CASE REPORT

Improvement in Both Raynaud Disease and Hyperhidrosis in Response to Botulinum Toxin Type A Treatment.

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Background: **A patient with concurrent Raynaud disease presented for hyperhidrosis of the axillae and palms. After a positive response to botulinum toxin type A (BoNTA) for axillary hyperhidrosis, she returned requesting palmar treatment.**

Objectives: **Our goal was to investigate the effect of BoNTA on Raynaud disease in concurrent hyperhidrosis with respect to color change, swelling, and digital pain.**

Methods: **The patient had treatment with 100 units of BoNTA to one hand at first, with the other being a negative control, followed by treatment of the second hand 1 week later.**

Results: **After the injection into the first palm, the patient demonstrated an 85% reduction in palmar hyperhidrosis and a significant improvement in her Raynaud symptoms. Specifically, the BoNTA-treated hand had reduced swelling, color change, and pain, whereas the untreated control hand remained affected. After the second hand was treated, it, too, demonstrated the same positive results.**

Conclusions: **Our case report of concurrent Raynaud disease and palmar hyperhidrosis shows significant improvement in both conditions to BoNTA administration. The physiology is multifactorial and relates to BoNTA's effect on acetylcholine, noradrenaline, substance P, calcitonin gene–related peptide, and glutamate release from nerve terminals. These results present an encouraging novel treatment option in dermatology for patients with Raynaud disease.**

Antécédents: **Une patiente souffrant d'une forme intercurrente de la maladie de Raynaud a été traitée pour l'hyperhidrose des aisselles et des paumes. Après avoir bien réagi au traitement à la toxine botulinique de type A (BoNTA) au niveau des aisselles, elle a demandé le même traitement pour les paumes.**

Objectifs: **Enquêter sur les effets du BoNTA sur la maladie de Raynaud en présence d'une hyperhidrose intercurrente, en ce qui a trait au changement de couleur, aux enflures et à la douleur digitale.**

Méthodes: **La patiente a reçu un traitement de 100 unités de BoNTA d'abord à une main, l'autre servant de témoin négatif, suivi d'un traitement à l'autre main 1 semaine plus tard.**

Résultats: **Après les injections à la première paume, il y a eu une réduction de 85 % de l'hyperhidrose palmaire ainsi qu'une amélioration des symptômes de la maladie de Raynaud. Plus précisément, il y a eu réduction de l'enflure, du changement de couleur et de la douleur au niveau de la main traitée au BoNTA, alors que la main témoin n'a subi aucun changement. Après le début du traitement de la main témoin, les mêmes résultats positifs ont été décelés.**

Conclusions: **Notre rapport de cas présentant à la fois la maladie de Raynaud et une hyperhidrose palmaire montre que le traitement au BoNTA améliore considérablement les deux conditions. La physiologie est multifactorielle et concerne les effets de BoNTA sur la libération de l'acétylcholine, de la noradrenaline, de la substance P, du calcitonin gene-related peptide, et du glutamate des neurones. Ces résultats représentent une nouvelle option encourageante pour le traitement des patients souffrant de la maladie de Raynaud.**

A *32-YEAR-OLD FEMALE PATIENT* presented in March 2007 for hyperhidrosis of the axillae and palms. The patient had concurrent Raynaud disease but was otherwise healthy and only using Allegra-D for hay fever as needed. Her allergies were to dairy, eggs, penicillin, and aspirin, and the family history included heart disease and diabetes but was not significant for hyperhidrosis or Raynaud disease.

She was treated with 100 units of botulinum toxin type A (BoNTA) (Botox, Allergan, Markham, ON, Canada) into each axilla; she returned 2 weeks later very pleased with the results of sweating reduction and now requested palmar treatment. Her Raynaud disease was managed by

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lifestyle alteration and had never been treated by a physician as she was reluctant to try systemic medications or surgical intervention. Because of the concurrent idiopathic Raynaud disease, Allergan was contacted with regard to possible contraindications to the use of Botox in her condition. There was no evidence of concern in treating concurrent Raynaud disease and hyperhidrosis, and, in fact, there was some early evidence showing a benefit to using BoNTA in Raynaud disease.

