 Advances in the Use of Botulinum Toxin for Neurogenic Bladders

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Disclosures

• Allergan: Consultant and Speaker
• Medtronics: Consultant and Speaker
Disclosures Continued

This continuing education activity is managed and accredited by Professional Education Services Group.
Learning Objectives

At the conclusion of this activity, the participant will be able to:

• A. Discuss the biology, pharmacology, and safety of BoNT in the lower urinary tract.

• B. Understand application of BoNT in the bladder and urethra of patients with neurogenic bladder

• C. Explain the latest clinical series and techniques of BoNT injection
Neurogenic Bladder

Spinal cord conditions (with or without detrusor sphincter dyssynergia)
- Spinal cord injury
- Multiple sclerosis
- Transverse myelitis
- Tropical spastic paraparesis
- Myelomeningocele
- Tethered cord syndrome and short filum terminale
- Ankylosing spondylosis and disc disease
- Acquired immune deficiency syndrome

Supraspinal conditions (without detrusor sphincter dyssynergia)
- Cerebrovascular accident
- Cerebral palsy
- Parkinson’s disease
- Dementia
- Neoplasm
- Cerebellar ataxia
Case Study

• Chief Complaint: Incontinence between self-catheterization
  – 33 year old female with SCI on oxybutynin extended release 30mg/day yet is incontinent and considering bladder augmentation.
  – Suffered T8 SCI after an auto accident
Case Study (More History)

- Bladder symptoms interfere with lifestyle
- Leaks during intercourse
- Fluid restriction limits social activities
- Side effects with anticholinergics
Urodynamics on Oxybutynin ER 30mg/day
Case Study (cont.d)

• Ideal candidate for bladder augmentation?
  – Pt engaged to be married
  – Concerned over bladder reconstruction affects

• Other option?
  – Botulinum toxin A
Case Study: Post-injection
Botox Approved, Again, This Time for Urinary Incontinence

By MEREDITH MELNICK Friday, August 26, 2011 | 54 Comments
BoNT: What is It?
Botulinum Toxin History

C. botulinum
1700’s-1800’s

900 kD Complex

E. Schantz
1944-6 Crystalline

Herman Sommer
1920s Purified

E. van Ermengem (1895)

BOTOX® (Vistabel)
Cosmetic Allergan 2002

2004 Axillary HH BoNT/A Allergan

2011 Urologic Allergan

2011 Reformation 25 to 5ng/100u

Allergan BOTOX® 1989

Strabismus

Before

After

1968

1970’s -80’s

Allergan BOTOX®

Blepharospasm

C. botulinum
1700’s-1800’s

900 kD Complex

E. Schantz
1944-6 Crystalline

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2011 Reformation 25 to 5ng/100u

Allergan BOTOX® 1989

Strabismus

Before

After
# Commercial BoNT’s

<table>
<thead>
<tr>
<th>Serotype</th>
<th>A</th>
<th>A</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>OnabotulinumtoxinA</td>
<td>AbobotulinumtoxinA</td>
<td>IncobotulinumtoxinA</td>
<td>RimabotulinumtoxinB</td>
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<tr>
<td>Brand name</td>
<td>Botox</td>
<td>Dysport</td>
<td>Xeomin</td>
<td>Myobloc/neurobloc(^a)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Allergan Inc (United States)</td>
<td>Ipsen (France)</td>
<td>Merz Pharmaceuticals GmbH (Germany)</td>
<td>US WorldMeds (United States)</td>
</tr>
<tr>
<td>Packaging, U/vial</td>
<td>100</td>
<td>500</td>
<td>100</td>
<td>2,500, 5,000, or 10,000</td>
</tr>
<tr>
<td>Preparation</td>
<td>Dry: vacuum dried</td>
<td>Dry: lyophilized</td>
<td>Dry: lyophilized</td>
<td>Solution (5,000 U/mL)</td>
</tr>
<tr>
<td>Storage of packaged product</td>
<td>−5°C or 2–8°C</td>
<td>Room temperature</td>
<td>Room temperature</td>
<td>2–8°C</td>
</tr>
<tr>
<td>Storage after reconstitution</td>
<td>2–8°C for 24 h</td>
<td>2–8°C for several hours</td>
<td>2–8°C for 24 h</td>
<td>For a few hours</td>
</tr>
<tr>
<td>Specific activity, U/ng</td>
<td>20</td>
<td>40</td>
<td>167</td>
<td>75–125</td>
</tr>
</tbody>
</table>

