Botulinum Toxin for Axillary and Palmar Hyperhidrosis

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Mônica Aribi, Gabriel Aribi,
and Thalita Domingues Mendes

The History of Botulinum Toxin: From Poison to Medicine

Botulinum toxin (BTX) type A (BTX-A) is a neurotoxin derived from *Clostridium botulinum*, an aerobic bacterium. BTX temporarily chemodenervates the eccrine glands involved in hyperhidrosis by binding to the receptor located on the presynaptic membrane, blocking the release of acetylcholine from skeletal and autonomic cholinergic nerve terminals.

The first recorded case of food poisoning caused by the neurotoxin-producing bacterium *C. botulinum* (botulism) is believed to have been in 1735. In 1817, Dr. Justinus Christian Kerner (1782–1862) published a very precise description of the symptoms of patients suffering from botulism after eating uncooked, smoked sausages or ham.

During World War II, much research was conducted in the USA at Fort Detrick, Maryland, specially by Edward J. Schantz who was searching for an antidote to counteract BTX, which was thought to be a potential biological weapon ready to be used by several other countries. In 1949, Burgen showed that the block of acetylcholine release by BTX occurred in the presynaptic nerve endings and not, as previously believed, by postsynaptic blockage of receptors such as atropine. In the 1960s, Alan Scott, an ophthalmologist, was searching for a non-surgical alternative for the treatment of strabismus. His idea to weaken the extraocular muscles with BTX brought him in contact with Ed Schantz. After several trials on monkeys, BTX-A was approved in 1989 by the US Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm, and hemifacial spasm. Other fields of medicine

M. Aribi (✉) · G. Aribi · T. D. Mendes
Department of Dermatology, Ipiranga Hospital, São Paulo, SP, Brazil
e-mail: recepcao@monicaaribi.com.br

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quickly became interested and BTX-A was used for a wide variety of indications, in particular for the treatment of hyperkinetic muscles. Bushara was the first to suggest a possible indication for BTX-A in the treatment of hyperhidrosis. Since 2002, BTX-A has been approved for the treatment of axillary hyperhidrosis in many countries and, most recently, in 2004, Botox® was approved in the USA by the FDA for axillary hyperhidrosis.

Commercially Available Botulinum Toxins

The seven serotypes of BTX that are produced by *C. botulinum* (A, B, C1, D, E, F, and G) affect the neural function, and there are many differences between each of them, such as size of the toxin complex, mechanism of action, formulation, and process of manufacture.

The first BTX available for clinical use was the BTX-A onabotulinumtoxin A, produced in the USA by Allergan Inc. under the name of BOTOX®/BOTOX_ Cosmetic®. In Great Britain, Ipsen Limited manufactured another type of BTX-A, abobotulinumtoxin A, commercially called Dysport®. Dysport® has also been distributed by Medicis in the USA, Canada, and Japan under the name of Reloxin®.

Other preparations of BTX-A available in the world are Linurase® (Prollenium Medical Technologies Inc., Canada); the Chinese BTX-A (CBTX-A), commercially named Prosigne®/Lantox®/Redux® (Lanzhou Biological Products Institute, China); the BTX-A named Neuronox®/Meditoxin®/Botulift® (Medy-Tox Inc., South Korea), and the incobotulinumtoxin A known as Xeomin®/Bocouture® (Merz Pharmaceuticals, Germany).

The only other commercially available serotype is the BTX type B (BTX-B) manufactured by Solstice Neuroscience Inc., known as Myobloc® or Neuroblock® which has FDA approval to treat cervical dystonia. This preparation is also being used off-label to treat facial wrinkles (Table 15.1).

Patient Management and Considerations

Before treating patients with BTX a detailed patient history should be obtained, focusing particularly on clues regarding the presence of secondary hyperhidrosis, since the underlying primary disease must be addressed first. As with every other treatment, the potential adverse effects of the therapy, contraindications, and the alternative treatments should be explained to the patient. It is also recommended that the patient understands the mechanism of action of BTX, in particular the need for re-injection after 6–9 months. Patients should know not to be treated during pregnancy and lactation.

