OBJECTIONS

• Review the pharmacology of botulinum toxin
• Review mode of action of botulinum toxin
• Be aware of diffusion characteristics of various formulations of botulinum toxin
• Know strategies to evaluate the patient that requires botulinum toxin or other form of spasmolysis/neurolysis.
• Yellow Fever
• Tuberculosis (consumption)
• Diphtheria, rabies, plague
• Skin alterations after burning
• Ulcers from malignant diseases
• Hypersecretion of body fluids
Urinary Incontinence due to Neurologic Detrusor Overactivity

BOTOX® for injection is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Cervical Dystonia
Upper Limb Spasticity
Chronic Migraine
Blepharospasm and Strabismus
Primary Axillary Hyperhidrosis

Therapeutic Indications:1

Timeline of FDA Approvals


Warning: See Important Safety Information on slides 4-6 and 36-42.
Botulinum Neurotoxin Serotypes Differ by Weight and Composition

- Type G forms a 500 KD complex
- 300 KD complex
- Types E, F, and HA-negative D, form only the 500 KD and 300 KD complexes
- Types A, B, C, HA (hemagglutinin) positive D, only one to form the 900 KD complex
- Type A
Botulinum Neurotoxin Type A (BoNT-A)

Structure & Function

Heavy Chain delivery/binding

Light Chain (50 kD)

Heavy Chain (100 kD)

BoNT-A inhibits calcium-dependent vesicle exocytosis.

Efficacy

Activation

Nicking

Coom

NH₂

Coom

NH₂

Heavy Chain

Light Chain

Coom

NH₂

Coom

NH₂
BOTOX®

Normal process of acetylcholine release

No BOTOX® present

BOTOX® attached

Acetylcholine vesicle unable to bind

Cleaved SNAP-25

Mechanism of action of onabotulinumtoxinA allows for:

- Targeted reduction of hypertonicity
- Transient and reversible effect


BOTOX® neurotoxin directly acts on motor neurons to reduce muscle activity.
Comparisons

Similarities & Differences Among Serotypes

**Similarities:**
- Clostridial neurotoxin
- Bi-chain structure
- Inhibition of acetylcholine release
- Production of flaccid paralysis which is reversible

**Differences:**
- Antigenically distinct
- Distinct binding sites
- Distinct enzymatic actions
- Pharmacologic differences
- Different species specificity
- Clostridial neurotoxin

### Characteristics of Approved BNT Preparations and NT 201

<table>
<thead>
<tr>
<th>Preparation</th>
<th>pH after reconstitution</th>
<th>Biological activity</th>
<th>Specific biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>7.4</td>
<td>100 MU-A/vial</td>
<td>500 MU-I/vial</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>7.4</td>
<td>60 MU-EV/ngBNT</td>
<td>100 MU-EV/ngBNT</td>
</tr>
<tr>
<td>RimabotulinumtoxinB</td>
<td>7.4</td>
<td>5 MU-EV/ngBNT</td>
<td>167 MU-EV/ngBNT</td>
</tr>
<tr>
<td>NT 201</td>
<td>7.4 (pH-reduced)</td>
<td>100 MU-M/vial</td>
<td>500 MU-EV/ngBNT</td>
</tr>
</tbody>
</table>

### Purification Process

<table>
<thead>
<tr>
<th>Preparation</th>
<th>SNAP25</th>
<th>VAMP</th>
<th>SNAP25</th>
<th>VAMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Hall A</td>
<td>Bean B</td>
<td>Hall A</td>
<td>Bean B</td>
</tr>
</tbody>
</table>

### Stabilization

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Vacuum drying</th>
<th>Freeze-drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RimabotulinumtoxinB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Biological activity**

1. **MU-A**: mouse unit in the Allergan mouse lethality assay; 1 MU-A = 100 MU-M
2. **MU-I**: mouse unit in the Ipsen lethality assay; 1 MU-I = 40 MU-E
3. **MU-E**: mouse unit in the Solstice mouse lethality assay; 1 MU-E = 1 MU-M

**SNARE target**

1. **SNAP25**
2. **VAMP**
3. **SNARE target**
4. **VAMP**

**Storage**

1. **Below 8°C**
2. **Below 4°C**
3. **Below 8°C**
4. **Below 4°C**

**Excipients**

1. Human serum albumin 125 µg/vial
2. Lactose 2500 µg/vial
3. Sucrose 5 mg/vial
4. Not reported

**Adapted from:** Dressler D, Benecke R. Disabil and Rehab 2007;29(3):1761-1768.
Toxin Dose, U/kg

Mean Peak DAS Response

BoNT-A
ED50 (4.4)
LD50 (70)
Diffusion (30)

BoNT-A (Allergan): Summary of Efficacy, Distal Atrophy and Systemic Safety
Aoki 2003; AAN Poster # P03.088
BoNT-A (Allergan) vs. BoNT-A (Ipsen): Comparison of Efficacy, Diffusion and Safety

