Optimizing the Safety Profile of Botulinum Neurotoxin

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In dermatologic practice, botulinum neurotoxin is a mainstay of use for facial aesthetics. It is also becoming an increasingly popular treatment for primary focal hyperhidrosis. Despite the impressive safety profile of botulinum neurotoxin for these indications, adverse events can potentially occur. An understanding of the potential adverse events associated with botulinum neurotoxin injections, including how to avoid them and how to treat them if they do arise, will help clinicians optimize outcomes.

Over the past decade or so, botulinum neurotoxins (BoNTs) have emerged as important agents in both aesthetic and therapeutic treatment armamentariums. Within the practice of dermatology, the efficacy of BoNT for aesthetic indications such as dynamic rhytides, as well as for therapeutic indications such as primary focal hyperhidrosis, is without debate. Furthermore, the use of BoNT continues to grow, not only because of the effectiveness of treatment but also because of increased public interest and a diminished social stigma surrounding its use. Also contributing to the popularity of BoNT is its highly favorable safety profile,[1,2] attributed in part to the localized site of action, as well as the exceedingly small doses used for facial aesthetics.

Despite the impressive safety profile of BoNT, adverse events (AEs) can potentially occur. Complications can be a function of the inherent properties of the agent used (including dose), injection technique, and patient selection. Proper training in the use of these agents is necessary to avoid AEs and to ensure the best possible outcomes.

In the United States, Botox® Cosmetic is the only available botulinum neurotoxin type A (BoNTA), although other BoNTA products (eg, Dysport®/Reloxin®) are undergoing clinical trials and are available in other countries. Myobloc® is a botulinum neurotoxin type B product that is approved by the US Food and Drug Administration for use in cervical dystonia. It has been evaluated in facial lines[3-5] but is believed by many to be of more limited overall clinical value to the cosmetic dermatologist because of its shorter duration of effect, more prominent pain on injection, and larger diffusion radius (or less predictable diffusion pattern) relative to BoNTA in facial lines. Some of the AEs and complications that can occur with BoNTs are listed in the Table. At usual doses, AEs are short lived, with no permanent sequelae.

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HEADACHE

Headache is the most common AE reported in BoNTA aesthetic clinical trials. In a multicenter, double-blind, randomized, placebo-controlled study of BoNTA for the treatment of glabellar lines (N=264), 15.3% (31 of 203) and 14.8% (9 of 61) of those receiving BoNTA and placebo, respectively, reported experiencing headaches.[6] Of those treated with BoNTA, 31 subjects reported 41 headaches, 53.7% (22 of 41) of which occurred within 2 days of treatment. Most of the headaches were rated as mild (92.7% [38 of 41]) and did not persist beyond a few hours (70.7% [29 of 41]). The equivalent incidence of headaches in the BoNTA group versus the placebo group suggests that headaches are not related to the product, but to the injection procedure (piercing of the skin and underlying muscle).

A prospective, double-blind, randomized, parallel-group, dose-ranging study of BoNTA in subjects with forehead rhytides (N=59) supports these findings, with headache again being the most common treatment-related AE, occurring in 20% (4 of 20), 15.8% (3 of 19), and 30% (6 of 20) of those receiving 16, 32, and 48 U

Potential Adverse Events Associated With Botulinum Neurotoxin Products

- Headache
- Eyebrow ptosis
- Blepharoptosis (eyelid ptosis)
- Transient swelling
- Asymmetries
- Systemic effects

of BoNTA, respectively.[7] Of the 13 reported headaches, 76.9% (10 of 13) were considered mild and 23.1% (3 of 13) were considered moderate.

Although BoNTA has been used to treat patients with a history of various types of ongoing or repeated headaches, such as tension, migraine, or other patterns of headaches, ironically there also have been a few cases in which BoNTA injections for cosmetic use were associated with severe, persistent, and debilitating headaches lasting 2 to 4 weeks.[8]

BLEPHAROPTOSIS

Blepharoptosis (eyelid ptosis)—which is caused by the unintended migration of BoNTA into the orbital septum and the resulting paralysis of the levator palpebrae superioris—is a complication seen in a small percentage of those receiving BoNTA for glabellar lines. It is believed to occur most commonly when injections are performed by novice injectors who are inexperienced with the technique. In the study involving treatment of the glabella, blepharoptosis occurred in 5.4% (11 of 203) of those receiving BoNTA; no instances of blepharoptosis occurred in those receiving placebo.[6] Of the 12 eyes affected (all but one patient experienced unilateral blepharoptosis), 66.7% (8 of 12) of events were considered mild (average duration, 20 days) and 33.3% (4 of 12) were considered moderate (average duration, 40 days).

Because blepharoptosis is thought to be technique dependent, its incidence can be minimized with improved skill. Recommendations aimed at helping clinicians avoid blepharoptosis include not injecting BoNTA near the levator muscle of the upper eyelid, especially in patients with larger brow-depressor complexes, and making sure corrugator injections are placed at least 1 cm above the bony supraorbital ridge.[6] In my opinion, treatment of any medial pull of the orbicularis oculi just above the mid brow (so-called "medial recruitment" seen in patients who have availed themselves of glabellar BoNTA treatments over many years) is the riskier injection of the glabellar area leading to this uncommon AE. Treatment of the medial recruitment should thus be performed with caution, and the injection site should be a bit higher—usually at least 1.5 cm above the supraorbital rim at or about the midpupillary line.