Table 15.1 Main commercial presentations of botulinum toxin A

	Onabotulinum-toxin A	Abobotulinum-toxin A	CBTX-A	BTX-A	Incobotu-linumtoxin A
Lab	Allergan, Inc.	Ipsen Inc./ Medicis Inc.	Lanzhou	Medy-Tox Inc.	Merz Pharmaceuti-cals
Commercial names	Botox® Botox cosmetic® Vistabel® Vistabex®	Dysport® Reloxin® Azzalure®	Prosigne® Lantox® Redux®	Neuronox® Meditoxin® Botulift®	Xeomin® Bocouture®
Type—size	Type A—900 kDa	Type A—400–500 kDa	Type A—900 kDa	Type A—940 kDa	Type A—150 kDa
Mechanism	SNAP 25/SV2	SNAP 25/SV2	SNAP 25	SNAP 25	SNAP 25
Storage	2–8 °C	2–8 °C	2–8 °C	2–8 °C	Before diluting 25 °C After 2–8 °C

BoNT-A botulinum toxin serotype A, *CBTX-A* Chinese botulinum toxin A

Many practitioners have the patient sign a written consent form that becomes part of the patient's permanent record. Good follow-up procedures and prompt response to any complaints after treatment are important. The potential risks in treating patients for focal hyperhidrosis with BTX are comparatively small. However, clearly the treating physician must know the pharmacologic effect of the drug and the anatomic sites tov inject. It is necessary to participate in one or two training workshops to learn the injection technique prior to initiating treatment. Every practitioner must know in advance how to manage patients with unsatisfactory results. Successful treatments are predicated upon choosing the right patient for treatment, injecting them with the proper technique, and insisting on adequate follow-up visits in order to administer appropriate follow-up care.

Contraindications

BTX injections are not offered to patients who suffer from hyperhidrosis secondary to an underlying disease, who have undergone previous surgical debulking of sweat glands, or who have severe blood-clotting disorders.

Patients who have a concurrent infection at the injection site or systemic infection are asked to return the office after the infection has cleared. Treatment of patients who have an existing medical condition that may interfere with neuromuscular function, such as myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis, should be avoided. Female patients who are pregnant or breastfeeding are also contraindicated.

Neutralizing Antibodies in the Treatment of Hyperhidrosis with Botulinum Toxin Type A (BTX-A)

BTX neurotoxins are bacterially derived, exogenous proteins that have the potential to elicit immune responses and antibody formation in humans. Neutralizing antibodies (NAbs) directed against the core neurotoxin can interfere with pharmacological activity, potentially leading to loss of clinical efficacy. Historically, the use of high doses of BTX-A at frequent injection intervals for the treatment of cervical dystonia was associated with the formation of NAbs in 4–10% of patients. However, studies across five different disorders show that NAb conversion was uncommon, occurring in only 11 of 240 subjects (0.5%) treated with BTX-A treatments.

The frequency and duration of treatment with BTX-A may also influence the rate of nAb formation. It is therefore good practice to administer doses that are sufficient to provide meaningful duration of clinical effect, but which are low enough to minimize the risk of seroconversion.

The present results suggest that NAbs are likely the cause of clinical non-responsiveness in only a small minority of patients.

Overall, the studies show strong evidence that BTX-A is associated with a low rate of NAb formation across multiple indications and suggests that other factors in addition to NAb serum conversion should be considered when subjects develop clinical non-responsiveness.

