Botulinum Toxins as Neuromodulators in Chronic Pain Management

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Learning Objectives

- Review the proven and proposed mechanisms of action of botulinum toxins (BTX)
- Contrast the different botulinum toxin products commercially available in the US
- Describe the emerging role and novel indications for the use of botulinum toxins in pain management
Disclosures

- Consultant/Speakers Bureau: Allergan, Ipsen

Neurotoxins as Neuromodulators

- Emerging role of botulinum neurotoxins in the management of complex/intractable chronic pain syndromes, including neuropathic pain more so than those believed to be of muscle overactivity etiology
- Chemical neuromodulation in neurogenic inflammation
- More players: wider and more promising horizon and greater availability but greater potential for errors and problems…..
The Current Playing Field….

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Forms</th>
<th>Process</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA (Botox® —Allergan, Inc.)</td>
<td>A</td>
<td>100U, 200U, 50U</td>
<td>Vacuum-drying (NSS/albumin)</td>
<td>Strab, CD, BS, CN7 d/o, AH, Cosm, U&amp;LLS, CM, OAB/DH</td>
</tr>
<tr>
<td>AbobotulinumtoxinA (Dysport™—Ipsen, Ltd)</td>
<td>A</td>
<td>300U, 500U</td>
<td>Lyophilized (fermentat/precipit/dialysis/chromatography)</td>
<td>CD, Cosm, U&amp;LLS; LLS (child)</td>
</tr>
<tr>
<td>IncobotulinumtoxinA (Xeomin®—Merz)</td>
<td>A</td>
<td>50U, 100U</td>
<td>Lyophilized Albumin, sucrose</td>
<td>CD, BS, Cosm, ULS</td>
</tr>
<tr>
<td>RimabotulinumtoxinB (Myobloc®—Solstice)</td>
<td>B</td>
<td>2.5k U, 5k U, 10k U</td>
<td>Ferm/precipitation/chromatography</td>
<td>CD</td>
</tr>
</tbody>
</table>
Botulinum Toxins

- BOXED WARNING
  - May spread to areas distant to site of injection producing symptoms consistent with botulinum toxin effects
  - Risk probably greatest in children treated for spasticity

- *** Units not interchangeable; No conversion factors recommended
- *** None approved for use in children

BTX Uses

- Dystonias
- Spasticity
- Tremors
- Cosmetic/wound healing
- Blpharospasm/CN VII disorders
- GI: achalasia, anismus, obesity
- GU: neurogenic bladder, vaginismus, BPH
- Pain management….
BTX in Pain Management

- Myofascial pain syndromes
  - Upper back/neck
  - TOS
  - Piriformis syndrome
- CLBP
- Facial and head pain
  (migraines, occipital neuralgia, TN, atypical facial pain, TMJ pain)
- Intractable joint pain
- Lateral epicondylitis/plantar fasciitis
- Focal/generalized neuropathies
- Vascular pain (Raynaud's)
- Postradiation fibrosis pain

Analgesia With Botulinum Toxins

*Initial thinking on BTX-A pain relief came from CD literature*

- 1980s: Clinical observations after BTX-A injections for cervical dystonia (CD)
  - Benefits on pain occurred sooner and outlasted posture, suggesting a dual effect
    (Brin, et al. 1986; Jankovic, et al. 1987)
Antinociception Observations Using Botox®

- Inhibition of release of AcH and sP (not NE) in rabbits (iris)¹
- Inhibition of release of AcH and sP (vesicle-dependent exocytosis) in cultured DRG neurons induced by capsaicin²
- sP inhibition (vesicle fusion inhibition) in the embryonic rat DRG model³


Antinociception Observations Using Botox (cont’d)

- Dose dependent inhibition of CGRP in TG nerve of rats¹
- Block release of glutamate induced by formalin and decreased activity at the WDR neuron upon stimulation (second pain)²
- Fos, a product of c-fos gene that is expressed with neuronal stimuli, was prevented³

¹ Durham P. Cephalgia 2003; 23(7): 690
² Aoki KR. Headache 2003; 43(1): S9-15
³ Cui ML. Pain 2004; 107(1-2): 125-33
Peripheral Sensitization Leads to Central Sensitization

Peripheral Stimulation → Release of Glutamate and Peptides → Antidromic Activation → Central Sensitization

Release of glutamate, substance P, CGRP → Increased afferent signals → Additional Activation

Botulinum Toxin Prevents Peripheral Sensitization (Direct) and Central Sensitization (Indirect)

Peripheral Stimulation → Release of Glutamate and Peptides → Antidromic Activation → Additional Activation