Only one palm was initially treated with BoNTA. Using topical ice therapy as anesthesia, 100 units of BoNTA was reconstituted with 3 cc of preserved normal saline and spread out over approximately 40 injection sites, each approximately 1 cm apart. The other palm was left untreated as an internal control and because of the discomfort associated with the treatment. The second palm was to be treated 1 week later.

The patient returned 1 week after the initial injection into the first palm and was pleased with the reduction in palmar hyperhidrosis (an 85% reduction according to the patient). She also reported very favorable comments regarding the symptoms of her Raynaud disease. In particular, she noted reduced swelling, color change, and pain in her treated hand, whereas the untreated control hand remained affected, as previously. Her second palm was treated similarly with 100 units of BoNTA over 40 injection sites with ice as local anesthesia, and she returned for follow-up 2 weeks later. On follow-up, she reported an 85% reduction in sweating on both palms and, more importantly, was again very pleased with the improvement in her Raynaud disease. In particular, both of her hands were now less cold and clammy (''not so sticky,'' according to the patient), and she had less swelling and much less pain. She noted that her hands used to turn from pink to red to purple (at their coldest and with the worst pain), but now her hands went only from pink to red, but no purple, so she now had only minimal discomfort. Furthermore, on a 6-week follow-up, she reported that her hands, which used to get cold and then swollen and painful daily, now become cold half as often and lasting for a shorter duration, with no swelling or pain. Additionally, she no longer required wearing gloves to sleep, which previously was necessary as her symptoms were worse at night. These benefits for her Raynaud disease were still fully in effect 12 months after we injected her hands. Curiously, she also stated that she used to develop some discomfort and pain in her axillae, but this has gone away along with the hyperhidrosis.

Pharmacophysiology of BoNTA

A complex of soluble *N*-ethylmaleimide-sensitive fusion attachment protein receptor proteins (SNARE) is involved in synaptic vesicle exocytosis from many types of neurons.[1] *Clostridium botulinum* neurotoxins (BoNT) are zinc-dependent endopeptidases that, once internalized into the neuronal cytosol, block neurotransmission by proteolysis of membrane-associated proteins that are involved in synaptic vesicle docking and fusion with the plasma membrane (the SNARE hypothesis).[2] Botulinum toxins cleave specific SNARE proteins, thereby affecting the release of various chemical classes of neurotransmitters. There are seven subtypes of BoNT, and each neurotoxin has a distinct cleavage site on its substrate. For example, BoNTA, BoNTC, and BoNTE cleave synaptosomal-associated protein SNAP-25.[3] Proteolytic cleavage of SNAP-25 or other transporter substrate proteins results in blockade of vesicle fusion and cessation of neuronal signaling. BoNTs are capable of inhibiting the release of neurotransmitters from a variety of synaptosomal and neuronal systems.

BoNTA's Effects on Cholinergic Nerve Terminals

BoNTA inhibits the exocytotic release of acetylcholine (ACh) from motor nerve terminals,[4] and its injection has been examined for the use of many motor or muscle conditions.[5] The inhibition of ACh release is mediated when the heavy chain of BoNTA binds to a specific receptor on cholinergic neurons, which is then internalized by the cell, and the light chain is translocated into the cytosol, where it can then act enzymatically to cleave SNAP-25.[6]

Botulinum toxin can also block activation of cholinergically innervated sweat glands and has thus proved useful in patients with severe axillary, palmar, and plantar hyperhidrosis, usually lasting 2 to 8 months for axillary sweating and 3 to 12 months for palmar sweating.[7] For sustained relief, additional injections of BoNTA after waning of response are usually required,[8] with recurrent hyperhidrosis perhaps secondary to either gradual recovery of the original nerve terminals, as seen in bladder autonomic regulation,[9] or potential new nerve ending regrowth, as in the musculoskeletal system.[10]

BoNTA's Effects on Vasodilator and Vasoconstrictor Neuropepetides

Cutaneous vasoconstriction and vasodilation are regulated by modulation of sympathetic and parasympathetic

neuronal inputs and the complex actions of released ACh, noradrenaline (NE), peptides, and small molecules such as nitric oxide on vascular smooth muscle.