Technique

Minor Starch Test

The first step is to determine the exact area of the hyperhidrosis. This is most commonly achieved using the Minor Starch Test. First the hyperhidrotic area is completely dried and covered with an iodine solution, Lugol or Betadine® solution (Fig. 15.1), and it is then sprinkled with powdered starch (e.g., cornflower starch)

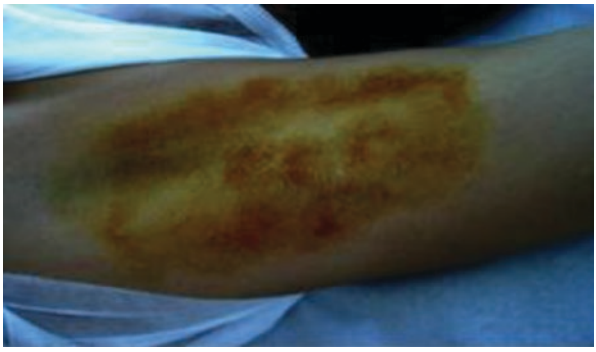

Fig. 15.1 Lugol solution applied to the hyperidrotic region

(Fig. 15.2). It is important that as little powder as possible is used to achieve a good colorimetric response. If too much powder is used, the powder will absorb the moisture of the sweat and the intensity of the patient's sweating may not be assessed correctly. After removing the excess purple color from the center of the outline, each injection site can be marked with gentian violet.

A semi-quantitative measurement of focal hyperhidrosis can be achieved using the Minor Starch Test, demonstrating the full extent of sweating in the affected area and, through the intensity of the purple coloration, the severity of sweating (Fig. 15.3).

Therefore, by performing a Minor Starch Test before each treatment, the physician can determine how many injection sites and how much BTX-A is needed prior to commencing therapy. It is important to take pictures of the result of the test prior to the treatment and during the follow-up visit, 15 days after the treatment, to assure the efficacy of the procedure.

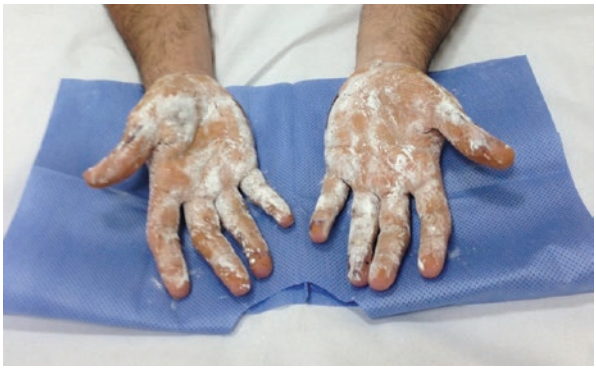

Fig. 15.2 Powder starch sprinkled to the same region

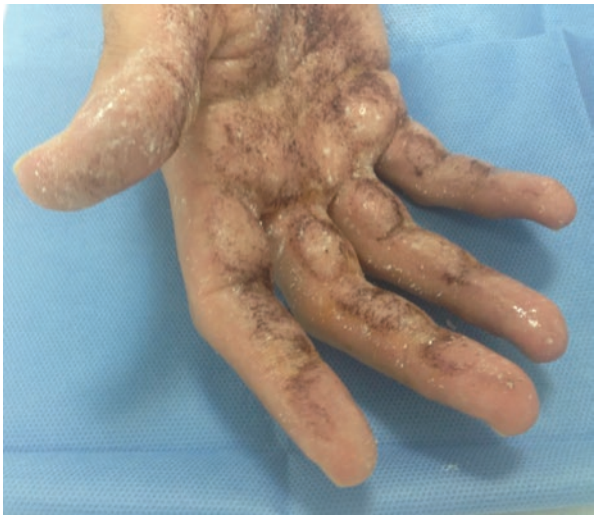

Fig. 15.3 Estimation of sweating areas allows to target the injection points

Therapy, Dilution, and Injection Technique

The volume of the dilution of the BTX-A depends on the option of the applicator. Once the vial of BTX-A is reconstituted without a preservative, it should be used in full within 4 h, due to the possibility the solution may not remain sterile for an extended period of time.

