8 Botulinum toxin type A treatment for Raynaud's phenomenon and other novel dermatologic therapeutic applications

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INTRODUCTION

This chapter will discuss the use of botulinum neurotoxin type A (BoNTA) in dermatology for the treatment of painful conditions including Raynaud's phenomenon, postherpetic neuralgia, headache, reflex sympathetic dystrophy (or complex regional pain syndrome), and a variety of other conditions. The use of BoNTA to improve upper thoracic posture and thus improve the appearance and presentation of female breasts will be discussed. An approach to the management of acute overdoses of BoNTA will also be described.

Since BoNTA was first reported to be useful for the reduction in the pain of spasmodic torticollis in 1985 (1), the number of references in Medline™ to "botulinum" and "pain" have been growing at an increasing rate, and by the end of 2009 there were over 1,130 references. The list of painful conditions reported to respond well to BoNTA is also growing, and now includes some dermatologic conditions, and other conditions like headache, which are treated by some dermatologists who have expertise in the use of BoNTA (2,3).

It is important to note that the BoNTA used by the authors in the management of these conditions was BOTOX®, and the doses described in this chapter refer to BOTOX®. Because the diffusion characteristics and dosing of other forms of BoNTA differ from BOTOX®, it is not possible to establish a simple ratio for the conversion of BOTOX® doses to other formulations of BoNTA, or to other botulinum neurotoxins serotypes, for example, BoNTB or BoNTE (chapter 1). To reduce the risk of confusion, the recently designated generic instead of the trade name of the BoNTA actually injected will be used throughout this chapter, which is onabotulinumtoxinA for Allergan's BOTOX®; abobotulinumtoxinA for Medicis' Dysport®; and incobotulinumtoxinA for Merz's Xeomin®. The term BoNTA will be used to refer to the general class and serotype of neurotoxin.

BoNTA TREATMENT IN RAYNAUD'S PHENOMENON

Raynaud's phenomenon is defined as an episodic digital asphyxia caused by vasospasm of the digital arteries triggered by cold exposure or stress. It is either idiopathic and known as Raynaud's disease, or secondary to diseases such as scleroderma, lupus erythematosus, rheumatoid arthritis, and occlusive arterial disease. Its symptoms include a progression from digital blanching and cyanosis to reactive hyperemia, to pain and dysesthesias, which if prolonged, can result in severe digital vascular compromise, ulceration, digital infarction, and may even necessitate amputation. The etiology of Raynaud's disease is complex, but both vasospasm and nociception appear to play a major role. The inhibitory effects of BoNTA on somatic and autonomic neurotransmission are well documented. BoNTA inhibits norepinephrine (NE)-mediated sympathetic vasoconstriction, thus improving perfusion of digits by opening up the vasculature and allowing for better oxygenation. It concurrently inhibits pain-mediating neuropeptides, namely substance P (SP), neuropeptide-Y (NPY), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and glutamate, thus interfering with nociception, both peripheral and central sensitization, and decreasing swelling and inflammation.

BoNTA is successfully used in Raynaud's phenomenon as a safer and easier alternative to surgical sympathectomy (4). It essentially produces a chemical sympathectomy that lasts for months and effectively improves hand temperature within 1 to 2 days as well as shortens warm-up time after exposure to cold (5), controls rest pain, shortens and reduces frequency and severity attacks (6) including stiffness, numbness, acute pain, color change, and swelling (7), prevents impending infarction of digits and successfully heals ischemic ulcerations caused by profound vasospasm in the majority of patients (1). These favorable changes of improved perfusion are quantified using visual analogue scale (VAS) and confirmed by digital surface temperature readings (1,2), imaging studies with laser Doppler interferometry (3), intravascular arteriography, or high-resolution digital magnetic resonance angiography (1). The adverse events reported are rare and include mild and temporary hand weakness. Amelioration of pain improves hand function despite occasional muscle weakness (1).

PHYSIOLOGICAL BASIS OF BoNTA FOR RAYNAUD'S PHENOMENON

Autonomic: Vasodilator and Vasoconstrictor

In addition to the widely recognized inhibitory effects on the release of acetylcholine (Ach) from neurons innervating striated muscle and sweat glands, BoNTA has been shown to produce a neuromodulating effect on autonomic nerves (8). Cutaneous vasoconstriction and vasodilation are regulated by modulation of sympathetic and parasympathetic neuronal inputs and the complex actions of released ACh, NE, peptides like NPY, and small molecules such as nitric oxide on vascular smooth muscle.

In an animal model of significantly constricted uterine arteries, BoNTA has been shown to reduce the amplitude of sympathetic NE-mediated vasoconstriction by 80% (9). Likewise, isometric contractions of venae cavae mediated by NE acting on alpha-adrenoceptors are substantially reduced by BoNTA administration (10). Concurrently, in parasympathetic neurons, BoNTA is found to significantly reduce the autocrine acetylcholine-mediated inhibition of vascular relaxation and also to reduce the slow component of neurogenic vasodilation mediated by the peptides VIP and CGRP (11). Thus, a differential effect of BoNTA on different classes of neurotransmitters is observed, whereby it may reduce neurotransmitter and neuromodulator release from vasoconstrictor and vasodilator neurons depending on various regulatory mechanisms.

Local BoNTA injection consistently shows an ability to improve perfusion of the injected tissue by both substantial opening of the vascular bed and an increase in aerobic metabolism. BoNTA inhibits the neurogenic contractions of tumor vessels by blocking NE, thus improving tumor perfusion and oxygenation and thus aiding in delivery of cancer therapy (11,12). In inflammatory muscle states due to decreased microcirculation, such as in lateral epicondylitis secondary to low intramuscular blood flow in extensor carpi radialis brevis, BoNTA injection allows for muscle relaxation, a shift toward aerobic metabolism and a decrease in lactate production, restoration in intramuscular blood flow, decreased pain, improved muscle strength, and function (13).

BoNTA Has Anti-Inflammatory and Antinociceptive Effects

BoNTA also acts on the nociceptive portion of the sensory system to reduce pain and neurogenic inflammation by attenuating the peripheral release of neuroactive compounds such as SP and glutamate from C-fibers, as well as reducing central sensitization (6). BoNTA does not directly decrease excitability of nociceptors, but acts by reducing inflammatory pain (14) and thus pathological pain (15).

Substance P

BoNTA inhibits substance P (SP), a peptide released both peripherally and centrally by nociceptive primary afferent C-fibers, thus producing the analgesic effect seen in treating primary headache disorders (16). It markedly inhibits SP secretion in dorsal root ganglia neurons (17) within hours and lasts for at least 2 weeks. Local inflammation sensitizes peripheral nociceptive neurons, and as the increase in peripheral pain input causes increased release of SP in the spinal cord, it induces central sensitization (6). BoNTA thus attenuates both the peripheral and central sensitization by its inhibition of SP.