In an animal model, BoNTA was shown to reduce the amplitude of sympathetic NE-mediated vasoconstriction of uterine arteries by 80% if the arteries were significantly rather than moderately constricted.[11] Likewise, isometric contractions of venae cavae mediated by NE acting on α-adrenoceptors are substantially reduced by BoNTA administration, suggesting that SNARE proteins involved in exocytosis of NE from synaptic vesicles at low frequencies of stimulation are effectively inhibited by BoNTA.[12] Concurrently, in parasympathetic neurons, BoNTA was found to significantly reduce the autocrine Ach-mediated inhibition of vascular relaxation and to reduce the slow component of neurogenic vasodilation mediated by the peptides vasoactive intestinal polypeptide and calcitonin gene–related peptide (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. The effect on the various classes of neurotransmitters from the same autonomic neurons appears to involve regulatory mechanisms with different sensitivities, varying neuronal release of cotransmitters in concert with the level of neuronal activation and inhibition.

Importantly, in a recent study investigating BoNTA's ability to interfere with neurotransmitter release at the perivascular sympathetic varicosities, BoNTA was shown to inhibit the neurogenic contractions of tumor vessels, thus improving tumor perfusion and oxygenation and aiding in the delivery of cancer therapy.[13] Specifically, by using electron paramagnetic resonance oximetry to monitor oxygen partial pressure in vivo, contrast-enhanced magnetic resonance imaging to measure tumor perfusion in vivo, and wire myography to monitor the neurogenic tone of arterioles, local administration of BoNTA demonstrated substantial opening of the vascular bed.[13] These findings correlate with the positive results of BoNTA use in place of surgical digital artery sympathectomy seen in Van Beek and colleagues' application of it to control rest pain, impending infarction of digits, or healing of ischemic ulcerations caused by profound vasospasm.[14]

BoNTA's Effects on Inflammatory and Nociceptive Peptides

A large body of evidence has accumulated suggesting that BoNTA may act on the nociceptive portion of the sensory system to reduce pain and neurogenic inflammation. The mechanism by which this occurs appears to be via the attenuation of the peripheral release of neuroactive compounds such as substance P and glutamate from C fibers. A consequence of the direct attenuation of the peripheral sensitization of nociceptors may be to further reduce pain by the reduction in central sensitization.[6] Because BoNTA has no direct effect on the excitability of sensory neurons, it may be effective in reducing neurogenic inflammation and inflammatory pain without affecting the acute pain response caused by direct stimulation of nociceptors.[15] It has been suggested that BoNTA has antinociceptive effects in humans under conditions of pathologic pain.[16]

Substance P

BoNTA has been found to inhibit substance P release, a peptide neuromodulator released both peripherally and centrally by nociceptive primary afferent C fibers. Substance P serves to sensitize peripheral nociceptors; thus, a reduction in substance P release may produce an analgesic effect, possibly accounting for the efficacy of BoNTA already seen in treating primary headache disorders.[17] In vitro, calcium-dependent substance P secretion in dorsal root ganglia neurons is markedly inhibited by BoNTA.[18] In this study, the effect was detectable within hours and lasted for at least 2 weeks. The reduction in substance P release was correlated with the dose of BoNTA administered and was accompanied by concentration-dependent cleavage of the SNARE protein SNAP-25.[18] As mentioned above, local inflammation can sensitize peripheral nociceptive neurons, and as the increase in peripheral pain input causes increased release of substance P in the spinal cord, it produces further central sensitization.[6] Thus, BoNTA may attenuate both peripheral and central sensitization by its inhibition of substance P release.