\(^a\)Myobloc is the brand name in the United States, Canada, and Korea. Neurobloc is the brand name in the European Union, Iceland, and Norway
Synaptic Transmitter Release
BoNT-A: MOA
BoNT: What Are the Results?
Reduction in number of UI episodes compared to baseline (%)

- **300U BTX**
- **200U BTX**
- **Placebo**

* *p < 0.05 for differences between BoNT-A group and placebo*

† † *p < 0.05 for differences within-group changes from baseline*
Randomized Trial

![Mean increase in MCC from baseline](chart)

*\(p < 0.05\) for within-group changes from baseline

\(\dagger p < 0.05\) for pairwise contrasts between BoNT-A groups versus placebo
Phase 3 OnabotulinumtoxinA Trial

Dysport BoNT-A Results

Ehren et al, Scan J Urol & Neph 2007
BoNT-A: Repeat Injections

Grosse et al, Eur Urol 2005
Dysport BoNT-A Repeated Injections

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
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</thead>
<tbody>
<tr>
<td>MCBC, ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>226.04</td>
<td>407.69</td>
<td>405.9</td>
<td>400.4</td>
<td>412.4</td>
<td>405.6</td>
<td>393</td>
<td>380</td>
</tr>
<tr>
<td>Median</td>
<td>230</td>
<td>409</td>
<td>410</td>
<td>400</td>
<td>412</td>
<td>400</td>
<td>395</td>
<td>380</td>
</tr>
<tr>
<td>± SD</td>
<td>22</td>
<td>26.8</td>
<td>37.5</td>
<td>34.4</td>
<td>21.0</td>
<td>35.6</td>
<td>33.6</td>
<td>26.0</td>
</tr>
<tr>
<td>CI</td>
<td>222.9/229.1</td>
<td>403.7/411.2</td>
<td>400.0/411.7</td>
<td>393.1/407.6</td>
<td>387.7/407.6</td>
<td>395.3/415.8</td>
<td>371.7/414.4</td>
<td>352.6/407.3</td>
</tr>
<tr>
<td>RV, ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>201.4</td>
<td>300.4</td>
<td>295.3</td>
<td>300.2</td>
<td>299.5</td>
<td>297.3</td>
<td>302.8</td>
<td>297</td>
</tr>
<tr>
<td>Median</td>
<td>219</td>
<td>320</td>
<td>317</td>
<td>320</td>
<td>311</td>
<td>311</td>
<td>302.5</td>
<td>296</td>
</tr>
<tr>
<td>± SD</td>
<td>48.3</td>
<td>56.8</td>
<td>56.5</td>
<td>55.5</td>
<td>49.8</td>
<td>50.2</td>
<td>20</td>
<td>11.9</td>
</tr>
<tr>
<td>CI</td>
<td>194.7/208.2</td>
<td>292.4/308.3</td>
<td>286.4/304.1</td>
<td>288.5/311.8</td>
<td>285.5/313.5</td>
<td>282.8/311.7</td>
<td>290.1/315.5</td>
<td>284.4/309.5</td>
</tr>
<tr>
<td>BC, ml/cm H₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.7</td>
<td>41.3</td>
<td>40.8</td>
<td>42.4</td>
<td>40</td>
<td>40.2</td>
<td>42.5</td>
<td>41</td>
</tr>
<tr>
<td>Median</td>
<td>26</td>
<td>42</td>
<td>42</td>
<td>43</td>
<td>41</td>
<td>41</td>
<td>40</td>
<td>41</td>
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<tr>
<td>± SD</td>
<td>4.8</td>
<td>6.2</td>
<td>6.6</td>
<td>6.5</td>
<td>7.2</td>
<td>8.2</td>
<td>5.8</td>
<td>2.3</td>
</tr>
<tr>
<td>CI</td>
<td>26/27.3</td>
<td>40.4/42.2</td>
<td>39.8/41.9</td>
<td>41.1/43.7</td>
<td>37.9/42.0</td>
<td>37.9/42.6</td>
<td>38.5/46.5</td>
<td>38.5/43.4</td>
</tr>
</tbody>
</table>

MCBC = maximum cystometric bladder capacity; RV = reflex volume; BC = bladder compliance; SD = standard deviation; CI = confidence interval.