CGRP

BoNTA inhibits the release of calcitonin gene-related peptide (CGRP), an inflammatory neuropeptide found on its own as well as colocalized with SP in sensory ganglia neurons, when pain stimulus is present, but not basally. It reduces bladder pain response by 62% through inhibition of CGRP release from afferent nerve terminals (18), and in trigeminal nerves (19), explaining the observed efficacy of BoNTA in migraine and cluster headache therapy. Curiously, CGRP released during inflammation causes vasodilation, thus BoNTA's analgesic effect in migraines may be secondary to vasoconstriction of the meningeal vasculature.

Glutamate

BoNTA dose-dependently inhibits inflammatory pain by decreasing glutamate release. Glutamate is a stimulant of local nociceptive neurons through activation of receptors on primary afferents (20). Peripheral glutamate release results in edema, pain, and inflammation (21), which is abolished by local BoNTA injection at doses below ones that would elicit muscle paralysis (15).

PRACTICAL TIPS

Assessment

Assessment of disability caused by Raynaud's phenomenon or disease should be performed prior to and after the BoNTA treatment at 1 week, 1 month, and then routine follow-up. This is done by asking patients to evaluate the level of their (a) pain and (b) hand function using the 10-point visual analogue scale (VAS) , as well as the dermatology quality of life scale. If digital ulcerations are present, a photographic record is useful.

Injection Parameters

There is no consensus of how many injection sites should be administered per affected hand, and whether the entire hand should be treated or just the most affected digits. The clinical decision will be based on the extent and severity of the patient's Raynaud's phenomenon/disease, with consideration given to the pharmacoeconomics of using BoNTA and also consideration of how best to avoid causing unwanted muscle weakness in the treated hand.

The authors consider that it is reasonable to administer up to 100 units of onabotulinumtoxinA per hand being treated, reconstituted in 3 to 6 cc of normal saline/100 U vial (1,4). This relatively high reconstitution volume is presently preferred as the increased volume may facilitate spread of the injected onabotulinumtoxinA from the injection point to the vessels we wish to relax. The trend is to inject the palm and all fingers at their base, with the exception of thumb unless it is specifically symptomatic (since thumb ischemia is uncommon in Raynaud's). Targeted anatomy includes the superficial palmar arch, common digital arteries, and proper digital arteries, with injections being just adjacent to the targeted vasculature (in order to avoid injury to vessels) and needle tip perpendicular to the palm and deep to the palmar fascia (Fig. 8.1) (1).

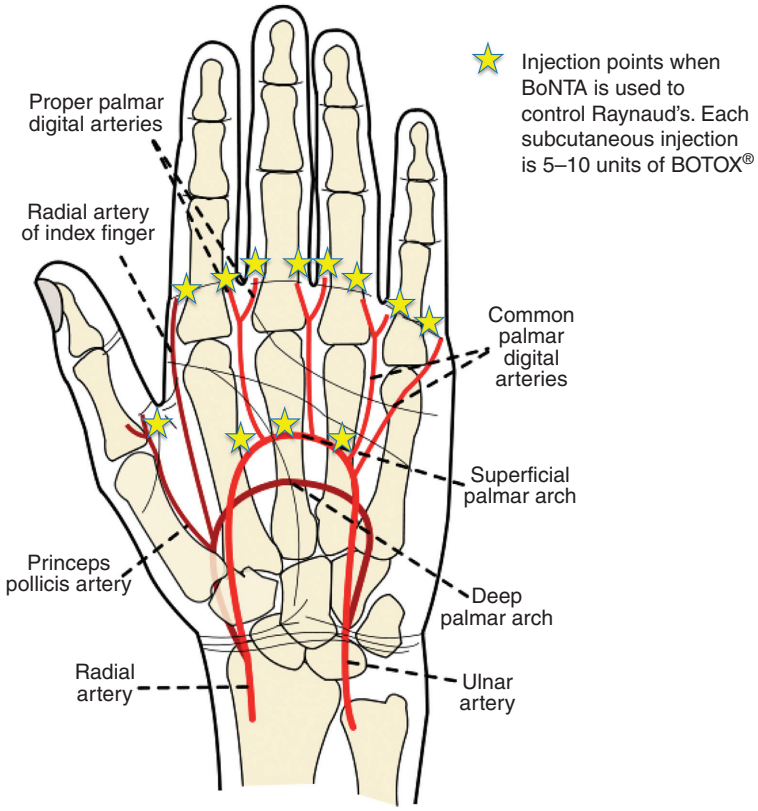


Figure 8.1 Typical injection points when BoNTA is administered for Raynaud's phenomenon. Each subcutaneous dose of onabotulinumtoxinA is 5 to 10 units.

A 30, 31, or 32G needle is used to infiltrate the soft tissues, with 10 to 40 injection sites spaced approximately 1 cm apart, of equally distributed volume of reconstituted 100 U of onabotulinumtoxinA (1,4). This is followed by a massage of the injected tissues to help distribute the medication throughout the region. Due to the discomfort associated with palmar injections, sufficient anesthesia (e.g., ice, vibration, or nerve blocks) is necessary to make the procedure tolerable (see chapter 11). To minimize weakness of the thumb, it is important to avoid injection into the thenar muscle group on the radial side of the proximal part of the palm (flexor, extensor and abductor pollicis longus, and extensor pollicis brevis).

OTHER NOVEL DERMATOLOGIC USES OF BoNTA

Targeting Hypersecretion

Based on the positive results seen with treatment of hyperhydrosis using onabotulinumtoxinA injections, onabotulinumtoxinA has been found to be helpful for other conditions made worse by increased sweating. These conditions include persistent facial flushing with or without localized sweating, gustatory sweating (Frey's syndrome), localized unilateral hyperhydrosis, Ross' syndrome (22), familial benign pemphigus (Hailey-Hailey disease), and dishydrotic eczema (23).

Frey's syndrome is facial hyperhidrosis in the preauricular region from gustatory stimulus, observed commonly after parotidectomy. On average, 40 units of onabotulinumtoxinA effectively alleviates the symptoms within days after injection and remission has been reported to persist for 15 to 18 months (24). Other glandular hypersecretory disorders, including sialorrhea, excessive lacrimation, chronic rhinitis (25,26) and parotid fistulas (27–29) also have been reported to respond to treatment with onabotulinumtoxinA.

