Botulinum toxin: issues and applications
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Botulinum toxin is becoming a useful therapeutic toll for the treatment of many diseases in several disciplines. Following its application for regional movement disorders, such as blepharospasm, strabismus, and spasmodic torticollis, this agent is now being used for the treatment of certain pain syndromes and in facial cosmetic applications. Despite the proliferation in use, issues involving the pharmacology of materials and bioeffects that are important to this therapy are only partially understood. In this review, some recent published literature on newer applications and significant issues pertinent to this important technology are outlined. 

Contemporary issues relating to botulinum toxin therapy and new indications
Botulinum toxin (Botox [Allergan, Irvine, CA]) has become a useful tool for the treatment of many afflictions. It was initially introduced for the treatment of strabismus by Alan Scott in 1981, with a composition prepared by Edward Schantz at the University of Wisconsin; however, the number of possible applications have increased considerably over the past 10 years. The unique pharmacologic properties of the material has added greatly to the therapy for many afflictions. Despite much interest in the technology, there are still many issues relating to the materials, nature of tissue responses, and clinical applications that are still unresolved.

Although botulinum immunotype A has been the initial agent used in the treatment of spastic disorders, it is anticipated that immunotype B will become available in the near future. The differences in clinical efficacy and safety represent a subject of importance.

The following is a review of recent literature and important topics relative to the botulinum therapeutic technology.

Blepharospasm
Botulinum toxin has become the treatment of choice for essential blepharospasm (Fig. 1) and blepharospasm associated with facial dystonia, replacing surgical procedures and medications as primary therapy. Injections given periodically to the orbicularis oculi muscle in several locations provide a method of reducing involuntary spasm without destroying the primary action of blinking, which is necessary to maintain the integrity of the ocular surface.

Recently, after depletion, lot 79-11 of the proprietary Botox has been replaced with new source material (Botox-CDG/CO lots), which is currently used in the United States.

The new source material provides an efficacious agent; however, the comparative clinical trials have revealed increased incidence of ptosis compared with the original trials, possibly indicating changes in the biologic behavior of this new agent. Ptosis can be avoided by using lower total doses (<40 IU) and by avoiding injections into the lid crease or fold. Ptosis is generally reversible over a period of 2 to 4 weeks. The cause of this complication relates to diffusion of the biologic effect into the orbit with weakening of the levator palpebrae superior muscle. Additionally, diplopia appears to be a more
Figure 1. Patient with essential blepharospasm.

Botulinum toxin has become the standard therapy for this condition. Reduction in blink rate and forced spasmodic eyelid closure helps with visual function and facial expression. Complications of injection include ptosis, which has been noted more frequently with recently manufactured lots of botulinum toxin.

common complication than previously experienced with the original formulations. The differences in complication rates can be explained by the greater diffusion potential of the newer material. Being cognizant of the differences, lowering doses previously used to treat blepharospasm, and administering the injections further from vital intraorbital structures can mitigate these complications.

A small number of patients may develop immunologic resistance to the repeated use of the drug, particularly if larger doses are used or there are short intervals between injections.

Cervical dystonia

botulinum toxin has become the treatment of choice for spasmodic torticollis and related forms of cervical dystonia (Fig. 2). The injections are given in several locations to dystonic muscles, effecting often an improvement in posture, and a lessening of pain, involuntary movement, and prominence of contracted cervical muscles.

Dosing levels are much greater than required for the treatment of blepharospasm-related syndromes, generally ranging from 100 IU to 300 IU (with Botox).

Recently, an effort to use more standardized endpoints in clinical studies of this condition has been underway, and long-term efficacy is possible [1,2].

Contemporary issues relating to the use of botulinum toxin for this condition involve induced immunity resulting from higher doses required for this affliction and possible impurities in the materials being used (toxoid formation). Edward Schantz has provided an excellent review with respect to history of development and production issues [3].

