performed the first clinical tests on humans in 1978. His results in the treatment of strabismus (an abnormal contraction of the extraocular eye muscles) were published in 1982 and led to the extensive use of BTX type A by ophthalmologists in the treatment of blepharospasm (an abnormal twitching and contraction of the muscles around the eye), hemifacial spasm and cervical dystonia.

By the late 1980s, the author, an oculo-facial and ophthalmic surgeon in Ireland, as well as colleagues in Canada and the United Kingdom, were each exploring different doses and methods for using BTX. The author worked on patients with facial asymmetry, especially Bell palsy, to calculate the doses required to 'balance' the innervation of the whole face.

Thereafter the story is well known. With good medical training and the correct selection of patients, BTX can be given easily, safely and repeatedly. There have been relatively few reported side effects despite ever-increasing demand in increasingly large doses, in particular for large muscle dystonia and spasm.

Thanks to Dr Scott, many lives have been enhanced and many more made bearable by this deadliest of poisons and astonishingly precise drug.

Botulinum Toxin: Mode of Action and Serotypes

Dr. Kate Coleman, BSc PhD FRCS FRCOphth

A working knowledge of the pharmacology of botulinum toxin (BTX) is essential to understand the contraindications and complications of treatment with it.

Botulinum neurotoxins are metalloprotease polypeptides, comprising a protein molecule (150 Kd), which can be cleaved enzymatically into a heavy (H) (100 Kd) and a light (L) (50 Kd) chain (Fig. 2.1). These chains are normally held together by a disulphide bond, which is heat labile. Disruption of this bond inactivates the neurotoxin. This explains why BTX must be stored at the correct temperature and reconstituted carefully, preserving the integrity of the two-chained molecule. Prior to reconstitution, characteristics of Incobotulinum toxin A (Xeomin) reflect the lack of a complexing protein with the neurotoxin, allowing long term stability and reduced immunogenicity.

BTX induces paralysis by blocking the release of acetylcholine at the skeletal alpha motor neurone neuromuscular junction, thereby inhibiting the transmission of nerve impulses across the synaptic junction to the motor end plate.

USER TIP

Always consider possible central, as well as obvious peripheral, changes to the injected muscle following treatment (neuromodulation).

Muscular Contraction: Normal Cholinergic Transmission (Fig. 2.2)

Voluntary muscle contraction is a response to stimulation by action potentials passing along a nerve to the muscle. Once these action potentials reach a synapse at the neuromuscular junction, they stimulate an influx of calcium into the cytoplasm of the nerve ending. This increase in

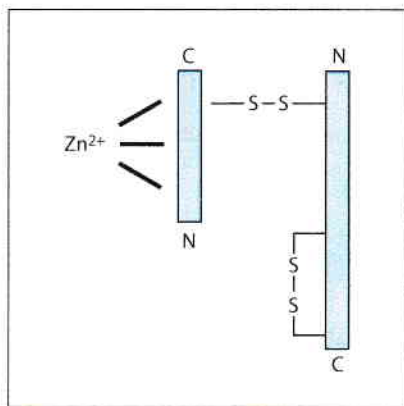


Fig. 2.1 Diagram of botulinum toxin molecule showing heavy and light chains. (From Aoki R, The development of Botox—its history and pharmacology, *Pain Digest*, 1998;8:337–341. With permission from Springer-Verlag.)