Hailey-Hailey disease is an autosomal-dominant acantholytic blistering disease affecting the intertriginous skin and is exacerbated by heat, sweat, moisture, friction, and infection. Intertriginous injections of BoNTA have been reported to induce significant improvement within 2 weeks with onabotulinumtoxinA (30) and improvement can be maintained for many months with abobotulinumtoxinA (31). Dyshidrotic hand eczema (pompholyx) is a chronic, relapsing inflammatory vesiculobullous disease also aggravated by hyperhidrosis (32). The addition of onabotulinumtoxinA injection to topical steroid therapy has shown significant benefit in managing pompholyx eruptions and the associated symptoms of pruritus (33,34). Inverse psoriasis is exacerbated by maceration, secondary infection, and inflammatory pain; onabotulinumtoxinA injections to affected intertriginous regions also improve the symptoms and eruptions of inverse psoriasis (35).

Targeting Pain

OnabotulinumtoxinA's antinociceptive properties have been used in the treatment of multiple cutaneous piloleiomyomas, with effective rapid and sustained resolution of pain (36). It has also shown substantial benefit in the treatment of notalgia paresthetica (37).

BoNTA enters neurons by binding to the synaptic vesicle protein SV2 receptor (isoforms A, B, and C) (38). SV2 is transiently exposed when synaptic vesicles fuse with the presynaptic membrane to discharge neurotransmitter into the synaptic junction (Fig. 8.2). This is the physiological basis for the important clinical observation that generally the most effective and efficient way to administer BoNTA for painful conditions is to inject BoNTA in the points and areas of maximum discomfort indicated by the patient, because it is in these areas that there is maximum discharge of pain mediating neurotransmitter and thus maximal exposure of the SV2 protein, which mediates uptake of BoNTA. This method of administration of BoNTA is commonly referred to as the "follow the pain" approach. Clinical trials of onabotulinumtoxinA for painful conditions sometimes use a rigid protocol of doses and injection sites rather than the "follow the pain" approach, which customizes the treatment to the needs of each individual patient, and this difference may explain why some clinical trials (in particular for headache) do not obtain the degree of improvement which is commonly achieved in clinical practice (39–42).

BoNTA for Postherpetic Neuralgia

Perhaps the first to use onabotulinumtoxinA for the treatment of postherpetic neuralgia (PHN) were Dr. Arnold Klein (43) and, later, Drs. Mariusz Sapijaszko and Richard Glogau (personal communication) who used onabotulinumtoxinA to treat PHN on the trunk. Their informal oral reports, together with a consideration of the well-established role of SP in the pathogenesis of PHN, and considering reports that BoNTA blocked the release of SP from vesicles in nerve terminals, provided the rationale

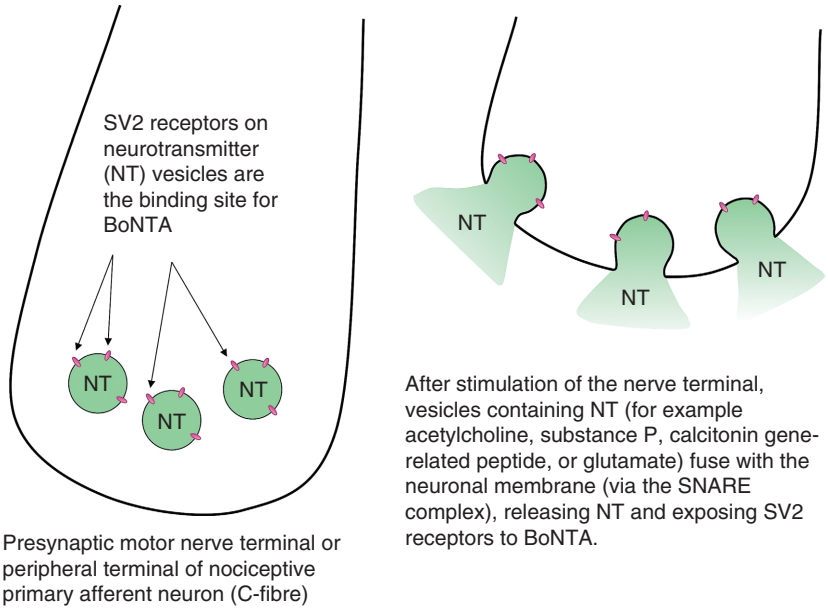


Figure 8.2 SV2 receptors for the binding domain (i.e., heavy chain) of BoNTA are exposed when the contents of vesicles of neurotransmitter are released at the presynaptic membrane.

for additional trials of treatment with BoNTA for severe, intractable PHN (44). One author (KCS) has found onabotulinumtoxinA to be a very reliable treatment for PHN on the face and scalp, but has had only treatment failures when attempting to use onabotulinumtoxinA to treat PHN on the trunk and extremities. The reason for this difference in responses is not known, and additional investigations are warranted.

It is important clinically, for communication with other physicians and with third party payers, and in terms of pharmacoeconomics to objectively quantify a patient's condition at baseline and in response to therapy. The four tools which are helpful include:

1. Likert pain scale and global assessment (Fig. 8.3).
2. Physician's global assessment (Fig. 8.4).
3. Number of doses of pain medication taken in the 7 days preceding evaluation, and the number of doses taken since the last visit.
4. Marking and photographing the boundaries of the area or areas of PHN before treatment and then marking and photographing the involved areas at every subsequent visit (Fig. 8.5).

Patients are advised to continue their usual pain medications, and only to reduce the dose of pain medication as they respond to their BoNTA treatment.

The patient identifies the area or areas of involvement. The boundaries of the area(s) of involvement are marked with washable pink fluorescent marker, photographed (Fig. 8.5), then injected with onabotulinumtoxinA intradermally or subdermally at doses ranging from 2.5 to 5 units per injection site, with the injections spaced 2 to 3 cm apart. The total dose of onabotulinumtoxinA is generally in the range of 1 to 2 units per cm or cm^2.

BoNTA is reconstituted using normal saline with benzyl alcohol preservative (which has local anesthetic properties and reduces injection discomfort). A reconstitution volume of 1 ml per 100 units of onabotulinumtoxinA is used by the author (KCS), but the reconstitution volume does not seem to influence efficacy—the only thing that matters is how many units of BoNTA are administered (45). Because there is commonly hyperalgesia in areas of PHN, it is best to use BD-II 0.3 ml insulin syringes with attached 31G needles (Becton Dickinson, Franklin Lakes, NJ). It is not usually necessary to pretreat patients with a topical anesthetic, but this could be used in cases where there is a likelihood of intolerable injection discomfort.

Patients should be informed that there will very likely be some unwanted relaxation of muscles in the treated area. Injecting BoNTA intradermally can minimize muscle weakness. Injections for the pain of PHN seem to be equally effective whether given intradermally, subdermally, or intramuscularly.

The maximum analgesic effect of BoNTA treatment for PHN often occurs at around 3 to 4 weeks. For this reason, patients are asked to return for reassessment and possibly additional treatment every 3 to 4 weeks until they are pain free.

