BOTULINUM TOXIN AND INTRATHECAL BACLOFEN

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INJECTABLES
MEDICAL MANAGEMENT OF SPASTICITY

Leonard, J In: Botulinum toxin: 2009
A protein and neurotoxin produced by the anaerobic bacteria *Clostridium botulinum*

- Blocks neurotransmitter release at the peripheral cholinergic nerve terminals in 4 steps
  - Binds to receptors on the presynaptic membrane
  - Endocytotic uptake into nerve terminals
  - Translocation across the endosomal membrane
  - **Inhibition of neurotransmitter endocytosis**
Botulinum toxin injections reduce the force created by the contraction of spastic muscles.

- Reduction in muscle tension improved passive and active range of motion, facilitates stretching techniques (casting and splinting)
  - Injections should always be accompanied by rehabilitation protocol
    - Formal PT/OT or HEP
- Patients may experience improved motor control following the injections

Injectables – Botulinum Toxin

(always wear gloves!)
- Injected under EMG or US guidance based on clinical exam findings and clinical judgement
  - A recent consensus statement noted there is insufficient evidence to support or refute the use of one localization technique over another
- Dosing is based on amount of tone present, patient’s prior response to injections, residual function of the spastic muscles, and potential impact of excessive tonal reduction
  - Input from therapists and caregivers
- One study showed a larger dilution had greater neuromuscular blockade

**INJECTABLES – BOTULINUM TOXIN**
Repeat injections after at least 3 months

- Administration frequency greater than 90 days increases the risk of antibody formation
  - Using the smallest effective dose also reduces the risk of antibody formation
- Coordinate with bladder botulinum toxin injections
- Peak effect 4-6 weeks, effects last 2 to 6 months
  - "3 days for initial effect, 3 weeks for peak effect, 3 months duration."

INJECTABLES – BOTULINUM TOXIN
Adverse reactions can be grouped into three broad categories:

- **Diffusion** of the toxin away from the intended sites of action can lead to unwanted inhibition of neighboring nerve endings
  - Localized diffusion, while undesirable, is rarely a serious problem
  - Distal diffusion to respiratory and swallowing muscles is more worrisome
    - More common in pediatrics
- Sustained denervation can lead to **atrophy**
- **Immunoresistance** to botulinum toxin
  - Due to development of antibodies that bind to the heavy chain, blocking association with the nerve membrane.
INTRATHECAL BACLOFEN
MEDICAL MANAGEMENT OF SPASTICITY

Leonard, J In: Botulinum toxin: 2009
Delivering baclofen directly into the CSF, enhancing delivery to target neurons in the spinal cord

- 100:1 ratio when comparing oral to intrathecal dosing
Patients must be carefully selected due to the level of commitment and compliance required

- Candidates
  - Poorly controlled despite maximal therapy with other modalities
  - Poorly controlled due to limited patient tolerance of other modalities
  - FDA approved indications include spasticity of spinal and cerebral origins
    - Traumatic SCI, MS
    - Acquired brain injury, CP, Stroke
  - Also beneficial in degenerative conditions
    - ALS, hereditary spastic paraparesis

INTRATHECAL BACLOFEN
Intrathecal trial of medication

- Typical procedure is to perform a lumbar puncture and inject a test dose into the CSF
  - Test dose is typically 50mcg of Baclofen
  - Clinical effects are seen within 1-3 hours
  - Peak effect seen in 4-6 hours
  - Effect usually last 6-8 hours
- Of note, trials can differentiate between spasticity vs contracture as the cause of impaired ROM

INTRATHecal BACLOfen -INITIATION OF THERAPy
Pump implantation

- Starting dose is typically 100-200% of the trial dose divided over a 24 hr period
- Important for the implanting physician to coordinate dosing with the physician responsible for the trial to determine accurate dosing
- Wean off oral medications as pump dose is increased

INTRATHECAL BACLOFEN - INITIATION OF THERAPY
Dose modification
- Can occur immediately after implantation
- Reasonable to wait 24 hours between each dosing adjustment
  - Non-ambulatory patients can tolerate adjustments of 20%
  - Ambulatory patients may require adjustments of 5-10%
- Adverse effects seen in this period
  - Excessive hyper- or hypotonia
  - Change in bowel or bladder status
Post-implantation rehabilitation in acute inpatient rehab
  ▶ If ITB is anticipated to affect the patient’s functional status
  ▶ For caregiver training

INTRATHecal BACLOFEN - INITIATION OF THERAPY
Once titration of baclofen dose is complete, the patient enters the maintenance phase.
Dosing:

- In a non-progressive neurologic condition, *dosing should be relatively stable* though there is some chance for pharmacologic tolerance necessitating an increased dose.

- Any sudden increase in tone should be worked up before adjusting the dosing
  - Noxious stimuli - UTI, bladder distention, urolithiasis, pressure ulcers, fecal impaction, etc
  - Assess for system malfunction
Refilling the reservoir
  - Frequency based on the dosing schedule

Troubleshooting any system malfunction

Replacing the pump when battery life is up (about 4-7 years)
- Programming errors, mechanical problems involving the pump or catheter (kinks, holes, occlusions)
  - Worked up systematically by pump interrogation, determining the actual volume in the reservoir, imaging of the catheter, aspirating CSF to verify catheter patency
Withdrawal symptoms

- Potentially fatal
- Severity not necessarily related to the dosing
- Most common symptom of withdrawal is return of spasticity to the pre-medications baseline level of hypertonia

Other symptoms

- Puritis
- Seizures
- Hallucinations
- Autonomic dysreflexia
- Withdrawal symptoms
  - Life-threatening syndrome
    - Symptoms of:
      - Exaggerated or rebound spasticity
      - Fever
      - Hemodynamic instability
      - Altered mental status
    - If not treated, can progress to:
      - Rhabdomyolysis
      - Multi-organ system failure
      - Death (rare)
Withdrawal symptoms

- Treatment includes:
  - Supportive care
  - Observation
  - Replacement of baclofen enterally until can be given intrathecally
    - Ciproheptadine
Overdose

- Generally due to human miscalculation during dosage adjustments or concentration changes
- Errors in refilling
- Management
  - ABCs
  - Adjust pump settings
INTRATHECAL BACLOFEN – POTENTIAL COMPLICATIONS

- Overdose
- Symptoms:
  - Profound hypotonia or flaccidity
  - Hyporeflexia
  - Respiratory depression
  - Apnea
  - Seizures
  - Coma
  - Autonomic instability
  - Hallucinations
  - Hypothermia
  - Cardiac rhythm abnormalities