Botulinum Toxin: Applications in Urology
Dr. Lee Jonat, PGY-4
Department of Urologic Sciences
University of British Columbia

Outline
• Mechanism of Action
• Technical Considerations
• Adverse Events
• Neurogenic Detrusor Overactivity
• Idiopathic Overactive Bladder
• Other Uses in Urology
Botulinum toxin

- 1817: Kerner
- 1897: van Ermengem

FDA Indications

- Strabismus
- Blepharospasm and hemifacial spasm
- Cervical dystonia
- Moderate-to-severe frown lines between the eyebrows
- Primary axillary hyperhidrosis

no current urological indications
Acetylcholine Release at NMJ

Botulinum Toxin
Mechanism of Action
Secondary Pathways

- Inhibits release of substance P from afferent nerves
- Inhibits release of ATP from urothelial cells
- Down regulates expression of capsaicin receptors on afferent neurons within the bladder

Suggests that botulinum toxin works by both sensory and motor pathways

Types of Botulinum Toxin

- A (Botox, Dysport)
- B (Myobloc)
- 5 other serotypes
Technique and Dosage

- No standardized technique
- 10-30 sites
- General or local anaesthesia
- Pre-operative antibiotics
- 100-200 units for idiopathic OAB
- 200-300 units for neurogenic DO

Tips and Tricks

- Don’t shake the vial (breaks disulfide bonds)
- Methylene Blue
- Ask about other Botox use (i.e. spasticity)
- Culture 7 days prior, if positive treat 3-5 days before Botox injections
The Trigone

- Spare the Trigone
  - Interference with adrenergic control in the smooth muscle of intramural ureter could induce vesicoureteric reflux
- Afferent Role in OAB
- Afferent Role in Pelvic Pain Disorders
The Trigone

- Karsenty et al. JU 2007 (McGill)
  - 11 women
  - 200 units over 10 sites
  - VUDS @ baseline, 6 weeks
  - 0/10 had reflux
  - 0/1 had worsening reflux

Duration of Effect and Repeat Injections

- 6-9 months
- Onset usually by 2 weeks
- Tolerance doesn’t seem to develop
- If it doesn’t work the first time, do not try again
Time to Failure
Brubaker et al. JU 2008

What to do with the Anticholinergic?

• Poorly reported
• EUA Systematic Review 2008
  – Discontinued 28-58% of time
What to do with the Anticholinergic?
Bladder Capacity

Nool et al. JU 2007

What to do with the Anticholinergic?
Detrusor Pressure

Nool et al. JU 2007
Cost

$300 / 100 units

200 units twice a year = $1200

Adverse Events

- UTI (20%) and Injection site pain (5-10%)
- Retention/Elevated PVR
  - 0-50% de novo CIC rate (5-15%)
  - Mean time to resolution 14 weeks
- Generalized Weakness
  - Variable duration (2-12 weeks)
  - Self limited
Why Botox?

- Effect on Quality of Life
- Danger of High Pressure Storage
- Failure Rate of Anticholinergics 30-40%
- Side Effects of Anticholinergics
- Morbidity of Augmentation
- Cost of Sacral Neuromodulation

Neurogenic DO and OAB (ICS)

- Detrusor overactivity (DO): UDS finding of involuntary detrusor contractions during filling
- Neurogenic DO: associated with a neurological condition
- OAB: symptom complex with urgency, with or without urgency incontinence, usually associated with frequency
GOALS

Neurogenic DO: 
continent low pressure storage

Idiopathic OAB: symptomatic relief

Case

• 43 year old male
• SCI due to skiing accident 10 years ago
• Level: T8
Pre-Botox Urodynamics

Capacity 170cc

Post-Botox Urodynamics

Capacity 344cc
**Neurogenic DO**
Schurch et al. JU 2000

- 36 week, 21 SCI patient uncontrolled trial
- Capacity: 296cc $\rightarrow$ 480cc
- $P_{\text{det max}}$: 65 $\rightarrow$ 35 cm H$_2$O
- 17 of 19 Completely Continent at 6 weeks
- 11 of 11 Completely Continent at 36 weeks

**Neurogenic DO**
EUA Systematic Review 2008

- MEDLINE and EMBASE until March 2007
- 18 articles
- 698 patients, mostly SCI and MS
- 2 RCTs (Schurch 2005, Giannantoni 2004)

Karsenty et al. 2008
Neurogenic DO
EUA Systematic Review 2008

• Completely continent: 40-90%
• Daily incontinence episodes: Decrease 60-80%
• Quality of Life: Increase 35-65%
• Capacity: Increase 100-200%
  – Baseline 175-300cc

EUA - Continence

![Graph showing percentage of patients becoming continent](image)
EUA - Pdet$_{\text{max}}$

Fig. 3 - Mean maximum detrusor pressure (Pdet$_{\text{max}}$) at end point (lowest value per study included) [17, 30, 33, 34].

Incontinence Episodes

Fig. 1. Mean change from baseline in daily frequency of incontinence episodes.