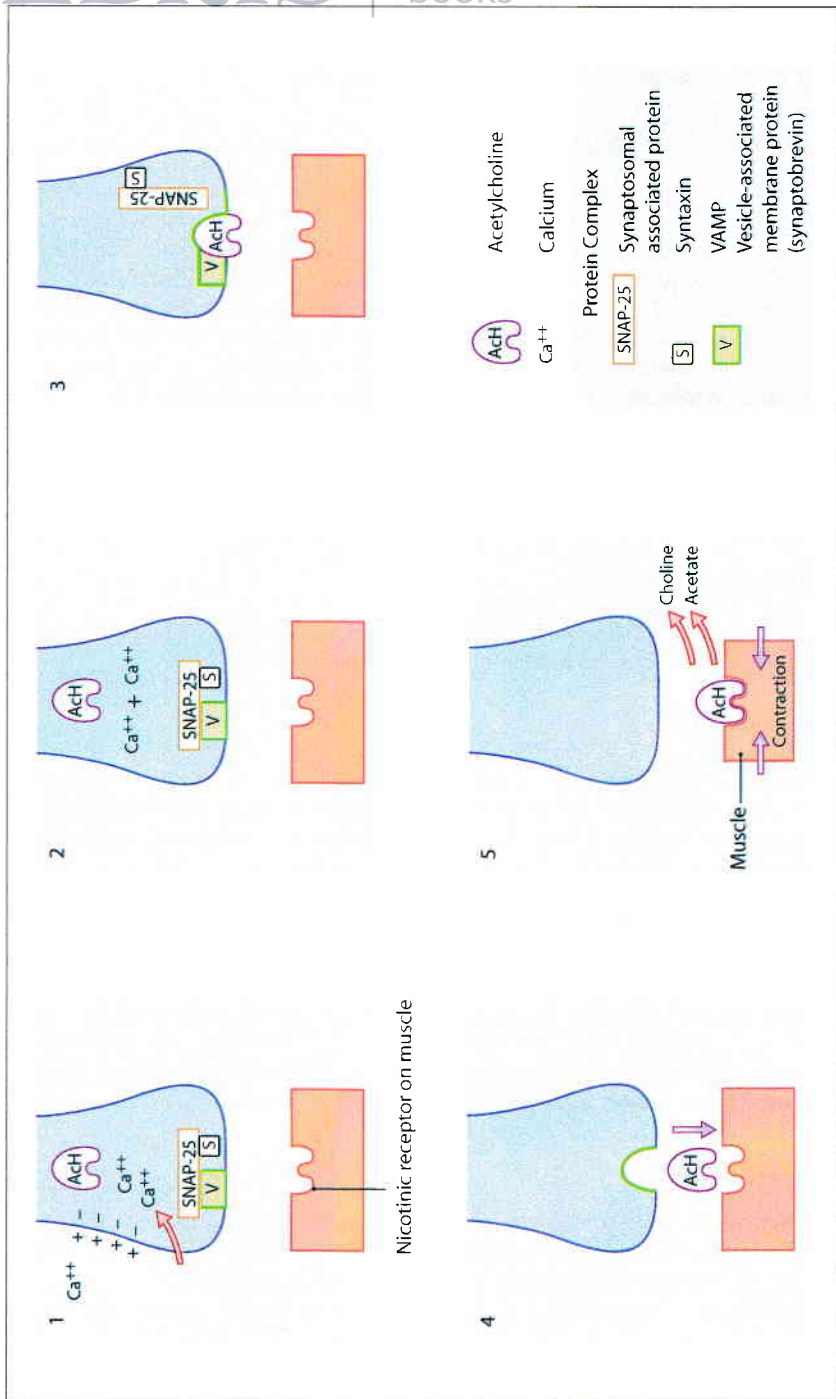


Fig. 2.2 Normal cholinergic transmission: (1) A signal passes down the cholinergic nerve, causing calcium to pass through the depolarising presynaptic membrane. (2) The calcium then triggers the binding of the acetylcholine molecule to a protein membrane complex. (3) The protein membrane complex allows the acetylcholine to pass into the synaptic cleft. (4) The acetylcholine travels across the synapse to a nicotinic receptor on the muscle, where it stimulates contraction before disintegrating into acetate and choline (5). VAMP, Vesicle-associated membrane protein.

calcium concentration allows acetylcholine to fuse with the membrane, using a protein complex, before crossing the synapse and fusing with nicotinic receptors on the muscle fibre. The protein complex consists of three types of protein: vesicle-associated membrane protein (VAMP; synaptobrevin), synaptosomal-associated protein (SNAP)-25 and syntaxin.

Mode of Action of Botulinum Toxin (Fig. 2.3)

Acetylcholine depends on a protein complex for its release from the nerve ending into the synapse. BTX, using a specific enzyme in the L-chain, interacts with one component of the protein complex of the nerve terminal, thereby inhibiting the discharge of the acetylcholine. The protein attacked is specific to the different serotypes of BTX; for example BTX-A blocks SNAP-25, whereas BTX-B blocks VAMP. BTX-B acts on a different cytoplasmic protein complex. The secretion of acetylcholine is disrupted when the L-chain of the BTX-B molecule cleaves a protein called synaptobrevin, also known as VAMP. Clinical trials have shown BTX-B to be effective for the treatment of patients with cervical dystonia, including those resistant to BTX-A.

Both the H- and L-chains of the BTX molecule are needed to block the release of acetylcholine. The H-chain attaches the BTX to the nerve membrane, allowing the L-chain to be transported to its site of action—the protein complex. The L-chain enzyme then cleaves the protein specific to the particular neurotoxin. Neuromuscular transmission ceases, and the target muscle atrophies reversibly.