Earlier comparison and experience has revealed a discrepancy concerning the occurrence of this complication (Table 1) as it relates to dose. Recently, the Botox

Table 1. Dose-dependent formation of botulinum a toxin antibodies after repetitive injections: literature evaluation (clinical studies)

<table>
<thead>
<tr>
<th>Dose (IU)</th>
<th>Protein load (ng)</th>
<th>AB n(%)</th>
<th>Indication</th>
<th>Source</th>
<th>Duration (yr)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum A: Botox</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10-52.5 (30)</td>
<td>12</td>
<td>0(0)</td>
<td>Blepharospasm</td>
<td>Garnering et al [29]</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>25-600 (225)</td>
<td>100</td>
<td>5(4,13)</td>
<td>Torticollis</td>
<td>Jankovic et al [28]</td>
<td>2</td>
<td>133</td>
</tr>
<tr>
<td>Dysport</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125-250</td>
<td>3.6</td>
<td>0</td>
<td>Blepharospasm</td>
<td>Package insert</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>NG</td>
<td>14</td>
<td>3(3)</td>
<td>Torticollis</td>
<td>Zuber et al [30]</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>600-1000</td>
<td>21.2 (63-582)</td>
<td>7</td>
<td>Torticollis</td>
<td>Hamilton et al [31]</td>
<td>NG</td>
<td></td>
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</tbody>
</table>

Assessments:
i. Antibodies occur to active neurotoxin after repetitive injections with both American botulinum toxin and British toxin.
ii. Sensitization appears to be a dose-dependent phenomenon for both Botox and Dysport.
iii. Although Dysport (25-40 IU) contains a higher specific activity than Botox (2.5 IU), more international units often need to be administered.
NG, not given.
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manufacturer, it has been reported, has increased the purity (specific toxicity-activity, Allergen-CDG lots) of the basic materials, which may impact of incidence of secondary resistance after repeated therapeutic injections.

Despite recognition of the secondary immunity problem, therapeutic efficacy has been lost for a significant number of patients with cervical dystonia because they have developed neutralizing antibodies to materials previously used as therapeutic agents. For this reason, botulinum type B toxin has been developed for therapeutic use. Many articles dealing with cervical dystonia, published in the past 2 years, deal with efficacy, dose finding, and safety studies involving the botulinum toxin immunotype B and immunotype F [4,5]. Botulinum type F has been used for patients who are resistant to type A. However, resistance to type F can occur, and its occurrence appears to be related to dose per injection cycle.

Assessing immunity status

Conventionally, the mouse bioassay has been the gold standard for assessing a patient's immunity status. In the past, many efforts have been made to substitute the mouse bioassay with non-neutralizing forms of assays (eg, ELISA); however, repeatedly the mouse bioassay has been the best predictor of future clinical outcome. The interpretation of discrepancies between neutralizing and non-neutralizing assays is thought to relate to differences in epitope site reactivity between various forms of antibodies [6].

The expense of the mouse neutralization assay is considerable. Many clinicians today are using the concept of remote point injections to assess the presence of neutralizing antibodies in a resistant patient. The test involves the administering of an injection to a point that is distant from the disease location, to ascertain if a weakening effect could be elicited. If a weakening effect can be elicited, it would be unlikely that the patient response is being effected by a circulating neutralizing antibody. If there is no weakening, it would be probable that there is a circulating antibody. This concept has been applied to the forehead dystonia patients, with brow excursion and forehead wrinkle reduction recognized as the cause of remote point weakness (Fig. 3) and Table 2. Electromyography (EMG) assessment on the limbs has also been used to demonstrate the same concept [7]. The remote point effect with respect to forehead weakening has been correlated with the presence of neutralizing antibody (see Table 3), and these findings have been substantiated [6]. The EMG analysis of extensor digitorum brevis correlated with the antibody test for mouse bioassay neutralization.

![Figure 3. Forehead remote point injection test for immunologic resistance](image)

Note the depressions in the forehead creases and the reduced brow excursion in this patient with cervical dystonia. The presence of the remote point weakness (remote from neck injections) seen here 2 weeks after the forehead injections indicate the absence of circulating neutralizing antibodies to the botulinum toxin used in treatment. The absence of this remote effect concords to presence of measured circulating antibodies in small patient samples.