Prevents:
- Release of glutamate, CGRP, SP
- Peripheral sensitization
- Formalin phase II pain
- TRPV1 expression

Indirectly Prevents:
- Central sensitization
- c-Fos expression
- Receptive field expansion
- Allodynia

Clinical relevance of these preclinical results remain to be established
Current Theory: Regulated Exocytosis

The **common link** between both effects

BTX-A cleaves SNAP-25, inhibiting exocytosis of co-located substances
• BTX-A inhibits ACh release
• BTX-A inhibits vesicular release of neuropeptides

Clinical Applications
Headaches

- FDA-approved for chronic migraine prophylaxis
- Not tension-type HAs
- Mechanism—proposed to be related to action at the TG nucleus
- Still difficult to predict responders
  - Concept of “exploding” vs “imploding”
  - Ocular migraine/menstrual migraine

IHS Classification

- A1: Migraine
  - A1.1. Migraine w/o Aura
    - Pure menstrual
    - Menstrually-related
    - Nonmenstrual
  - A1.2. Migraine w/ Aura
  - A1.5. Chronic Migraine
Chronic Migraine Headache

BTX in MPS: Theories

- Reduction of intrafusal muscle spindle discharges
- Changes in sympathetic transmission
- Reduction of the inhibitory effect of Renshaw cells on the Ia inhibitory interneurons
- Reduction in muscle spasm
- Analgesic effects of BTX
Myofascial Pain Syndromes

- Most consistent and better studied responses in clinical practice have been in the cervicothoracic region.\(^1\)
- Compartment techniques vs trigger point approach—midbelly of muscle, not tender areas (TPIs); may be targeting motor points.\(^2\)
- Follow the pain but beware of pain referral patterns.\(^3\)

\(^3\) Reilich J Neurol 2004; 251(Suppl 1): I36-I38

Forward-Head Syndrome

- Cervical protraction, capital extension with shortened cervical paraspinals, elevated and shortened upper trapezius and levator scapula, scalene and pectoral shortening
- Eccentric lengthening of the rhomboids and middle trapezius
- Scapular protraction/internal rotation of the shoulder girdles
Forward-Head Syndrome (cont’d)

Thoracic Outlet Syndrome

- Not a common condition
- High index of suspicion needed and special techniques\(^1\)
- Target scalenes, particularly, anterior/middle\(^2,3\)
- Technically difficult injection: risk of dysphagia and neurovascular injury

\(^1\) Cuevas-Trisan R, Cruz-Jimenez M. Am J Phys Med Rehabil. 2003; 82(9) 712-715
\(^3\) Odderson I. Arch Phys Med Rehabil 2008
Scalene Contribution

- Part of df/dx of “sciatica”
- Seen often postspinal surgery, or prompting it
- Commonly postural; less common compressive
- 100 units of Botox® IM\(^1,2\)
- Must use targeting techniques (EMG/fluoro)
- A more effective than B with less S/Es\(^3\)

Piriformis Syndrome (cont’d)

- RCT – double blind
- N = 31  CLBP
  (>6 months; lateralized)
- 15 received 200 U of Botox®
  (40 units/site – 0.4 cc);
  16 received NSS
- Unilateral paraspinals
  (5 levels – L1-L5 or L2-S1)


Low Back Pain

- RCT – double blind
- N = 31  CLBP
  (>6 months; lateralized)
- 15 received 200 U of Botox®
  (40 units/site – 0.4 cc);
  16 received NSS
- Unilateral paraspinals
  (5 levels – L1-L5 or L2-S1)

Postlaminectomy Syndrome

- 26 consecutive patients with persistent somatic and radicular pain, who had failed multiple other treatments
- Treated with repeated BTX-A injections every 3 months for over 3 years
- Significant pain reduction and functional improvement sustained
- Subgroup of 10 patients most benefited: postlaminectomy patients with cutaneous allodynia as a complication


Novel Uses
Intractable Joint Pain

- Degenerative joint disease
- Limited/emerging evidence¹
- Working theory: inhibition of low-grade inflammatory mediators
- Role of IL-1
  - Blocking of IL-1 receptor signaling complex²


BTX-A in Joint Pain

- Multiple retrospective / open label / small case series¹
- Various joints:
  - hip, knee, ankle, shoulder, zygapophyseal, sternoclavicular, sacroiliac
- Prospective RCT in Mod-Sev knee pain 2ary to OA²
- N = 23 per group; 100U IA Botox vs education
- Botox: superior providing pain relief and improved function short- (1 week) and long-term (6 months)

¹ Mahowald M, Singh J, Dykstra D. Neurotox Res 2006
BTX-A in Joint Pain (cont’d)

- Evidence remains inconsistent and controversial for the use of IA therapies for knee OA