This issue is questioned by the studies, and we have learned that there are no adverse events or significant loss of potency resulting from the storage of reconstituted BTX-A for a few days and even a few weeks. After the dilution, the solution must be stored in a refrigerator (2–8 °C).

Some studies show that the volume of diluent used to reconstitute the product could increase the diffusion capacity of BTX-A [1], and thus some doctors prefer to increase this volume in order to have better results. Therefore, this author prefers to reconstitute a 100 U vial of onabotulinumtoxin A in 4.0 mL of sterile saline.

The injection of BTX-A should be with a 30-gauge needle or insulin syringe (Fig. 15.4). A needle is inserted at a 45 ° angle, approximately 2 mm into the dermis. For beginners, a very useful tip is to cut the lid of the syringe to be sure that the application is at the right depth level (2–2.5 mm) (Fig. 15.5).

The number of injection sites, and consequently the total dose of injected BTX-A, should no longer be defined as a total recommended dose for a given anatomic site, but instead by the number of units used per injection site. The minimum dose for each injection is from 2.0 to 2.5 U, but this also depends on the size of the colorimetric response exhibited by the Minor Starch Test. Since the diffusion capacity of BTX-A is about 1.0–1.5 cm in diameter, the injected points should be this distance apart (Fig. 15.6).

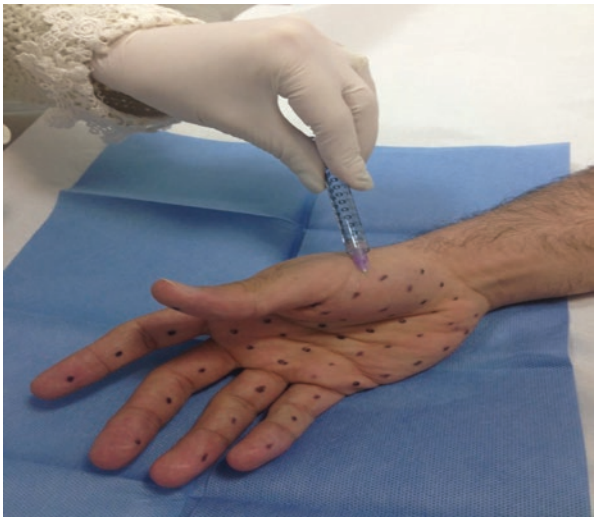

Fig. 15.4 Injection of BTX-A at the selected points

Fig. 15.5 The tip of cutting the lid of the syringe to avoid deeper injections

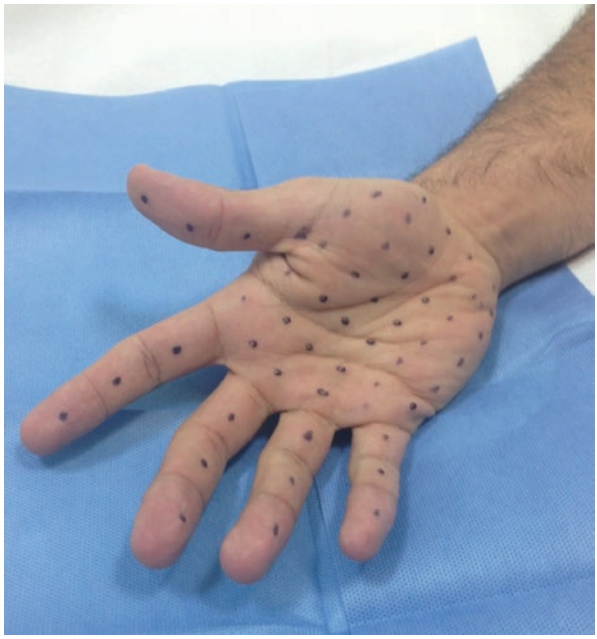

Fig. 15.6 Injection point distant 1.5 cm one to another

