Botulinum Toxins: Pluses and Minuses

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Disclosure Information

• In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Purpose

• Discuss FDA-approved botulinum toxin preparations.
• Compare the available toxins.
• Pluses and minuses, side effects.
• Other considerations.
Introduction

• There are seven known botulinum neurotoxins (BoNT A-G).
  • Note: BoNT-D does not affect humans.
• Only two are FDA-approved for use in humans (BoNT-A and BoNT-B).
Introduction

- BoNT appears to have an affinity for hyperactive nerve terminals.
- In general, after injection:
  - Paresis in 2-5 days.
  - Maximum effect in 5-6 weeks.
  - Duration 2-5 months.
  - NB: Varies among formulations.
- Recovery from BoNT occurs in two stages:
  - Neuronal “sprouts” form that allow for neuronal function (minor effect).
  - Recovery of the original terminals and regression of the sprouts (major effect).

Botulinum Toxin

- The heavy and light chains are attached by a very fragile disulfide bond that is crucial to toxin efficacy.
- This bond is susceptible to environmental factors (temperature, etc).

**Figure 1** Botulinum neurotoxin consists of two amino acid chains connected by a disulfide bridge: a heavy amino acid chain with a molecular weight of 100 kDa and a light amino acid chain with a molecular weight of 50 kDa.
NORMAL NERVE-MUSCLE JUNCTION

Acetylcholine release

“HYPERACTIVE” NERVE TERMINAL

BoNT ENTERING NERVE

BoNT ATTACHMENT TO NERVE ENDING

Xeomin® entering the nerve ending

Acetylcholine release

BoNT ENTERING NERVE

Xeomin® working in the nerve to block acetylcholine release

BoNT BLOCKING ACH RELEASE

NERVE “SPROUTS” FORMING

Muscle

Sprouts
Variables Among Toxins

• Composition:
  • Toxin complex size.
  • Molecular weight.
  • Chemical properties.
  • Protein load (toxin + nontoxic accessory proteins).
  • “Excipients” (other stuff in the bottle):
    • Sucrose, lactose, gelatin, serum albumin, dextran.
    • Buffering systems.
  • Biologic properties.
    • Includes risk of antigenicity.

• Preparation:
  • Amount of neurotoxin (units).
  • pH
  • Storage before and after reconstitution.
  • Indications.
  • Geographic distribution.
  • Insurance coverage.

Other Considerations

• Anatomy:
  • Specific muscle activity pattern.
  • Muscle architecture.
  • Thickness of epidermis and skin.
  • Fascial planes.
  • Eyelid anatomic planes.
  • AGE!

• Injection techniques:
  • Dilutions/doses.
  • Volumes of injection.
  • Depth.
  • Number.
  • Pattern.

• Direct and indirect effects:
  • Direct: Neuromuscular junction, muscle atrophy.
  • Indirect: Retroaxonal transport into the central nervous system (e.g. migraines).*

*NB: There has NEVER been a report of any deleterious CNS symptoms from BoNT injection. There is no evidence that BoNT is found in the bloodstream after usual injection doses for BEB or HFS.
Two Simple Rules

• Higher doses of BoNT result in higher efficacy _BUT_ also result in higher “adverse events” (e.g. droopy eyelid, double vision, lagophthalmos, dry eye).

• Higher volumes of BoNT at each site result in more diffusion, with higher adverse events.

• The usual algorithm physicians use is:
  • Start at a lower dose and then increase as needed.
  • Use smallest volume (0.1cc) at each site.

# The Toxins

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade name (USA)</th>
<th>Manufacturer</th>
<th>FDA Approval</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Botox</td>
<td>Allergan, USA</td>
<td>1989</td>
<td>2-8°C</td>
</tr>
<tr>
<td>BobotulinumtoxinA</td>
<td>Dysport</td>
<td>Ipsen, France</td>
<td>2009</td>
<td>2-8°C</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Xeomin</td>
<td>Merz, Germany</td>
<td>2018</td>
<td>25°C (room temperature)</td>
</tr>
<tr>
<td>RimabotulinumtoxinB*</td>
<td>Myobloc</td>
<td>Solstice, USA</td>
<td>2019</td>
<td>2-8°C</td>
</tr>
</tbody>
</table>

*Higher incidence of autonomic side effects. Not often used for motor dystonias (BEB, HFS).
The Toxins: General Information

- All supplied in powder form.
- All need to be reconstituted with saline.
- Debate on preservative-free vs preserved saline:
  - No decrease in efficacy with preserved saline.
  - Preserved saline injections are less painful.
  - Most physicians use preserved saline.
- Shaking the bottle does NOT affect potency.
- Botox maintains potency for up to 2-6 weeks after reconstitution with refrigeration.
- Xeomin maintains potency for at least 7 days at room temperature.
• QUICK FACT: All three BoNT preparations (Botox, Xeomin, Dysport) are effective.