All variables improved significantly after treatment in comparison with baseline values (ANOVA test p < 0.001). No statistically significant changes in the improvement of urodynamic parameters were found after each retreatment and in relation to the Dysport dose (ANOVA test p > 0.05 after each retreatment).
BoNT-A for Poor Compliance

Klaphajone et al, Arch Phys Med Rehab 2005
BoNT-A for Low Compliance
# Histologic Changes After BoNT-A Injection

Comperat et al, Eur Urol 2006

<table>
<thead>
<tr>
<th></th>
<th>Inflammation</th>
<th>Oedema</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With botulinum toxin (n = 22)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>11 (50%)</td>
<td>4 (18%)</td>
<td>13 (59%)</td>
</tr>
<tr>
<td>++</td>
<td>11 (50%)</td>
<td>18 (82%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td><strong>No botulinum toxin (n = 23)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.09</td>
<td>p = 0.78</td>
<td>p = 0.00073</td>
</tr>
<tr>
<td>+</td>
<td>17 (74%)</td>
<td>6 (26%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>++</td>
<td>6 (26%)</td>
<td>17 (74%)</td>
<td>22 (96%)</td>
</tr>
</tbody>
</table>

+ weak; ++ strong.

<table>
<thead>
<tr>
<th></th>
<th>Inflammation</th>
<th>Oedema</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Botulinum toxin responder (n = 13)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>7 (54%)</td>
<td>3 (23%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>++</td>
<td>6 (46%)</td>
<td>10 (77%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td><strong>Botulinum toxin non-responder (n = 9)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 1</td>
<td>p = 0.1</td>
<td>p = 0.1</td>
</tr>
<tr>
<td>+</td>
<td>4 (45%)</td>
<td>1 (11%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>++</td>
<td>5 (55%)</td>
<td>8 (88%)</td>
<td>6 (66%)</td>
</tr>
</tbody>
</table>

+ weak; ++ strong.
BoNT: How to Do It?
Principles of Treatment Plan for BoNT Therapy

- **Diagnosis and baseline assessment**
- **Specific symptoms**
- **Co-morbid conditions**
- **Patient expectations**
  - Patient needs and goals
  - Reduce or discontinue use of acute pain medications
  - Decreased intensity of symptoms and/or pain
  - Improved function and reduced dysfunction
  - Increased intensity of physical therapy and rehabilitation
- **Patient education**
  - Goals of therapy
  - Purpose of each component of the treatment plan
  - Importance of follow-up evaluation and care
  - Potential side effects
Guidelines for BoNT Treatment

- Consider if BoNT therapy is appropriate for the patient and condition being treated
- Determine which muscles need to be injected
- Use the smallest effective total dose and volume
- Determine the appropriate dosage and the number and volume of injections per session
- Use appropriate techniques to achieve precise injection and reduce the risk of complications
- Follow-up with the patient to assess efficacy, safety, and satisfaction with treatment
- Record details of treatment (dose, volume, sites) and patient response to treatment to guide future injections
- Administer subsequent injection with as long an inter dose interval as possible
- Reassess the treatment regimen and the patient’s response
Injection Technique
Bladder Injection Techniques
How Deep to Inject?
BoNT: What are Risks?
Risks: Black Box Warning

BOTOX® and BOTOX® Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX® or BOTOX® Cosmetic:

- **Problems swallowing, speaking, or breathing.** These problems can happen hours to weeks after an injection of BOTOX® or BOTOX® Cosmetic usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with BOTOX® or BOTOX® Cosmetic.

- **Swallowing problems may last for several months.** People who already have swallowing or breathing problems before receiving BOTOX® or BOTOX® Cosmetic have the highest risk of getting these problems.

- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include: loss of strength and muscle weakness all over the body, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing.
Risks

- Incomplete emptying/Need for CIC
  - Dose dependent
  - 0-33%/6-88%

- Urinary Tract Infection
  - 2-32% (24% in Phase 3 trial)
  - Symptomatic UTI’s reduced by 88% (Game et al 2008)
Risk: Antibody Formation

• Primary versus Secondary
• New OnabotulinumtoxinA formulation: risk reduced from 9.5% to 0.5%
• Case reports of elevated ab’s and failure to respond following bladder injection
• Drug holiday recommended: 6-12 months
  – Alternatively try different isotype (BoNT-B)
Conclusions

• Effective for Neurogenic induced urinary incontinence
• Reversible yet durable
• Questions
  – Injection technique
  – Need for continued anticholinergics
  – Coordinating injections with multiple providers
  – Cost-effectiveness
    • Will it ever be primary therapy?
Obtaining CME Credit

• If you would like to receive CME credit for this activity, please visit:

  http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.