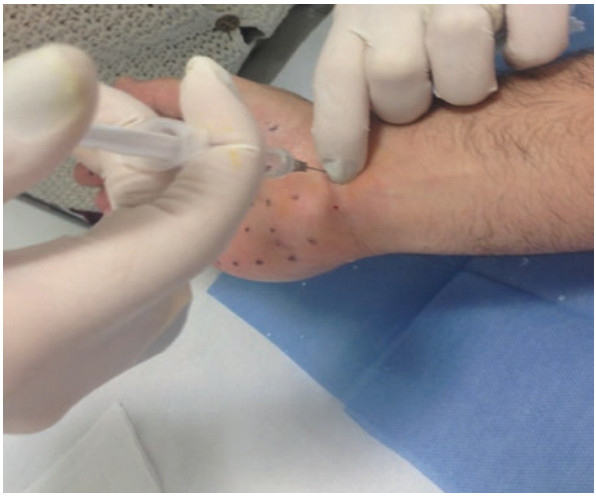

Fig. 15.7 Nerve block anesthesia for radial nerve

Anesthesia

Many trials of regional anesthesia have been reported, with differing results. For axillary hyperhidrosis the treatment can be performed using lidocaine cream or EMLA® 30 min before the treatment.

However, for treatment of the palm or in very sensitive patients the nerve block is the best choice, although this is commonly poorly accepted by patients. The nerve block requires careful and expert training and can be painful. The risk of nerve injury and severe adverse effects (anaphylactic shock, cardiac problems) also should not be underestimated. The different injection points of a nerve block of the hand can be found on the site of the three tendons (Fig. 15.7): for an ulnar nerve block the site of injection is over the *flexor carpi ulnaris*. For a median nerve block the site is on the tendon of *flexor carpi radialis*, and for the radial nerve the injection site is over the tendon of *extensor carpi radialis* and medial of the radial artery.

The needle should be inserted 0.5–1 cm perpendicular to the skin until firm resistance is felt and the deep fascia is pierced. It should then be retracted about 2 mm before 2 mL of lidocaine 2.0% without vasoconstrictor is injected.

Full anesthesia is achieved after 15–30 min in the palm and back of the hand (Figs. 15.8 and 15.9).

Finally, another type of anesthesia is cryotherapy used on the sites of injections (15 s spray) (Fig. 15.10), combined or not with iontophoresis with 2% lidocaine for 15 min per side. The collateral effect of this type of anesthesia is the formation of blisters in the day after.