Calcitonin Gene–Related Peptide

BoNTA has demonstrated significant inhibition of CGRP release when pain stimulus is present but not at baseline. CGRP is an inflammatory neuropeptide found on its own and colocalized with substance P in sensory ganglia neurons. In a preclinical model of bladder pain, BoNTA was shown to significantly reduce pain response by 62% through inhibition of CGRP release from afferent nerve terminals.[19] Likewise, in trigeminal nerve terminals, evoked but not basal CGRP release is directly inhibited

by BoNTA,[20] confirming the hypothesis of why BoNTA has shown promising results as an effective tool in migraine and cluster headache therapy. Importantly, CGRP found in the peripheral terminals of primary afferents, and released during inflammation, causes cutaneous vasodilation. It is possible that the effect of CGRP is largely, if not purely, vascular, where its importance in migraine potentiation relates to the dilation and sensitization of the meningeal vasculature. Thus, BoNTA's analgesic effect in relation to CGRP may be due to a combination of both anti-inflammatory sensory and antivasodilatory properties.

Glutamate

Glutamate is a stimulant of local nociceptive neurons through activation of receptors on primary afferents, and its administration evokes nociception in both animals and humans.[21] Subcutaneous formalin injection induces peripheral glutamate release, edema, and inflammation.[22] Administration of BoNTA has been shown to dose-dependently inhibit formalin-induced inflammatory pain in rats. This was associated with a significant decrease in glutamate release in the injected hindpaw. Thus, with local administration of BoNTA (below doses that would elicit muscle paralysis), analgesic, anti-inflammatory, and anti-edematous effects were achieved.[15]

Discussion and Future Implications

The etiology of Raynaud disease is complex, and many components factor into its potentiation and deleterious effects. Certainly, both vasospasm and nociception play a major role. The inhibitory effects of BoNTA on somatic and autonomic neurotransmission are well documented, and studies demonstrate that it inhibits peripheral sensitization, thus producing a lasting analgesic effect. It concurrently interferes with NE-mediated sympathetic vasoconstriction, thus allowing for improved perfusion of digits by opening up the vasculature and allowing for better oxygenation. Whether the mechanisms by which BoNTA affects the vasomotor system are a primary benefit and the antinociceptive effects are a secondary benefit to the improved perfusion is yet to be elucidated.

More importantly, BoNTA shows promise in the treatment of Raynaud disease. In fact, a recent study of 11 patients with digital vasospasm producing severe rest pain and digital ulcerations who had undergone BoNTA injections reported subjective improvement of hand temperature and highly improved pain level in all subjects within 1 to 2 days and lasting for months, along with spontaneous healing of ulcers in 9 of 11 subjects.[14] Two other studies to date have demonstrated the clinical benefit of BoNTA in Raynaud disease, primarily by shortening warm-up time after exposure to cold[23] and an overall reduction in the frequency and severity of symptoms, including reduced pain and improved hand circulation[24] secondary to the inhibition of vasoconstriction, as measured by Doppler ultrasonography. The adverse events reported are rare and include mild hand weakness.[14]

This is a singular case report of concurrent Raynaud disease and hyperhidrosis responding to BoNTA treatment with significant improvement in both conditions, still fully effective at the 4-month follow-up. Its efficacy is secondary to the inhibition of release of transmitter-containing vesicles that target different structures: ACh-stimulated sweat glands, NE-stimulated vasoconstriction, and neuropeptide-stimulated nociception. The improvement in pain, swelling, and inflammation seen in Raynaud disease is secondary to the concurrent action of BoNTA on inhibiting pain-stimulating neuropeptides: substance P, CGRP, and glutamate. Not only does it act locally at reducing nociception and inflammation, it also prevents the potentiation of both local and central sensitization to pain as a result of decreased release of neurogenic pain peptides. The improvement in vasoconstriction secondary to a complex inhibition of both ACh- and NE-mediated pathways results in clinical improvement in cold tolerance, as well as in the change in the color of the hands, thus minimizing discomfort. These results present an encouraging new treatment option for patients with Raynaud disease and should be considered in the armamentarium of dermatologists who manage this condition.

