Management of Tone in Cerebral Palsy

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Disclosures

• Personal Disclosures:
  – Consultant: Allergan Corporation, Orthopediatrics, Merz Pharmaceuticals

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Off Label Use

• All of the medications in this talk are off label for children with cerebral palsy
• The use of an intrathecal baclofen pump for dystonia is an off label use

What Is Cerebral Palsy?

• Is it brain damage due to obstetrical trauma?
• Was the baby too big or too small?
• Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, by epilepsy and by secondary musculoskeletal problems

Modified after Bax et al. DMCN 2005
**Epidemiology: The Cerebral Palsies**

- Risk is 25-30 times in neonates < 1500g
  - 1 in 3 children with VLBW will have CP
  - Most children with CP were not premature
- Prevalence in 8 year olds: 3-4 patients/1000
  - (1 in 278)
  - 10,000 new diagnoses each year
- Prevalence: ~950,000 Americans with CP
- 87% 30-year survival rate
- There are now more adults with CP than children. My clinic has over 2200 adults.

**Some Statistics**

- 54 million Americans have a disability
- 72 percent of unemployed adults with disabilities would like to work
- Lifetime cost of child born today with CP:
  - ~$1 million

**Motor Disorders**

- Spasticity
- Athetosis
- Ataxia
- Dystonia
- Rigidity

**Other Important Problems**

- Loss of Selective Motor Control
- Sensory Deficits
- Weakness
- Visual Impairment
- Mental Health Issues
Current Treatment Options: General

- Exercise and physical modalities
- Systemic drugs
- Anesthetic and neurolytic injections
- Chemodenervation injections
- Intrathecal drugs
- Orthopedic methods
- Neurosurgical methods

Oral Medications for the Treatment of Spasticity

Primary and Secondary Antispasticity Drugs

- **Primary ASDs**
  - Benzodiazepines
  - Baclofen
  - Dantrolene
  - Tizanidine

- **Secondary ASDs**
  - Tiagabine
  - Cyproheptadine
  - Clonidine
  - Lamotrigine
  - Gabapentin
  - Cannibis

Myotactic Reflex

- Baclofen
- Tiagabine
- Diazepam
- Tizanidine
- BTX
Primary Oral/Systemic Agents: Diazepam

• Suggested indications
  – Flexor and extensor spasms
  – Stiffness, pain and associated insomnia
  – Spasticity and seizures
  – Combined with baclofen in patients with severe spasticity
  – Postoperative spasm
  – Preprocedure sedation


• Suggested starting dose
  – Infants: 1 mg qhs
  – Young adults: 5 mg qhs
  – Maximum dose in children:
    • 0.8 to 1.0 mg/kg/d total, q 6-8 h


Primary Oral/Systemic Agents: Baclofen

• GABA\(_B\) agonist
• Mechanism of action
  – Alters release of excitatory neurotransmitters and substance P in the spinal cord
  – Depresses mono- and polysynaptic reflexes
  – Enhances Renshaw cell activity


• Suggested indications
  – Flexor and extensor spasms
  – Stiffness
  – Pain and associated insomnia
  – Severe spasticity in combination with diazepam


Primary Oral/Systemic Agents: Baclofen

• Potential side effects
  – Sedation
  – Respiratory depression
  – Hypotension and bradycardia
  – Paradoxical irritability
  – Withdrawal syndrome
  – Paradoxical sleep disorders
  – Increased oral secretions

Primary Oral/Systemic Agents: Baclofen

- Potential side effects
  - Sedation, drowsiness, fatigue
  - Decreased seizure threshold
  - May potentiate weakness
  - Orthostatic hypotension
  - Withdrawal syndrome
  - Increased oral secretions
  - Elevated transaminases


Primary Oral/Systemic Agents: Dantrolene

- Hydantoin derivative
- Mechanism of action
  - Acts upon skeletal muscle fibers
  - Inhibits release of Ca$^{2+}$ from the sarcoplasmic reticulum
  - Uncouples excitation from contraction


Primary Oral/Systemic Agents: Dantrolene

- Indications
  - Symptomatic relief, especially clonus, in all types of UMN syndromes


Primary Oral/Systemic Agents: Dantrolene

- Dosage in children
  - Initial: 0.5 mg/kg qhs
  - Increase slowly to 0.5 mg/kg 2-4 times/d at 4-day intervals
  - Then, increase dose by 0.5 mg/kg to a maximum of 3 mg/kg/dose (2-4 times/d) to maximum of 400 mg/d

Primary Oral/Systemic Agents: Dantrolene

- Potential side effects
  - Hepatotoxicity
  - Muscle weakness
  - Diarrhea, mild drowsiness, paresthesias
  - Dysphagia
Primary Oral/Systemic Agents: Tizanidine

- An $\alpha_2$ adrenergic agonist
- Mechanism of action
  - Reduces excitatory amino acid and substance P release
  - Depresses polysynaptic reflexes
  - Decreases activity in the locus ceruleus


Primary Oral/Systemic Agents: Tizanidine

- Indications
  - Nighttime spasms, pain, and clonus

- Dosage in children
  - <10 years
    - 1 mg qhs
    - Increase q week to qid dosing as tolerated
  - >10 years
    - 2 mg qhs
    - Increase q week to qid dosing as tolerated
  - Target dose is 0.3 to 0.5 mg/kg/d