While the occasional patient will respond in a dramatic manner to a single session of treatment with BoNTA, it is more typical for patients to improve in a stepwise manner. Patients generally need between one and four treatment sessions to become pain-free. Objective quantification of the area of involvement, medication intake, Likert pain score, and patient's and physician's global assessment will help both the patient and the physician to determine whether or not additional treatment is justified. The author (KCS) has only had success treating PHN on the face and scalp with BoNTA, and has not found BoNTA useful for the treatment of PHN on the trunk or extremities. The reasons for treatment failure on the trunk and extremities are not known, and further studies are warranted.

Usually, serial photographs of the involved area demonstrate progressive reduction of the surface area (Fig. 8.5). Patients find this encouraging. There is often a paradoxical increase in the patient's Likert pain score as the total area of involvement shrinks. The reason for this phenomenon is not well understood. It could be that the mildest areas of PHN resolve first, with the result that because of "averaging" by the patient, the pain score in the residual area of involvement

Last Name _____ First Name _____ Chart # _____ Date _____

Patient's rating scale:

Please circle the number which best describes the amount of pain you are having today in the involved area:
When you are not touching the area:

NO Pain 0 1 2 3 4 5 6 7 8 9 10 WORST possible pain

When the area is touched or rubbed:

NO Pain 0 1 2 3 4 5 6 7 8 9 10 WORST possible pain

Please circle the number which best describes your PAIN in the involved area is BETTER or WORSE compared with how it was at your last visit:

BETTER 5 4 3 2 1 0 1 2 3 4 5 WORSE

Please circle the number which best describes your OVERALL impression of how you are doing, compared with the previous visit:

BETTER 5 4 3 2 1 0 1 2 3 4 5 WORSE

Figure 8.3 Visual analog scale used to measure patients' perception of their pain and of their global well-being.

Last Name _____ First Name _____ Chart # _____ Date _____

Patient's rating scale:

Please circle the number which best describes the amount of pain the patient appears to be having today in the involved area:
When the area is not touched:

NO Pain 0 1 2 3 4 5 6 7 8 9 10 WORST possible pain

When the area is touched or rubbed:

NO Pain 0 1 2 3 4 5 6 7 8 9 10 WORST possible pain

Please circle the number which best describes whether the patient's pain in the involved area appears to be BETTER or WORSE compared with how it was at the patient's last visit:

BETTER 5 4 3 2 1 0 1 2 3 4 5 WORSE

Please circle the number which best describes your OVERALL impression of how this patient is doing, compared with the previous visit:

BETTER 5 4 3 2 1 0 1 2 3 4 5 WORSE

Figure 8.4 Visual analog scale used to measure the physician's assessment of the patient's pain and of the patient's global well-being.

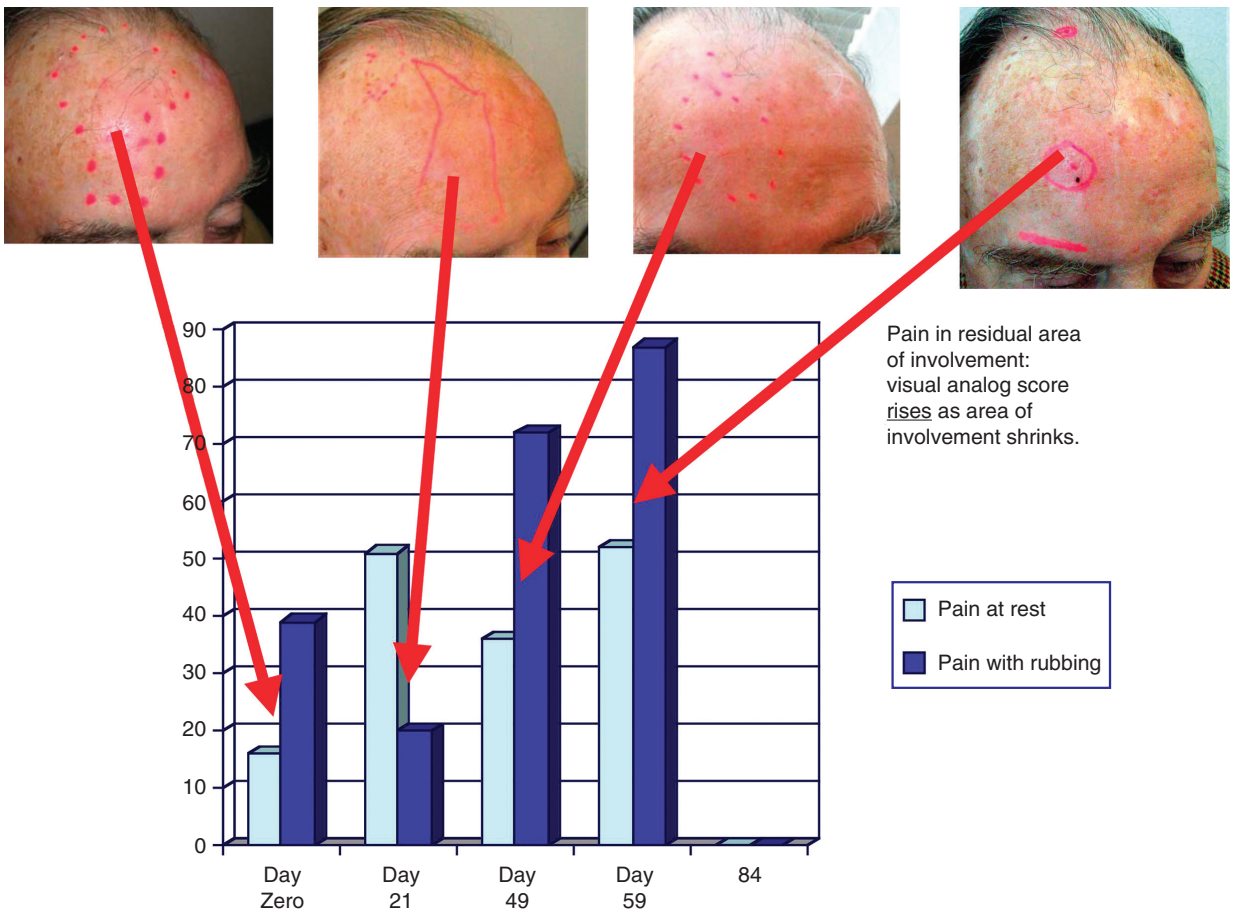


Figure 8.5 The area identified by the patient is marked and photographed, the patient completes a visual analog pain score (Fig. 8.3), and then the painful area is injected with onabotulinumtoxinA.