Postarthroplasty Intractable Pain

- Of particular interest given lack of options
- Must r/o correctable causes: low grade infection, loosening, hardware failure
- 100 units intraarticular—strict sterile technique
- Main goal: opioid-sparing effect
- Personal experience: n = 8

Kamen ICoN 2006 Meeting Abstract, Hollywood, FL
Other Painful Syndromes

Lateral Epicondylitis

Wong¹: 60 U Dysport®
- RCT; N = 60 (30 placebo-saline/ 30 active), significant differences in pain reduction (66% in BTX group) at 4 & 12 weeks; no statistically significant difference in grip strength in 13% of BTX group

Hayton² - 50 U Botox®
- RCT; N = 40 (20 - placebo / 20 - active
  – IM 5cm distal to max point of tenderness
- At 3 months: no significant difference in grip strength, pain, and QOL

Plantar Fasciitis

- Babcock\(^1\): N = 43 feet (27 subjects); RCT (70U Botox vs NSS)
  - 40 U over medial tender aspect of heel
  - 30 U arch of foot at most tender area
  - Statistically-significant improvement at 3 and 8 weeks:
    - Maryland Foot Score / pain / pressure algometry
- Placzek\(^2\): N = 9; open label
  - 1 injection of 200U of Dysport subfascially into painful area
  - Improvements in rest and weight-bearing pain (up to 14 weeks)


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Facial Pain

- Atypical, TN, TMJ (including bruxism\(^1\)), etc
- Various studies
- Dose: highly variable; 20-150 U
- Injection site: variable; depends on painful area; SQ/intradermal\(^2,3\)
- Maintain cosmetic symmetry

2 Cuevas-Trisan R. AAPM Meeting 10/07, LV, NV
Occipital Neuralgia

- Retrospective series (N=6) severe occipital neuralgia
- Failed conservative and interventional therapies
- GON blocks using BTX-A 50U / side (100U if bilateral)
- Significant decreases in pain / improvement in Pain Disability Index (PDI) @ 4 wks in 5 patients
- Duration of the pain relief averaged 16.3±3.2 weeks (median 16 weeks)

Others

1 Kapural et al. AAPM meeting 2/07 New Orleans

Raynaud’s Syndrome

- Retrospective series (N=33) severe Raynaud's
- Failed conservative and interventional therapies; some amputations
- Technique using BTX-A 100U
- 85%: significant decreases in pain / improvement in perfusion
- Duration of relief averaged
- 16.3±3.2 wks (median 16 wks)

Raynaud’s Syndrome

Postradiation Fibrosis Pain

- Two publications on the use of toxins for management of symptoms associated with post-radiation fibrosis have reported a possible role yielding modest results$^{1,2}$
- Patient selection and dosing paradigms are yet to be determined
- Recent case report with remarkable results$^3$

$^1$ Stubblefield Arch Phys Med Rehabil 2008
$^3$ Cuevas-Trisan R. (Abst) PainWeek 9/13, LV, NV
Other Uses

- Stump / neuroma pain
- Intractable pes anserinus bursitis
- Other focal / generalized peripheral nerve injuries

Peripheral Neuropathies

- DPN\(^1,2\)
- Dysport 100 U intradermal vs saline; n=20/group
- Statistically significant decrease in neuropathic symptoms in Dysport group
- Botox 50 U intradermal vs saline; n = 18/group
- Statistically significant decrease in neuropathic symptoms in Botox group
- PN3
- Dysport up to 300 U vs Saline; n=34 vs 32/group x 2 (12 wks apart)
- Statistically significant decrease in neuropathic pain in Dysport group

Focal Neuropathies

- Focal neuropathy case – painful paresthesias/dysesthesias in distal leg
- Excellent relief with SQ injections to affected area

Current Clinical Trials

- Raynaud’s—Southern Illinois Univ, Emory, Johns Hopkins
- Skin injections for SCI-related pain—Mt. Sinai, NY
- Chronic neck and back pain—VA Connecticut
- Pelvic pain in endometriosis—NINDS (NIH)
- Shoulder & knee OA pain—Minneapolis VAMC
- Peripheral neuropathic pain / Painful diabetic neuropathy—Taipei Medical Center
- Cervicobrachial MPS—UCLA / TOS—University of British Columbia
- Neuroma pain—Southern Illinois Univ/Stanford
- LE CRPS—Stanford
- TKR pain—University of Minneapolis-completed
- Ganglion impar injections for proctalgia—Nantes University
- Psoriasis—University of Minnesota
- Peyronie’s disease, vaginismus, restless legs, alopecia aereata

Source: NIHclinicaltrials.gov
Thanks!