AUTONOMIC ACTION

BTX also blocks autonomic cholinergic receptors. The duration of action is longer than for skeletal nerve endings, and effects can last for up to 12 months.

CENTRAL ACTION

BTX affects the gamma motor neurone, reducing muscle spindle afferent input to the central nervous system, and at high doses has been shown to reach the brain. Functional magnetic resonance imaging has shown that glabellar injections of BTX have resulted in functional uncoupling of brain stem centres with the amygdala. Other studies have confirmed reduction in the size of areas of basal ganglia in response to high-dose injections for spasticity. These central effects help to explain how BTX can ameliorate pain and chronic migraine, as well as supporting some studies suggesting improvement of depression. Studies have demonstrated retrograde and anterograde axonal transport along the branches of nociceptive neurones following peripheral nerve blockade. Pain relief has been shown to start prior to paralysis, outlasting the duration of the paralysis, supporting a noncholinergic mechanism. The antinociceptive effect is mediated by blockade of neuropeptides and inflammatory mediator release. There is evidence of inhibition of plasma membrane exposure of pain sensors at the peripheral level.

MUSCLE RECOVERY

Cleavage of the protein complex is irreversible, but the changes following BTX include a proliferation of axonal nerve buds to the target muscle and the regeneration of muscle end plates. New nerves 'bud' out across the motor endplates, albeit with irregularly spread cholinergic receptors.

Muscle function takes between 24 hours and 5 days to cease; in contrast, recovery takes from 6 weeks with rimabotulinumtoxin B (Neurobloc) and an average of 14 weeks with onabotulinumtoxin A (Botox), Incobotulinumtoxin A (Xeomin) and abobotulinumtoxin B (Dysport). In the author's experience, duration of effect is dose and location dependent. Some muscles, the frontalis in particular, remain paralysed in some patients for as long as 5 months, after only one