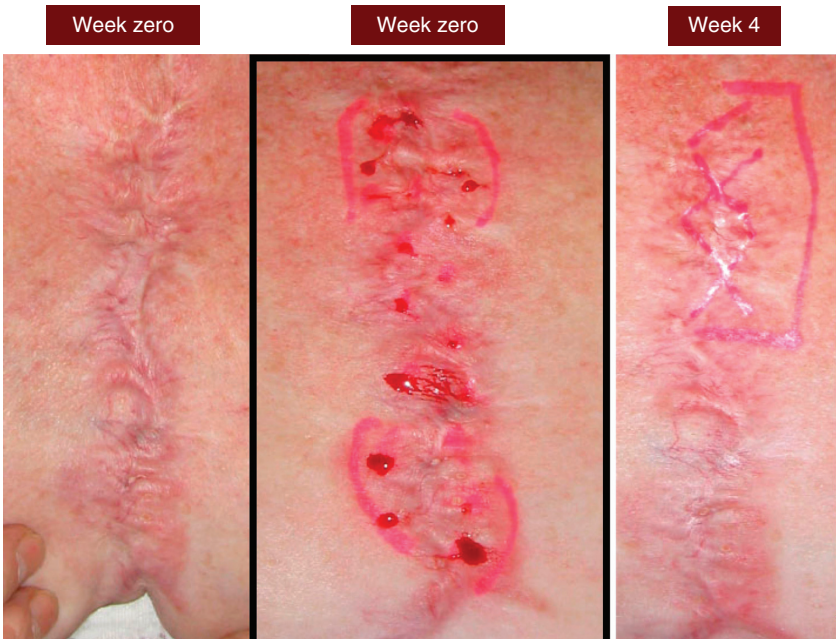


Figure 8.6 Keloid scar on the chest of a woman who had 8 years previously had a coronary artery bypass grafting procedure, and whose pain had not responded adequately for surgical resection of the keloid, or to injections of triamcinolone acetonide, or to the application of silicone gel.

would tend to rise. When the patient with PHN has been rendered pain-free by treatment with BoNTA, there is usually a long-term drug-free remission of pain.

BoNTA in the Management of Painful Scars

Immunohistochemistry has demonstrated substantial numbers of nerves staining for SP and CGRP in some scars (46). This observation, together with successful experience treating PHN, formed the rationale for offering a trial of treatment with injections of BoNTA to patients suffering from chronic intractable painful scars. Objective quantification of the patient's pain is of great importance in the management of painful scars. Tools that are useful for this purpose are essentially the same as those used in the assessment of patients who have PHN.

1. Likert pain scale and global assessment (Fig. 8.3).
2. Physician's global assessment (Fig. 8.4).
3. Marking the boundaries of the area or areas of pain prior to treatment and then marking and photographing the involved areas at every subsequent visit (Figs. 8.5 and 8.6).

Injections are usually performed using a 30G 1-inch needle, or a BD-II 0.3 ml insulin syringe with 31G needle, inserted into the scar. In the case of a thick scar (for example, a keloid on the central chest after thoracotomy (Fig. 8.6), the patient may offer advice about whether the pain is deep or superficial and the injection can be adjusted to take this into account. Application of ice for 30 to 60 seconds, or injection of lidocaine around and below the scar, are generally not necessary but could be used in a very sensitive patient to reduce the pain of injection. The author (KCS) has successfully used injections of onabotulinumtoxinA to treat pain associated with keloid scarring, hypertrophic scarring, and normal scarring.

The author (KCS) uses a reconstitution of 1 ml in 100 units of onabotulinumtoxinA. The amount of onabotulinumtoxinA administered in each treatment has ranged from 10 to 50 units per ml (cubic volume) of scar tissue.

As with the treatment of PHN, the antinociceptive effect of BoNTA for painful scars seems to reach a maximum at around 3 weeks, so it is advisable to have patients return for reassessment and retreatment every 3 to 4 weeks until the patient is pain-free. The required number of treatments has ranged from one to four. As with PHN, the visual analog or Likert pain score may rise in residual areas of involvement even as the patient globally improves (Fig. 8.7), and patients typically remain pain-free for a long time once they have been rendered pain-free by treatment with BoNTA. In one case, there have been partial relapses at 6 to 12-month intervals, and these have responded within 5 to 10 days to additional injections of BoNTA.

There has been no clinically significant improvement in the appearance (assessed by serial photography) of the scars injected by the author (KCS) with onabotulinumtoxinA, but one hypertrophic scar on the breast (Fig. 8.8) seemed much softer 6 months after two injections with onabotulinumtoxinA. Because SP and CGRP interact with some of the cytokines involved in collagen remodeling and collagen deposition (47–49), it is conceivable that treatment with BoNTA could affect the physical properties of some scars, perhaps with repeated treatments or after longer follow-up.

BoNTA in the Management of Reflex Sympathetic Dystrophy (Complex Regional Pain Syndrome)

Reflex sympathetic dystrophy syndrome (RSDS) is characterized by constant burning pain and hyperesthesia in an extremity. Swelling, sweating, vasomotor instability, and sometimes trophic changes often accompany pain. There is often a history of injury or other trauma. Muscle spasms, myoclonus, or focal dystonia may occur. Diffuse pain, loss of function, and autonomic dysfunction are three main criteria suggested for diagnosis. Successful use of BoNTA for this entity has been reported (50,51).

Over the past five years, the author (KCS) has treated a 41-year-old woman who had an 8-year history of severe, refractory RSDS rendering her right arm and leg useless since injuries in a motor vehicle accident. She also had posttraumatic headaches with muscle spasm pulling her head to the right. The headaches and muscle spasm were also treated with onabotulinumtoxinA. Initially injections were exceptionally painful and anxiety provoking. Anxiety was reduced in subsequent injection

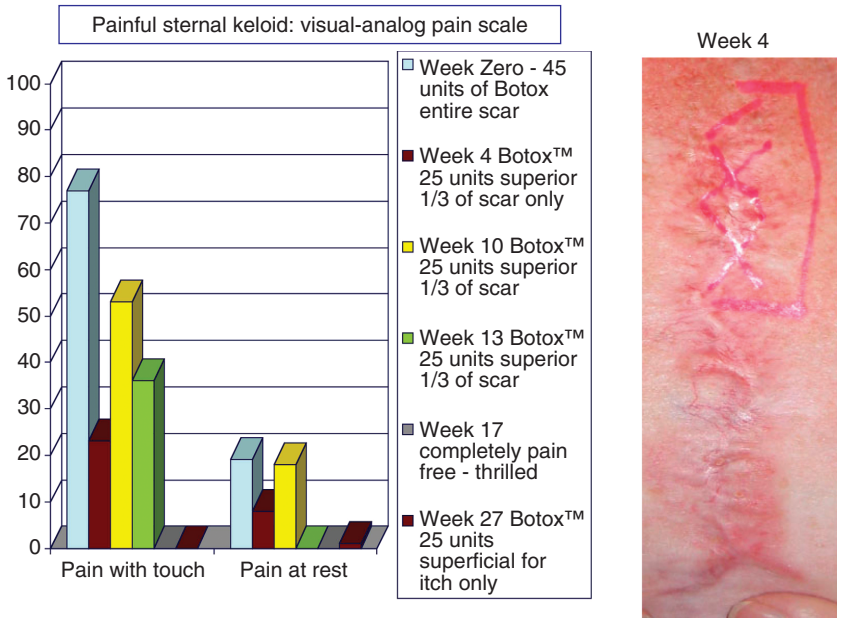


Figure 8.7 Chart illustrating gradual reduction in visual analog pain scores in response to injection of painful areas in the keloid scar with onabotulinumtoxinA.