* Indicates within group statistical significance in mean change from baseline
+ Indicates between group statistical significance in mean change from baseline.
Neurogenic DO

- **Goal:** Continent low pressure storage
- **Expectations**
  - Capacity: 100% increase
  - Continence: 40-90% of patients
  - $P_{\text{det}}_{\text{max}}$: 30-50% decrease
  - Duration: 6 months
Pediatrics
Gamé et al. Systematic Review

- EMBASE and MEDLINE up to March 2007
  - 6 Open label studies
  - 108 patients with f/u 12-26 weeks
  - 10-12u/kg to a maximum of 300 units
- 65-87% became dry
- Capacity ↑ 35-80%
- Well tolerated
Pre-Botox Urodynamics #1

Capacity 159cc

29 cm H2O

Post-Botox Urodynamics #1
2 months

Capacity 320cc

16 cm H2O
Post-Botox Urodynamics #1
8 months

15 cm H20
Capacity 242cc

Pediatric Case #2

- 10-year-old boy, ambulatory MM
- Neurogenic bladder
  - CIC q2h
  - Ditropan 5mg po TID
Pre-Botox Urodynamics #2

Capacity 227cc
Pdet 41 cm H20

Post-Botox Urodynamics #2

Capacity 189cc
Pdet 25 cm H20
Idiopathic OAB

- 18% of Canadians
- Effect on Quality of Life and Morbidity
- Refractory to anticholinergics (30%)
- Other Options: Interstim
- Goal: Symptomatic Relief

Urgency Mechanism

- Sudden detrusor contraction with increased intravesical pressure
- Enhanced afferent nerve sensitivity
- Increased release of chemical neurotransmitters from urothelium
- Involuntary relaxation of urethral sphincter and pelvic floor (wet)

Chapple CR 2009
Idiopathic OAB

Urgency

Nocturia

Frequency

Reduced Voided Volumes

Incontinence

Quality of Life/Bother

Urgency Mechanism

• Sudden detrusor contraction with increased intravesical pressure
• Enhanced afferent nerve sensitivity
• Increased release of chemical neurotransmitters from urothelium
• Involuntary relaxation of urethral sphincter and pelvic floor (wet)

Chapple CR 2005
Idiopathic OAB
Sahai et al. JU 2007

- 34 patients with OAB and DO refractory to anticholinergics
  - Frequency 15x, urgency 10x, urge incontinence 4x
- 200 units vs placebo with 12 week follow-up
- Improved urgency, frequency, and incontinence by 1/3
- Increased capacity:
  - ↑ 150cc @ 4wks (baseline 200cc)
- Quality of Life improved significantly
- 37.5% CIC rate

BOTOX Demonstrates Dose-Dependent Efficacy and Safety in Idiopathic Overactive Bladder: A Double-Blind, Placebo-Controlled Randomized Trial
Dmochowski et al. AUA 2009

- 36 weeks, 313 patient RCT
- Idiopathic OAB (mean >8 voids/day) and/or urgency incontinence (>8/wk) refractory to anticholenergics
- Placebo, 50, 100, 150, 200, 300u
- Primary end time 12 wks
- Primary endpoint: change in UUI episodes per week
Efficacy: Dose Response

- Minimal additional benefit above 150U
- Decrease in weekly voids and urgency episodes across all doses
- Dose dependent increase in capacity
  - @12 weeks with 300U → 120cc increase
AUA 2009

- Dose dependent increase in PVR>200cc, especially over 150U
- PVR>200 associated with increased AE (UTI and CIC)

Idiopathic OAB
Flynn et al. JU 2009

- 6 week RCT
- 22 patients (7 to placebo and 15 to Botox)
- OAB with urge incontinence
- Anticholinergic discontinued
- Placebo vs. 200/300 units (10 sites)
- Outcomes: UDS, Pad weights, Voiding diaries, Questionnaires
Flynn et al. JU 2009

IE per Day

Flynn et al. JU 2009

IIQ-7
Idiopathic Overactive Bladder

- Goal: Symptomatic Relief
- Dose response curve suggests 150U is the optimal dose
- Expectations
  - Decrease incontinence episodes by 50%
  - Decrease frequency and urgency by 33%
  - Risk of de-novo CIC 5-15%

Other Uses in Urology

BPH

Interstitial cystitis
BPH
Rationale for Botox

- Denervation of prostate leads to atrophy in rat model
- BoNT-A induces prostatic atrophy and apoptosis in animal models
- High doses: inhibits NE as well (contractile property of stroma under adrenergic control)

BPH
Maria et al. Urology 2003

- 1 year, 30 patient RCT
  - 200u vs. placebo
  - Mean prostate size 52g, IPSS 23

- @ 2mo: 87% subjective improvement vs. 10%
- @ 12mo:
  - IPSS ↓ 62%
  - Qmax ↑ 85%, PVR ↓ 85%
  - Size ↓ 61%, PSA ↓ 38%
BPH

• Limited data to show that Botox effective at 12 months, likely through both effects on cholinergic and adrenergic pathways
• Role of Botox in light of effective, minimally morbid procedures is limited

Interstitial Cystitis

• Giannantoni et al. Eur Urol 2006
  – 1-year uncontrolled trial of 15 patients using 200 units in the trigone and bladder base
  – 87% response rate on VAS scale @ 3 months
  – 27% response rate @ 5 months
  – Retention Rate: 2/15
• Giannantoni et al. Curr Drug Deliv 2009
  – 2-year uncontrolled trial of 13 patients
  – Repeat injection at a median of 5 months
  – Initial response rate in 10 patients, persisted at 2 years
Interstitial Cystitis

- Kuo and Chancellor, BJU 2009
  - 67 patient unblinded 2-year RCT comparing BTX-A and Hydrodistention (HD) vs. HD alone
  - 100U (n=29) or 200U (n=15)
  - All patients on Elmiron
Future Directions

- Larger RCTs
- Dosage and frequency of administration
- Long term safety
- Cost analysis

Take Home Messages

- Remember the goals of treatment
  - 200-300U for neurogenic DO
  - 100-200U for idiopathic DO
- Most robust data exists for the neurogenic DO population
- Accruing data for idiopathic OAB
- Experimental for IC and BPH
Thank You