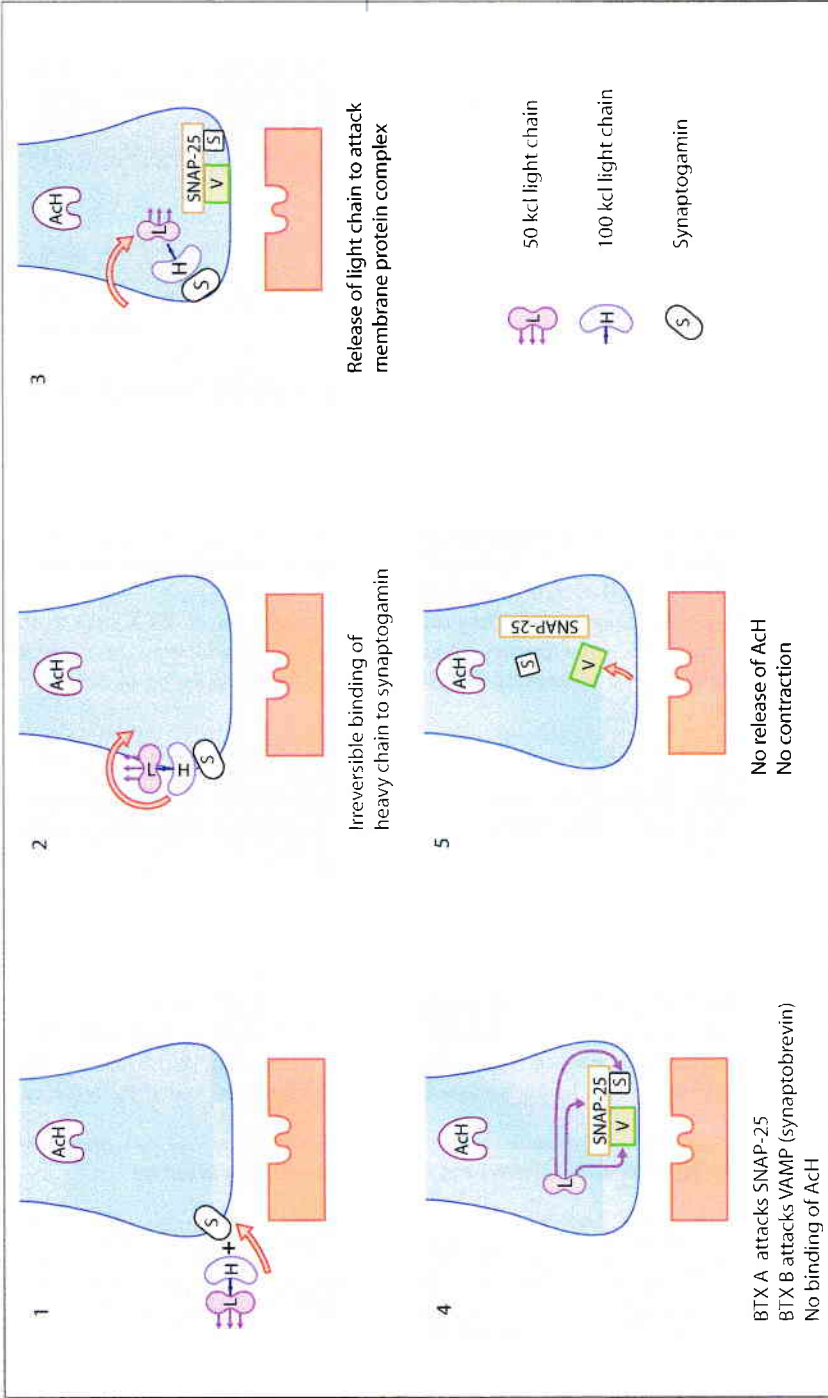


Fig. 2.3 Action of botulinum toxin (BTX) at the neuromuscular junction: (1) The heavy chain of the BTX binds to synaptogamin on the presynaptic membrane. (2) The heavy chain/synaptogamin complex enables the BTX light chain to enter the cell. (3) The light chain attacks the membrane complex and disables it so that NO ACETYLCHOLINE (ACh) BINDS. (4) BTX-A attacks the SNAP-25 protein of the membrane protein complex, and BTX-B attacks VAMP (synaptobrevin). (5) There is no release of ACh. SNAP, Synaptosomal-associated protein; VAMP, vesicle-associated membrane protein.

treatment. Prolonged paralysis results in muscle atrophy, which has been shown to last years in the forehead musculature. There is also a suggestion of long-term reduction in central voluntary control, 'breaking the frown habit', as evidenced by other basal ganglia imaging studies following BTX-A administration.

The orbicularis oculi muscle requires 3 to 6 months to recover its function, but, even then, the muscle returns to only 70% to 80% of its original bulk. This explains the fact that even an isolated treatment can help the 'crow's feet' of patients who are reluctant to engage in a series of treatments.

USER TIP

Choose your dose to modify the desired duration of action.

IMMUNOGENICITY

The development of antibodies to one serotype does not preclude an effective response to another one. Reports suggest an incidence of 2% rate of antibody formation with serotype A (onabotulinumtoxin A, BOTOX) as opposed to 20% to 40% with serotype B (rimabotulinum toxin B, Myobloc). Research suggests that the production of these antibodies is related to the protein load of the neurotoxin. This has led to the development of incobotulinumtoxin A, Xeomin/Bocouture, with its free 150-kD molecule and no haemagglutinin complexing. The original Onabotulinumtoxin A (Botox) contained 25mg Protein/100units. The more recent Botox preparations have a reduced protein load of only 5mg/100units in comparison.

Immunogenicity has been linked to the frequency of administration of BTX and to its concentration. Ideally, therefore, good therapy should be spaced at a minimum of 12-week intervals and should use the lowest concentration effective for the desired duration of action.

Serotypes

There are seven serotypes of BTX, five of which are effective at the human neuromuscular junction (BTX-A, B, E, F and G). The different serotypes act by cleaving different proteins at the presynaptic vesicle.

Four types of BTX are currently licensed and available commercially in Europe and the United States (Table 2.1); three are BTX serotype A: Botox/Botox Cosmetic (onabotulinumtoxin A), Dysport/Azzalure (abobotulinumtoxin A) and Xeomin/Bocouture (incobotulinumtoxin A). Neurobloc/Myobloc is BTX type B. Several types of BTX-A have been emerging in other countries, some also from the HALL strain of BTX (e.g. Meditox, South Korea).

Concern must be highlighted about unlicensed online availability of poorly regulated toxins from other countries, including 'copies' of Allergan BOTOX with no toxin in the bottles. The author had experience with a toxin being launched in the Middle East, which caused local

TABLE 2.1 ■ Botulinum Toxin Currently Licensed and Available Commercially in Europe and the United States

BTX-A	BTX-A	BTX-A	BTX-B
Abobotulinumtoxin A	Incobotulinumtoxin A	Onabotulinumtoxin A	Rimabotulinumtoxin B
Dysport	Xeomin	Botox	Neurobloc
Azzalure	Bocouture	Vistabel	Myobloc

BTX, Botulinum toxin.