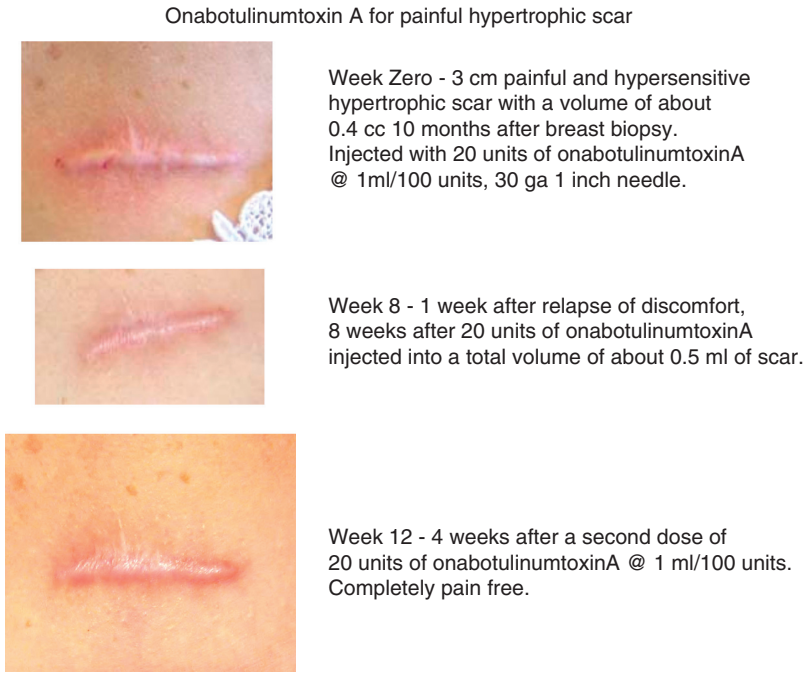


Figure 8.8 Pain in a hypertrophic scar on the upper chest after breast biopsy resolved in response to intralesional injection of onabotulinumtoxinA.

sessions by pretreating this patient with 80 mg of oxyprenolol (a very lipid-soluble beta blocker, which crosses the blood–brain barrier quite well and attenuates the central effects of adrenaline) together with 4 mg of lorazepam, 1 to 2 hours before injection of onabotulinumtoxinA. Over the past several years, fentanyl 100 to 150 mcg administered intravenously 10 minutes before the injection sessions has been very helpful to reduce both anxiety and pain. Gradual improvement in the hyperalgesic component of her RSDS has also contributed to improved tolerance of the BoNTA injections.

The patient characterized her pain as coming predominantly from bone, and deep injections close to bone using a 30G 1-inch needle were of particular benefit. Subcutaneous and intramuscular injections of onabotulinumtoxinA (a total of 120–400 units per session, about once a month) into the areas of discomfort in the right hand and arm gave substantial pain relief (for which the patient was very grateful) and also normalized skin color and temperature in the right hand and forearm within several minutes, but after one year of treatments there has not been any improvement in her ability to use the right hand. Even though the right hand remains useless, it is less of an impediment. It should be noted that reduction in pain and sensitivity has allowed this patient to take part in a greater range of activities of daily living and to participate more fully and effectively in physiotherapy and in society, so there has

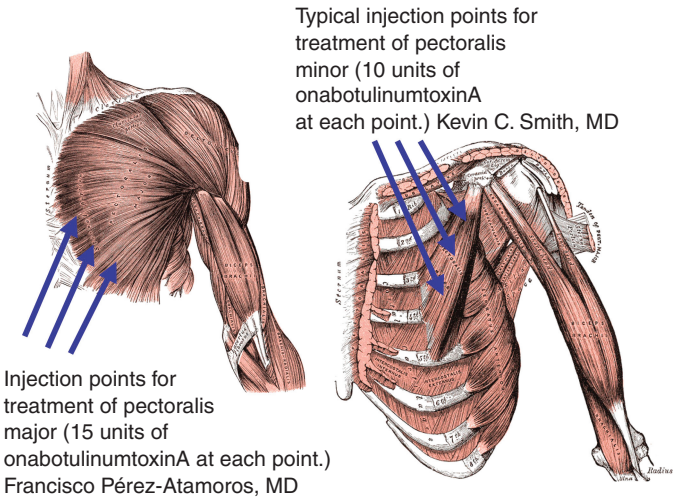


Figure 8.9 Typical injection sites for onabotulinumtoxinA treatment of the pectoralis minor and pectoralis major muscles.

been an overall improvement in general functional ability. Treatment of the involved areas in the right lower leg and foot were also helpful. At times the total dose of onabotulinumtoxinA for treatment of headache and for treatment of RSDS in the right arm and leg reached 1,200 units per month. This was well tolerated. After about four years of treatment, her headaches, neck spasm, and RSDS in the right arm and lower leg improved to the point where onabotulinumtoxinA in those areas was stopped, and the dose of onabotulinumtoxinA declined to about 400 units every 2 to 3 months to control her headaches, neck spasm, and pain in the right shoulder.

This is consistent with the observations of Cordivari et al. (45), who noted that four out of four of their patients with dystonia-complex regional pain syndrome affecting the hand had pain relief after treatment with abobotulinumtoxinA, but only one of the four had functional improvement.

There is less concern now than in the past about the risk that a patient such as this, who was treated with high doses of onabotulinumtoxinA, will develop antibodies against the onabotulinumtoxinA formulation of BoNTA. Jankovic et al. (21) found that blocking antibodies were detected in 4 of 42 (9.5%) cervical dystonia patients treated only with the original onabotulinumtoxinA, but in none of the 119 patients ($p < 0.004$) treated exclusively with the current onabotulinumtoxinA, which has been on the market since late 1997.