<table>
<thead>
<tr>
<th>Table 2. Comparative analysis in patients reporting reduced responses after repeated botulinum toxin injections</th>
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<tr>
<td>Mean dose per injection</td>
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<tr>
<td>Mean cumulative dose</td>
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<tr>
<td>Mean number of injections</td>
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<tr>
<td>Rate of reduced response (4 months)</td>
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<tr>
<td>Frontalis remote effect</td>
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<tr>
<td>Duration of therapy</td>
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<tr>
<td>Botulinum A-blocking antibody in patients with reduced response</td>
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This graph depicts the fraction of the LD 50 unit that is needed to produce regional paralysis in the hindlimb of the mouse typically used for bioactivity estimations. This assay quantifies the effects of botulinum toxin according to regional denervation potential. Note differences in the curves between two widely used agents. This curve highlights the weakness of the LD 50 in predicting regional denervation potency between varying preparations of botulinum toxin. (From Pearce et al. [27]; with permission.)
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Figure 5. Forehead crease reduction

Reduction of transverse forehead creases to address facial disfigurement in a patient with facial paralysis.

Figure 6. Age-related glabellar rhytides

Cosmetic application of botulinum toxin to address prominent age-related glabellar rhytides.

The diagnosis of myasthenia was confused by the facial weakness created by the botulinum toxin. The unusual response to botulinum toxin with the demonstration of high...
titers of circulating acetylcholine-receptor antibodies made the diagnosis. Untreated myasthenia may be an absolute contraindication to the use of botulinum toxin [16].

**Newer indications**

Recently, the recognition that botulinum toxin can be useful for the treatment of certain forms of primary pain syndromes has been recognized [17]. Many have confirmed the usefulness of these initial observations [18,19]. Other studies show less convincing results [20]. It has been well recognized that pain is the most sensitive and responsive component of the cervical dystonia syndrome [21]. Additionally, facial pain that is associated with aberrant nerve regeneration often responds to botulinum toxin injection, so it is not surprising that it is possibly efficacious in the treatment of pain. A direct effect on the afferent sensory system has been postulated related to the perceived benefit in human essential headache disorders [17,22].

Additional studies are clearly needed to perfect the application of botulinum toxin for human essential headaches, myofascial pain syndromes, or other pain applications. Long duration of action, systemic side effect profile, and the absence of patient self-medication may provide distinct advantages for this therapy in the spectrum of pain management.

The expansion in headache application now has included migraine. Patients treated for cosmetic wrinkle reduction have noted improvement in essential headaches, including migraine. Similar observations have been made in patients receiving the injection for the treatment of blepharospasm. A regional effect involving pain reduction is often noted around the injection sites that is consistent with botulinum toxin's diffusion potential. Over the past several months, applications in migraine as well as other forms of essential headache disorders will be the subject of placebo controlled studies, which are being conducted at this writing. This application also fits the hypothesis that botulinum toxin has a direct effect on the sensory side of the peripheral nervous system. The nature of this effect will most certainly be a subject of future study.

**Cosmetic applications**

Botulinum toxin has long been known to diminish dynamic facial lines. The earliest results were obtained in suppressing the lines of Langer, which are circular in character and follow the contour of underlying orbicularis oculi muscle, which surrounds the eye. This muscle is reduced in tone with the injection of botulinum toxin for the treatment of blepharospasm, and often the underlying dynamic lines are reduced. Other lines responsive to botulinum toxin include the glabellar lines and transverse frontalis lines (Fig. 5). Both these sets of lines are generally associated with the masculine face. Reducing the tone in the facial area of such lines reduces the prominence of such lines and may give a more youthful appearance. Additionally, if such lines are present in a female, decreasing such lines feminizes the forehead (Fig. 6). Care must be instituted to avoid injections around the orbit, as ptosis and diplopia can result. The duration effect is generally between 4 and 6 months.

**Other indications**

Botulinum toxin has been known to be effective in relieving the acoustic aberration associated with palatal myoclonus [23]. It is helpful for bruxism and recurrent jaw dislocation [24] and sweating disorders, particularly Frey's syndrome [25,26].

**References and recommended reading**

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22 Giardi N: The mechanism of action of botulinum toxin type A in focal dystonia is most probably through a dual effect on efferent (motor) and afferent pathways at the injection site. J Neurol Sci 1997, 152(2):132-135.