References

1. Gerber SH, Sudhof TC. Molecular determinants of regulated exocytosis. Diabetes 2002;51 Suppl 1:S3–11.
2. Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature 1993;365: 160–3.
3. Verderio C, Rossetto O, Grumelli C, et al. Entering neurons: botulinum toxins and synaptic vesicle recycling. EMBO Rep 2006; 7:995–9.
4. Simpson LL. The origin, structure, and pharmacological activity of botulinum toxin. Pharmacol Rev 1981;33:155–88.
5. Hallett M. One man's poison—clinical applications of botulinum toxin. N Engl J Med 1999;341:118–20.
6. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology 2005;26:785–93.

7. Odderson IR. Hyperhidrosis treated by botulinum A exotoxin. Dermatol Surg 1998;24:1237–41.
8. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med 2001;344:488–93.
9. Haferkamp A, Krengel U, Reitz A, et al. Are botulinum-A toxin injections into the detrusor of patients with neurogenic detrusor overactivity safe? Ultrastructural data of detrusor biopsies. Neurourol Urodyn 2003;22:499–500.
10. de Paiva A, Meunier FA, Molgo J, et al. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Proc Natl Acad Sci U S A 1999;96: 3200–5.
11. Morris JL, Jobling P, Gibbins IL. Differential inhibition by botulinum neurotoxin A of cotransmitters released from autonomic vasodilatior neurons. Am J Physiol Heart Circ Physiol 2001; 281:H2124–32.
12. Morris JL, Jobling P, Gibbins IL. Botulinum neurotoxin A attenuates release of norepinephrine but not NPY from vasoconstrictor neurons. Am J Physiol Heart Circ Physiol 2002;283: H2627–35.
13. Ansiaux R, Baudelet C, Cron GO, et al. Botulinum toxin potentiates cancer radiotherapy and chemotherapy. Clin Cancer Res 2006;12:1276–83.
14. Van Beek AL, Lim PK, Gear AJ, Pritzker MR. Management of vasospastic disorders with botulinum toxin A. Plast Reconstr Surg 2007;119:217–26.
15. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain 2004;107:125–33.
16. Türk N, Ilhan S, Alp R, Sur H. Botulinum toxin and intractable trigeminal neuralgia. Clin Neuropharmacol 2005;28:161–2.
17. Aurora S. Botulinum toxin type A for the treatment of migraine. Expert Opin Pharmacother 2006;7:1085–95.
18. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to *Clostridium botulinum* neurotoxins. Toxicon 2000;38:245–58.
19. Rapp DE, Turk KW, Bales GT, Coock SP. Botulinum toxin type A inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol 2006;175:1138–42.
20. Durham PL, Cady R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache 2004;44:35–43.
21. Carlton SM, Hargett GL, Coggeshall RE. Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin. Neurosci Lett 1995;197:25–8.
22. Wheeler-Aceto H, Porreca F, Cowan A. The rat paw formalin test: comparison of noxious agents. Pain 1990;40:229–38.
23. Stadlmaier E, Müller T, Hermann J, Graninger W. Raynaud's phenomenon: treatment with botulinum toxin [abstract]. Ann Rheum Dis 2005;64(Suppl III):275.
24. Sycha T, Graninger M, Auff E, Schnider P. Botulinum toxin in the treatment of Raynaud's phenomenon: a pilot study. Eur J Clin Invest 2004;34:312–3.