BoNTA for Improvement of Upper Thoracic Posture and "BOTOX® Breast Lift"

BoNTA has a long history of being used to improve posture in a variety of conditions (52,53). The position of the shoulders is determined largely by the balance of forces between the pectoralis minor and pectoralis major muscles (Fig. 8.9), which tend to rotate the shoulders medially and to depress the shoulders and the opposing muscles of the back, for example the rhomboids. The use of onabotulinumtoxinA to improve upper thoracic posture and so improve the presentation of the female breast has been detailed in the previous edition of this textbook (54) by the present author (KCS) and by Dr. Francisco Pérez-Atamoros.

This proposed mechanism of action has been criticized by Dr Otto Wegelin (personal communication, April 2004), who argues that

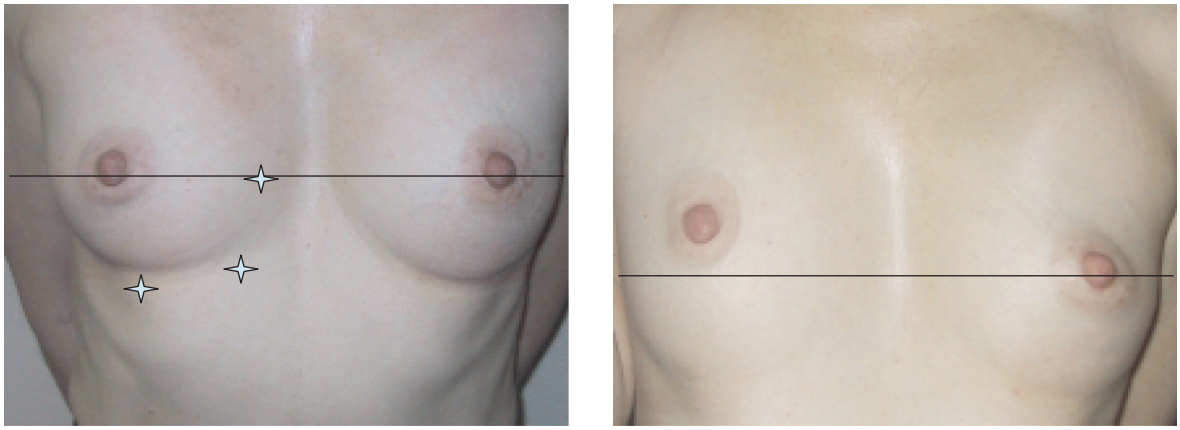
1. the muscles (pectoralis minor and rhomboid minor) invoked to carry out the postural changes are far too small to do what is expected of them,
2. the muscles do not in fact rotate the shoulder but rather act primarily to stabilize the scapula,an entirely different function,
3. the muscles are not antagonistic in action, as are the frontalis and the orbicularis oculi, but rather synergistic,
4. there is no way to determine how much, if any, of the onabotulinumtoxinA is actually acting on the pectoralis minor as the onabotulinumtoxinA can diffuse widely in a three-dimensional plane unlike the forehead where there is the bony skull limiting diffusion.

Dr. Doris Hexsel (personal communication, July 2004), in a study of six women, was not able to obtain satisfactory results, and in two cases noted that the nipples hung lower.

On the other hand, Pérez-Atamoros has successfully achieved elevation of the breasts when the nipples are projecting downward by injecting three doses of 15 units of onabotulinumtoxinA into the part of the pectoralis major which lies medial and inferior to the pectoralis minor (Fig. 8.10). In a series of 100 female patients between 30 and 55 years of age with different degrees of breast ptosis, elevation of the ptotic breast has been achieved, averaging 1.1 cm with the maximum elevation being 1.8 cm. Each patient was injected with onabotulinumtoxinA on only one side in this pilot study, with the contralateral side as control. Sixty-five of the 100 patients rated the results as good to very good, and 73 of the 100 patients would repeat the procedure. Pérez-Atamoros has noted that the best candidates are physically fit women between the ages of 30 and 55 years, with small or moderate-sized breasts. The dose recommended per breast is three injections ranging from 15 to 30 units of onabotulinumtoxinA each. The total dose in one application is 90 to 180 U. Approximately 89% of the study patients presented with asymmetry of the breasts before the treatment. It is important not to correct naturally occurring breast asymmetry by giving higher doses on one side of the chest or the other, but to inject the same total dose of onabotulinumtoxinA on each side. Five patients had pain lasting longer than a week after treatment. Pérez-Atamoros has suggested that relaxation of the inferior medial portion of the pectoralis major muscle allows the superior portion to lift the ptotic breast (Fig. 8.11). For a comparison of the injection sites used by Pérez-Atamoros and one of the authors (KCS) see Fig. 8.9.

The ideal candidates for this treatment seem to be non-obese women with slightly rounded shoulders or who are slightly stooped forward, with breasts of cup-size A or B. Older women, and those with larger breasts, tend to respond more slowly and to a lesser extent (Fig. 8.10).

The benefits of onabotulinumtoxinA treatment usually develop over a period of 1 to 2 weeks, and persist for 3 to 4 months (Fig. 8.12). The duration of effect is somewhat longer than might be expected considering the



(**A**) (**B**)

Figure 8.10 (**A**) A patient with symmetrically positioned breasts and nipples before receiving three injections of 15 units each of onabotulinumtoxinA into the right lower and medial aspect of the pectoralis major as indicated by the stars. (**B**) The same patient one month after the injection of onabotulinumtoxinA. Note the elevation of the right breast and nipple at approximately 1.1 cm elevation.