Aoki, 2003 AAN Poster # P03.088

BoNT-A (Ipsen) Lost From Injected Site Before Reaching Maximum Local Effect

BoNT-B (Elan) Lost From Injected Site Before Reaching Maximum Local Effect

Comparison of Toxin Dose (U/kg) vs. Mean Peak DAS Response

BoNT-A (Allergan) Local Effect

BoNT-B (Elan) Local Effect

Toxin Dose, U/kg

Mean Peak DAS Response
BoNT-A (Allergan)

Diffusion

BoNT-A (Ipsen)

Diffusion

Response

R

Dose

Composition of Botulinum Toxin Components

Adapted from Dressler D. Der Nervenarzt. 2006;77(8):912-921
FDA BLACK BOX WARNING

FDA ALERT [08/2009]: As announced on April 30, 2009, based on a safety evaluation of the botulinum toxin products, FDA has concluded that the prescribing information for OnabotulinumtoxinA (marketed as Botox/Botox Cosmetic) and RimabotulinumtoxinB (marketed as Myobloc) must be updated to ensure their continued safe use. On July 31, 2009, FDA, under the authorities granted by the Food and Drug Administration Amendments Act (FDAAA) of 2007, approved the following revisions to the prescribing information of Botox/Botox Cosmetic and Myobloc:


FDA ALERT

• Boxed warning
• Highlight the possibility of life threatening consequences from distant spread of BTX after local injection
• Risk assessment and mitigation strategy (REMS)
• Change to the established drug names
• Reinforce individual patient names
• Prevent medication errors
• Prevent medication errors
• Prevent medication errors

FDA ALERT
Considerations for Health Care Professionals

- Unexpected loss of strength/development of weakness
- Hoarseness or trouble talking (dysphonia)
- Loss of bladder control
- Difficulty breathing
- Difficulty swallowing
- Droopy eyelids
- Double vision
- Unusual eyelid or eyebrow drooping
- Unusual facial asymmetry
- Unusual neck swelling or drooping
- Unusual change in facial expression

The safe and effective use of BOTOX® depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX® must understand the relevant anatomy of the area involved and any alterations to the related neuromuscular and/or orbital anatomy or surgical procedures. An understanding of standard General Dosing Information

In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units in a 3 month interval. The safe and effective use of BOTOX® depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX® must understand the relevant anatomy of the area involved and any alterations to the related neuromuscular and/or orbital anatomy or surgical procedures. An understanding of standard General Dosing Information

In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units in a 3 month interval.
Spasticity
Definition of Spasticity

Adult Spasticity Overview

“Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggeration of tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome.”

— Lance, 1980

Upper Motor Neuron Syndrome

Positive Symptoms

• Spasticity
• Clonus
• Flexor/extensor spasm
• Hyper-reflexia
• Dystonia
• Rigidity

Negative Symptoms

• Decreased dexterity
• Weakness
• Paralysis
• Fatigability
• Slowness of movement
Etiologies

- Stroke
- Traumatic brain injury
- Multiple sclerosis
- Spinal cord injury
- Cerebral palsy
- Anoxia
- Neuropathic disease
- Multiple sclerosis
- Traumatic brain injury
- Stroke

Evaluation of the Spastic Patient

- Participation of patient/caregiver in
  - Life-style maintenance/improvement
  - Level of support
  - Performance with ADL
  - Assessment of spasticity

ADL=activities of daily living
Common Clinical Patterns: Lower Limbs

- Equinovarus
- Striatal Toe
- Extended Knee
- Adducted Thighs

Patient Evaluation (cont'd)

Therapist Feedback

- Valid assessment measures
- Provide consistency in outcome
- Use a fixed evaluation sequence - important to obtain unbiased results
- Standard and consistent technique is

Physical Examination

Limb Patterns

Common Clinical Patterns: Lower
MAKING DECISION: BOTULINUM TOXIN OR OTHER MODALITY?

TIBIAL NERVE BLOCK

EVALUATION

NERVE BLOCK
BEFORE LOCAL ANESTHETIC BLOCK

RESULT = ↑TONE AND CONTRACTURE

AFTER LOCAL ANESTHETIC BLOCK
Spinal Cord Injury

- Twenty-plus year old female
- Spastic paraparesis
- Spastic hip flexion contractures and dystonia
- Spastic knee flexion contractures and dystonia

Evaluate to determine management
MEDIAN NERVE BLOCK:

1% LIDOCAINE

SPASTIC TETRAPARESIS

SIX % PHENOL

EVALUATION

But

1% LIDOCAINE

NERVE BLOCK
SCiATiC NERVE

AfTER Bi洛克K

T. L.
STROKE

TOE HYPERFLEXION

AFTER BOTULINUM TOXIN
EMG NEEDLE PLACEMENT

EMG of the Tongue

OROMANDIBULAR & LINGUAL DYSFUNCTION

TOE HYPEREXTENSION

EMG NEEDLE PLACEMENT
SAMPLE EMG NEEDLE PLACEMENT

CERVICAL DYSTONIA

Splenius Capitis

R. H.
SUMMARY

• Botulinum toxins inhibit release of acetylcholine at the neuromuscular junction
• Botulinum toxin: Useful tool for Rx of focal spasticity
• Cases must be well selected
• EDX skills helpful in choosing appropriate procedures and muscles for injection
• Set clear, attainable treatment goals