• The debate is really about conversion factors between BoNTs.

• Objective: Different number of molecules in “one unit” in each preparation.

• Subjective:
  • Efficacy and comparisons between BoNTs are difficult because of inherent subjectivity.
  • Most studies depend on a variety of “scoring scales”
What Does “One Unit” Mean?

• It is NOT based on a defined number of BoNT molecules per volume.
• 1 unit of BoNT = the dose needed to kill 50% of group of female Swiss-Webster mice after intraperitoneal injection.
• Newer method uses “cell-based potency assay”:
  • Now used by essentially all manufacturers and Swiss-Webster mice are much happier.
How Do You Rate the Toxins?

• “BEB Rating Scales”:
  • Clinical (doctors): Jankovic.
  • Activities of daily living (patients): BSDI.
  • Global activity: Secondary outcomes.

Easy Rule

- Botox:Xeomin – 1:1-1.2
  - Verified by numerous studies.

Scaglione F. Toxins (Basel) 2016;865.
More Complicated

- Botox/Xeomin:Dysport = 1:3-4 *BUT*
  - Ranges from 1:1-11.
  - Dysport may also have a wider “spread” than Botox or Xeomin.
- Botox:Myobloc = 1:24-100.
- General rule: It’s easier to switch between Botox and Xeomin than Dysport. Don’t use Myobloc.
  - Underdose.
  - Overdose.
  - Adverse events.

Scaglione F. Toxins (Basel) 2016;865.
Where You Are Injected Matters

ORBITAL ORBICULARIS
Where You Are Injected Matters

86% effective

96% effective, longer duration, fewer AEs.

How Old You Are Matters

• Older patients (>65yrs) required less BoNT than younger patients.
• Probably due to loss of muscle mass with age.
• Less muscle mass = Less BoNT needed.

# Adverse Events

## Table 2. Summary of Adverse Events Reported*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Botox (%)</th>
<th>Dysport ‡ (%)</th>
<th>Xeomin (%)</th>
<th>Meditoxin (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>4.5—29.4²,⁶,¹⁷,²³,³³,³⁴</td>
<td>13—58²²</td>
<td>6.1—18.9⁶,⁴⁴,⁴⁵</td>
<td>6.4³³</td>
<td>5.9⁴⁵</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0—8.6²,¹⁷,²³</td>
<td>10—16²²</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Facial weakness ‡</td>
<td>3—11¹⁷,²³</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>8.6—22.6²,⁴⁴</td>
<td>NR</td>
<td>2.7⁴⁵—27.3³⁴⁴</td>
<td>NR</td>
<td>2.9⁴⁵</td>
</tr>
<tr>
<td>Dry eye/eye burning</td>
<td>0—2.7²,⁶,³³</td>
<td>3²²</td>
<td>0.7—18.9⁶,⁴⁴,⁴⁵</td>
<td>7.6³³</td>
<td>11.8³⁴⁵</td>
</tr>
<tr>
<td>Mouth droop</td>
<td>1.7²</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Photophobia</td>
<td>0—3.4²,⁶</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0—3.2²,⁶</td>
<td>23—42²²</td>
<td>1.4—5.4⁴⁵</td>
<td>NR</td>
<td>5.9⁴⁵</td>
</tr>
<tr>
<td>Epiphora</td>
<td>0—0.6²,²³</td>
<td>6—17²²</td>
<td>2.7⁴⁵</td>
<td>NR</td>
<td>2.9⁴⁵</td>
</tr>
</tbody>
</table>

NR = not recorded.

*An additional 24 patients who received onabotulinumtoxinA (oBTX-A) for treatment of entropion were not included in this review.

†Data from Truong et al²² are listed as a range of dose-related adverse events.

‡In patients with hemifacial spasm.

Ptosis
Worsening Dry Eye Symptoms

- Lagophthalmos.
- Incomplete blink.
How About “Antigenicity”? 

• All BoNTs contain nonhuman complexing proteins.
• These may behave like antigens and provoke a antibody response by the body’s immune system, either directly against the BoNT (“neutralizing”) or one of the other proteins (“nonneutralizing”) or both.
• May increase with repeated injections or with more frequent injections (<2 months apart).
• A much bigger concern when large volumes of BoNT are injected (torticollis vs BEB/HFS).
Summary

- All 3 BoNT are effective in BEB/HFS.
- Conversion is much easier with Botox and Xeomin than with Dysport.
- Other considerations:
  - Dose, dilution, frequency.
  - Location on lids/face.
  - Age.