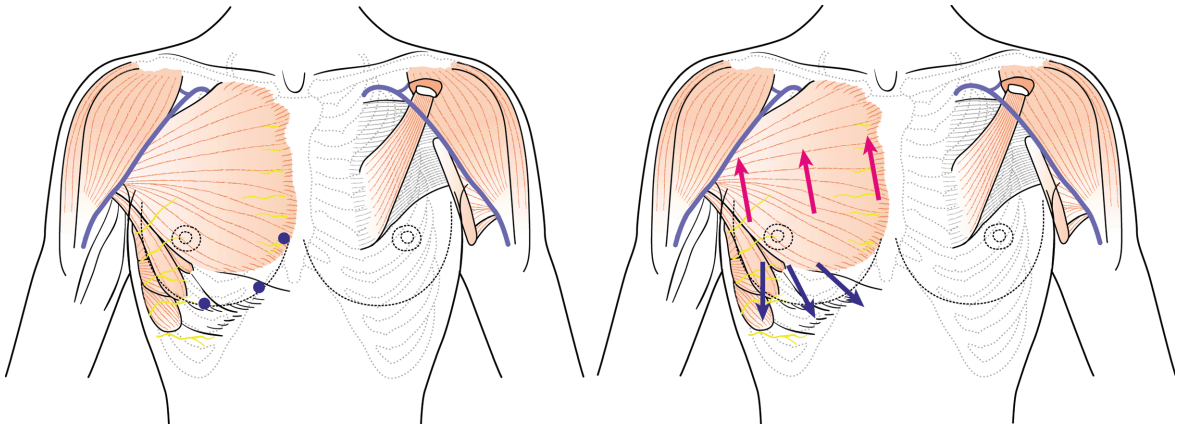
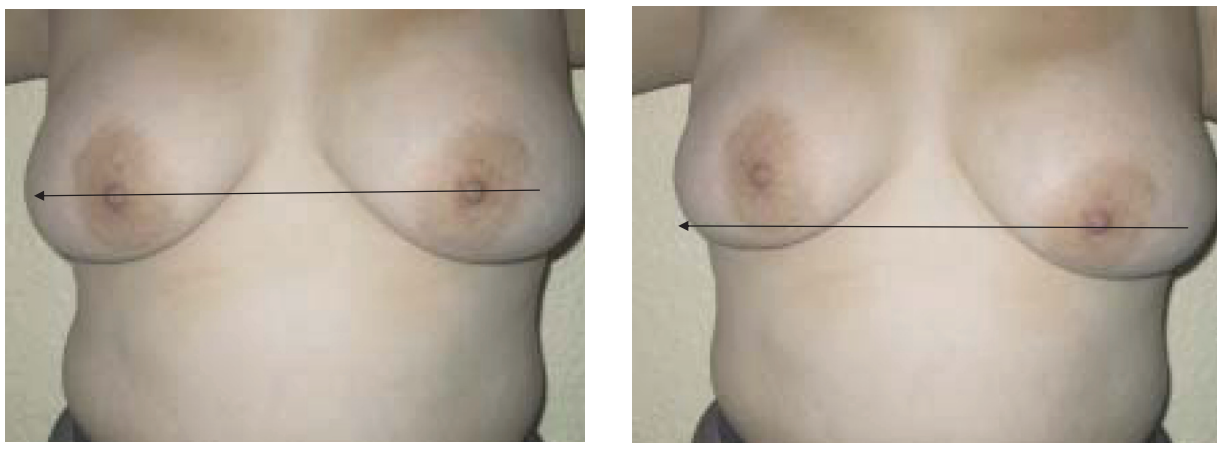


Figure 8.11 The areas in which onabotulinumtoxinA can be injected into the lower and medial aspect of the pectoralis major.



(**A**) (**B**)

Figure 8.12 (**A**) A patient with symmetrically positioned breasts but with the right breast slightly rotated laterally. She received 3 injections of 15 units each of onabotulinumtoxinA in the right lower and medial aspect of the pectoralis major. (**B**) Same patient one month after the injection of onabotulinumtoxinA. Notice the elevation of the breast and nipple on the side of approximately 1.3 cm.

relatively low doses of onabotulinumtoxinA in proportion to the size of the muscles. It may be that improvements in shoulder posture persist for a while once posture has been improved by onabotulinumtoxinA, altering the balance of forces between the pectoralis minor and/or major muscles and the opposing muscles in the back (Fig. 8.11).

Some women have noted that not only are the breasts and nipples elevated by their more erect posture with shoulders back, but also that there is a pleasing outward projection of the nipples which develops about a week after the onabotulinumtoxinA treatment and persists for 3 to 4 months. The reasons for this are not known. Perhaps projection

of the breasts as a result of improved shoulder posture leads to increased mechanical stimulation of the nipples under some circumstances. Another more speculative hypothesis is as follows: SP and CGRP have been demonstrated in neurovascular structures related to the nipple–areolar complex in animals (55) and in humans (56). BoNTA has been shown to block the release of SP and CGRP from nerve terminals. If some of the injected onabotulinumtoxinA makes its way from the injection sites to the nipple–areolar complex, it might affect smooth muscle in the nipples by way of its effect on the release of SP and CGRP.

OnabotulinumtoxinA is administered using a 30G 1-inch needle. Pneumothorax or bleeding has not been seen, and would not be expected with a 30G needle. The risk of entering the pleural space can be reduced by limiting needle insertion depth to less than 2 cm.

Recently it has been reported that the combination of BoNTA to relax muscles in the chest, when combined with a program of stretching to relax the chest muscles and exercises to strengthen muscles in the back, can produce a higher response rate and a greater duration of effect on upper thoracic posture than treatment with BoNTA alone (57–59).

Issues which remain to be resolved include optimization of patient selection, onabotulinumtoxinA dosing, injection placement, the issue of placebo effect versus biomechanical effect, and elucidation of the mechanism of action if indeed there is a biomechanical effect from onabotulinum toxin A treatment of the pectoralis minor and/or pectoralis major muscles with onabotulinum toxin A (60,61). It is our position that until these issues have been addressed, the "BOTOX® breast lift" will not be ready for commercialization as a medical procedure (62). T-2-weighted magnetic resonance imaging (MRI) before and immediately after exercise is being evaluated as a technique to visualize and perhaps partially quantify the degree of flaccid paralysis induced by onabotulinumtoxinA treatment (63).

Management of BoNTA Overdose

Overdoses of BoNTA are most commonly the result of accidental injection of small quantities of BoNTA, causing unintended localized muscle weakness. In some cases this will be annoying for the patient, but will resolve in a matter of weeks or months without treatment. Resolution in such cases may be accelerated if the patient tries to exercise the affected muscle as hard as possible for 5 minutes, five times a day.

If the local overdose is more serious (e.g., if an extraocular muscle has been injected) and if the mistake was immediately recognized, it might be possible to limit the uptake of BoNTA into the affected neurons by flooding the area with lidocaine. This might both dilute and wash away the injected BoNTA, and would also reduce or stop depolarization of the affected motor neurons, and so greatly reduces the exposure of the SV2 receptors that BoNTA binds to.

Because the uptake of BoNTA into motor neurons is an energy-dependent process, and considering that the rate of metabolic processes drops by about 50% for every 10°C reduction in temperature, it can also be useful in some circumstances to apply ice immediately after flooding the injected area with lidocaine, and to keep the injected area iced for a couple of hours. Pretreatment with lidocaine can directly reduce uptake of BoNTA as discussed above, and also reduces the discomfort that can result from the application of ice. Icing may reduce the temperature of the affected tissue from about 37°C to around 7°C, resulting in perhaps an eightfold reduction in the metabolic rate in the treated area (KCS, D Schachter, R Schachter, unpublished observations).

In a severe systemic intoxication with BoNTA, if the exposure was recognized almost immediately (e.g., in a laboratory or industrial accident), it might be beneficial to paralyze the patient temporarily in an intensive care unit setting using a medication like Pavulon®, and perhaps also to reduce the patient's body temperature as much as possible while the BoNTA was being flushed out of the patient's system and while awaiting delivery of immunoglobin directed against BoNTA.

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