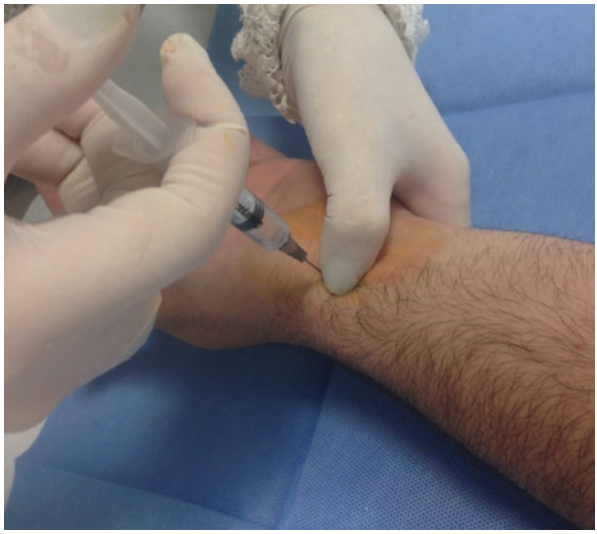

Fig. 15.8 Nerve block anesthesia for medial nerve

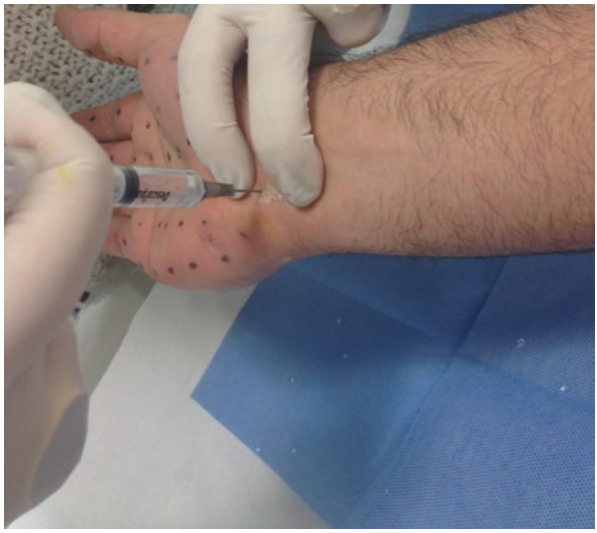

Fig. 15.9 Nerve block anesthesia for ulnar nerve

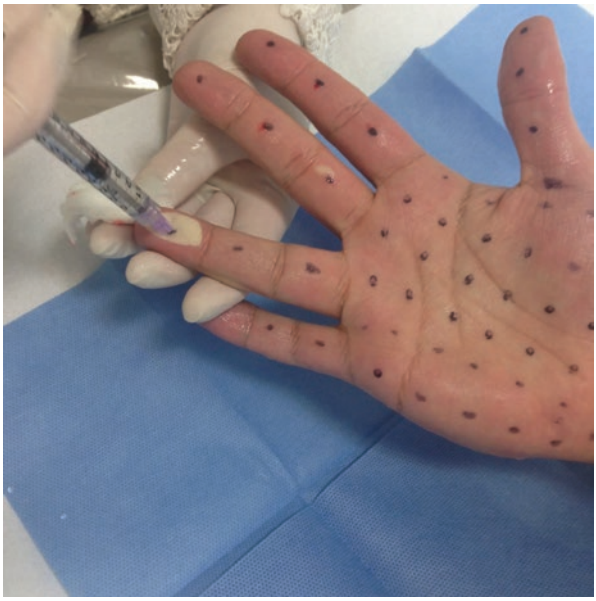

Fig. 15.10 Cryotherapy anesthesia just before BTX- A application

Advantages of BTX-A as Hyperhidrosis Treatment

Updated therapeutic algorithms are proposed for each commonly affected anatomic site, with practical procedural guidelines. For axillary hyperhidrosis, BTX injections are recommended as second-line treatment, oral medications as third-line treatment, local surgery as fourth-line treatment, and endoscopic thoracic sympathectomy as fifth-line treatment. For axillary and palmoplantar hyperhidrosis, topical treatment is recommended as first-line treatment.

Treatments with topical agents such as antiperspirant, mainly aluminum Chloridrate, have shown low efficacy. The anticholinergics, such as oxybutynin, show good results in palm, sole, axillary, and facial hyperhidrosis. The most common adverse effect is dry mouth, but it remains well-controlled at a dose of 10 mg/day.

Surgical resection of the sweat glands could be less sensible due to its collateral effects of scars, fibrosis, and hyperhidrosis recurrence. Sympathectomy surgery has shown to have compensatory hyperhidrosis as a collateral effect. The micro-needling radiofrequency could result in fibrosis and scars. Iontophoresis is considered the third-line therapy for palmar-plantar hyperhidrosis; its efficacy is high, but so are the initial levels of cost and inconvenience related to it [2].

Treatment with BTX-A is safe and efficient, and it has been approved by the FDA and EMA (European Medicines Agency). It is easily administered and recommended as second-line therapy in axillary hyperhidrosis. The lasting results provide great patient satisfaction and avoid the risks of a surgery procedure. In addition, recent studies have shown that repeated applications could improve the efficacy and

the duration of the effect [3]. Patients reported the duration of symptom relief to be from 4 to 12 months, with a mean of 5.68 months [4]. We have observed some results in palmar hyperhidrosis to last from 6 to 10 months.

Conclusion

It is important that each case be evaluated individually, and the treatment must be the most convenient to the patient in all respects—social, economic, and physical.

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