One treatment option for the unusual but occasional case of blepharoptosis is stimulation of Müller muscle (an adrenergic muscle located just beneath the levator muscle of the upper eyelid). Administration of an α_1-adrenergic agent such as naphazoline hydrochloride and pheniramine maleate, a decongestant with a weak adrenergic effect, 3 to 4 times daily until ptosis disappears (2–4 weeks) can cause contraction of this muscle. Other adrenergic agents include apraclonidine, an α_2-agent with weak α_1 activity, and phenylephrine, an α_1-agonist.

ASYMMETRIES

Mild facial asymmetries exist in almost everyone. For dermatologists, significant asymmetries are usually an infrequent but possible complication in those being treated with BoNTA injections, a result of unintended migration or diffusion from the site of injection or, in some cases, inexperience. Brow asymmetry, or eyebrow ptosis, appears to be dose and technique related. In the previously mentioned dose-ranging study in which patients received BoNTA for forehead rhytides, eyebrow ptosis did not occur in those receiving 16 U of product; it did occur, however, in 21.1% (4 of 19) of those receiving 32 U, and 10% (2 of 20) of those receiving 48 U.[7] The 3 investigators in this study (in which I was one) agreed that this brow ptosis was a result of the study medication and probably dose related. It should be noted that the doses associated with brow ptosis in this study were higher than those since recommended in a 2004 consensus statement on BoNTA (10–20 U for women, 20–30 U for men),[9] and currently, in 2007, the trend has been toward even lower doses in the forehead to preserve some forehead movement and avoid eyebrow ptosis.

To prevent significant brow asymmetries, all BoNTA injections for the treatment of forehead rhytides should remain 1 to 2 cm above the orbital rim; the upper two thirds of the forehead has also been identified as a landmark.[9] It should be emphasized that dosing should be tailored to the prominence of musculature of each side of the forehead rather than simply using the same doses on each side of the forehead. In addition, in patients who have clinically significant imprinted lines above the lateral brows resulting from compensating for redundant eyelid skin or dermatochalasis (through patients attempting to hoist up their lids with their frontalis muscle),

injections should be placed at least 3 to 4 cm above the orbital edge[10] to avoid accentuating the brow-lid redundancy. Many experienced physicians, myself included, often avoid treating the forehead entirely in these types of patients.

Some clinicians believe a small amount of BoNTA administered in the procerus at the time of treatment of the forehead area alone may help prevent medial brow ptosis. To help avoid lateral brow ptosis, injecting 1 to 3 U of BoNTA into the lateral orbicularis oculi can provide some degree of eyebrow elevation when also injecting the forehead, which can neutralize the potential for brow depression.[9] Injection of a small amount of product into the lateral orbicularis oculi to lift the lateral brow (often with 4–6 units per side)[11,12] also can be performed as a corrective measure should brow ptosis occur subsequent to forehead BoNTA treatment.

The use of BoNTA to treat the crow's-feet area can result in unintended migration into the zygomaticus muscles and an asymmetrical smile pattern. This complication is seen most often following lateral lower crow's-feet injection points that are too inferior and lie on or are immediately adjacent to the zygomatic arch.

SYSTEMIC EFFECTS

In the medical literature, systemic effects associated with the use of standardized formulations of BoNTs are rare and limited to the therapeutic use of BoNTA,[13,14] where much larger doses are used than with cosmetic applications. Two cases have been described in patients undergoing BoNTA treatment for primary focal hyperhidrosis; treatment of this indication requires notably higher doses than those used for facial aesthetics. Tugnoli et al[15] presented the case of a woman weighing 48 kg who was treated in the palm, including fingers, and axillary regions with 1400 U of BoNTA in one treatment session. Six days posttreatment, the patient complained of diffuse asthenia, diplopia, mild bilateral ptosis, and severe weakness in finger movements, as well as decreased lacrimation, salivary production, and sweating. She was monitored weekly, and her strength improved progressively, with complete recovery at 2 months postinjection. Despite these AEs, the patient was satisfied with her results and returned for re-treatment. The authors attribute the patient's modest body weight, the high BoNTA dose, and the fact that treatment of both the axillae and the palms occurred at one session (which was at the request of the patient using this high dose) rather than at separate visits (to reduce the total amount of toxin injected at one time) as contributing factors.

Another report of systemic effects following exposure to BoNT occurred with a man treated with 5000 U of botulinum neurotoxin type B.[16] Two days postinjection, the patient experienced bilateral blurry vision, indigestion, and a dry sore throat leading to dysphagia. The patient's indigestion and dysphagia resolved within 10 days; his blurry vision cleared within 3 weeks. All AEs resolved within 1 month, and the patient thought treatment was successful.

Serious systemic effects have been publicized regarding the use of an unapproved botulinum neurotoxin for facial aesthetics, in which 4 people were paralyzed following injection with a concentrated research-grade BoNTA.[17] Physicians are often solicited by companies distributing unlicensed or even black-market BoNT products. However, as demonstrated in the 4 cases of paralysis, the efficacy and safety of these unapproved agents (or those not obtained directly from the manufacturer) are unknown and can result in serious consequences. Dermatologists must be careful to use only US Food and Drug Administration–approved products and obtain all products only from the manufacturer.

CONCLUSION

BoNTs are valuable tools in the dermatologist's toolbox, owing to their highly favorable efficacy and safety profiles in dermatologic indications. Nonetheless, AEs can occur, particularly if BoNTs are improperly used. Therefore, an awareness of the potential AEs, as well as how to best avoid or manage them if they do occur, will maximize the success of BoNT within the practice of dermatology.

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