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permanent muscle atrophy and scarring when injected. Other adverse reports include four cases of botulism in Florida due to toxic levels of BTX in unlicensed vials. The author currently uses only Dysport/Azzalure, Botox and Xeomin and will refer to these products and their differences in the rest of this manual.

USER TIP

Botulinum toxin acts by blocking release of acetylcholine from the nerve terminal.

USER TIP

Conditions and/or drugs affecting the nerve/muscle junction could also affect the botulinum toxin results.

Clinical Indications and Use

The cosmetic indications for botulinum toxin have not changed since the first edition of this book and are listed in Box 3.1, but the noncosmetic indications now represent 55% of all botulinum toxin use. In the author's oculofacial practice, botulinum toxin is an essential first-line treatment for hemifacial and blepharospasm, post-facial nerve palsy synkinesis, chronic migraine, frontal 'trigeminal' headaches and hyperhidrosis. Table 3.1 provides a list of other uses at the time of press.

Much has been published on the differences between the different products, and the reader is referred to an excellent 2018 review on the same by Dr. Richard Glogau.

USER TIP

DIFFUSION is influenced by concentration, by product and by the concentration of receptors on the muscle being injected. More receptors mean less diffusion per volume injected.

BOX 3.1 ■ Cosmetic Indications For Botulinum Toxin

Crow's feet (periorcular rhytids)	Pebbly chin
Vertical (glabellar) frown	Nasolabial folds
Horizontal (frontalis) frown	Jaw line (platysma)
Wrinkles on nose	Venus rings (horizontal neck rhytids)
Upper lip rhytids	Turkey neck (vertical platysma bands)
Vermilion border	Décolleté
Angle of mouth	Scar management

TABLE 3.1 ■ Noncosmetic Indications for Botulinum Toxin

Movement Disorders	Internal Organs	Other
Focal dystonias	Detrusor muscle	Hyperhidrosis
Essential tremor	Bladder spasm pain	Chronic migraine
Parkinsonism	Urinary retention	Tension headaches
Spasticity	Hyperactive/overactive	Trigeminal neuralgia
Post-stroke spasticity	Pelvic floor pain	Temporomandibular pain
Traumatic spasticity	Anal fissures	Spinal muscle pain
Multiple sclerosis	Benign prostate hyperplasia	Frey's syndrome
Eye movement disorders		Sialorrhoea

TABLE 3.2 Botulinum Toxin Serotype Type A

Onabotulinumtoxin A BOTOX/visabel 900-kDa complex Vacuum-dried powder 2–8° HSA 500 µg NaCl (900 µg/vial) BOTOX: 100-U or 200-U vial Vistabel: 50 U 5 ng/100 U	Abobotulinumtoxin A Dysport/Azzalure <900 kDa Freeze-dried powder 2–8° HSA 125 µg Lactose (2.5 mg/vial) Dysport: 300 U or 500 U Azzalure: 125 U 4.35 ng/500 U	Incobotulinumtoxin A Xeomin/Bocouture 150 kDa Freeze-dried powder Room temperature HSA 1000 µg Sucrose (4.7 mg/vial) Xeomin: 100 U or 200 U Bocouture: 50 U 0.44 ng/100 U
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Concentrations

Botulinum toxin is the most potent toxin known to mankind. It functions at very low concentrations and so can be assessed accurately only in terms of lethal dose unit per Swiss-Webster mouse. (Research is ongoing in to cell-based potency assay.) Different serotype A brands are shown in Table 3.2. One mouse unit (mu) is the median intraperitoneal dose required to kill 50% (LD₅₀) of a batch of 18- to 20-g female Swiss-Webster mice over 3 to 4 days.

The types of mice used by different producers differ and so the units discussed are NOT interchangeable. One vial of onabotulinumtoxin A (BOTOX, Fig. 3.1) contains 100 mu, while one vial of abobotulinumtoxin A (Dysport, Fig. 3.2) contains 500 ‘Speywood’ mu. One vial of Xeomin (Fig. 3.3) contains 100 mu, similar to the BOTOX units assay. This variability of assay, coupled with the absence of a definitive human assay, means that the doses used have to be based


Fig. 3.1 Bottle of BOTOX.

Fig. 3.2 Bottle of Dysport.

Fig. 3.3 Bottle of Xeomin.