Primary Oral/Systemic Agents: Tizanidine

- Potential side effects
  - Sedation
  - Fatigue and drowsiness
  - Dry mouth
  - Dizziness
  - Visual hallucinations (3%)
  - Hepatotoxicity (5%)
  - Orthostatic hypotension
- Never use with dantrolene or valproic acid


Primary Oral/Systemic Agents

- Tiagabine
- Cyproheptadine
- Clonidine
- Lamotrigine
- Gabapentin
- Carbidopa-levodopa
- Cannibis

Local Anesthetics, Neurolytics, and Chemodenervation for the Patient with Cerebral Palsy and Spasticity

Physiologic Actions of Local Anesthetics and Neurolytics

- These agents may decrease focal or regional muscle overactivity by decreasing afferent and efferent nerve impulses
- Local anesthetics
  - Peripheral nerves may be blocked at a distance from the muscle they innervate, close to, or even within the target muscle
  - Blocks may be transient for diagnostic or other short-term purposes
- Neurolytics
  - Can produce long-term effects through nerve destruction or blockade of neuromuscular transmission

Therapeutic Options by Duration of Effect

- Short-duration nerve blocks (<half day)
  - Local anesthetics
    - Lidocaine
    - Bupivacaine
    - Etidocaine
- Long-duration nerve blocks (~2-5 months)
  - Neurolytics
    - Phenol
    - Ethanol
  - Chemodenervation
    - Botulinum toxin

Botulinum Toxins
Botulinum Toxins

• Botulinum Toxin A
  – OnabotulinumtoxinA - Botox (Allergan Corp)
  – IncobotulinumtoxinA - Xeomin (Merz Corp)
  – AbobotulinumtoxinA - Dysport (Ipsen Corp)

• Botulinum Toxin B
  – rimabotulinumtoxinB - Myobloc (Solstice Corp)

• Botulinum Toxins C-H?

Botulinum Toxins

• Used for focal spasticity and dystonia
• Can use for upper or lower extremity
• 12 Units/kg (Companies suggests 8)
• No more than 400 Units
• No more than 100 Units per muscle
• No more than 50 Units per injection

Black Box Warning

• FDA issued black box warning for children with severe CP
Gastrocnemius and Targeting

Other Uses of Botulinum Toxins

• Pain
• Drooling
• Bladder and Rectal Sphincter tone

Neurosurgical Approaches in Cerebral Palsy

• Selective dorsal rhizotomy
• Peripheral neurectomy
• Myelotomy
• Dorsal column electrical stimulation
Selective Dorsal Rhizotomy

- Of all the surgical procedures currently performed on patients with CP, selective dorsal rhizotomy (SDR) has undergone more thorough scientific scrutiny than any.
- Option for selected patients with spastic CP.
- The first report of dorsal rhizotomy in 1913
- No attention from neurosurgeons until the 1970s

Indications

- Neurosurgery is only considered for severe spasticity following the failure of noninvasive medical and physical therapy.
- Patients are carefully selected, based on rigorous multidisciplinary clinical assessment.

Selective Dorsal Rhizotomy: Candidates and Contraindications

- Candidates
  - Pure spasticity
  - Diplegia
  - Prematurity
  - 3-8 years of age
  - Ambulatory
  - Good Trunk Control

- Contraindications
  - Spasticity of spinal cord origin
  - Athetosis, rigidity, dystonia
  - Previous aggressive tendon releases/lengthening
  - Poor trunk control
  - Severe weakness
Technique

• The severely abnormal rootlets are cut.
• This technique is repeated for rootlets between spinal nerves L2 and S2.
• Half of the L1 dorsal root fibers are cut without EMG.
• The dura is closed, and fentanyl is applied directly.

Advantages of Technique

• Reduced risk of future spinal deformities
• Decreased weakness
• Reduced hip flexor spasticity by sectioning the L1 dorsal root
• Shorter-term, less intense back pain
• Earlier resumption of PT

Complications

• Paralysis of the legs and bladder
• Impotence, and sensory loss
• Wound infection
• Meningitis
• CSF Leakage
• Abnormal sensitivity of the feet and legs
• Transient change in bladder function
• Urinary tract infection
• Pneumonia.
Outcome

- Patients with spastic diplegia
  - Reduced spasticity
  - Recurrence rare.
  - Long-term return of spasticity is unlikely
- Patients with spastic quadriplegia
  - Can fail to reduce spasticity and most of these patients have dystonia
  - Recurrence of spasticity is common in nonambulatory patients

Outcome

- Patients with CP may not depend on spasticity for ambulation as much as patients with spasticity associated with spinal cord injury, in whom the spasticity sometimes does help with standing and taking steps.

Selective Dorsal Rhizotomy: Efficacy

- Meta-analysis of the data from three studies showed greater improvement in patients undergoing SDR and PT than in patients treated with PT alone
- Study documented a 27% reduction in $O_2$ cost during walking one year post SDR

SDR and Orthopedic Surgery

- It takes many months to improve contractures when present for years, and in older children and adults, may require surgical release.
- SDR at 2-4 years of age, can prevent or reduce deformities and makes it easier to treat later with orthopaedic surgery.

Intrathecal Baclofen for Spasticity in Cerebral Palsy

Intrathecal Baclofen: Selection Criteria

- Clinically stable patient with severe multifocal and regional muscle overactivity
- Failed adequate trial of oral agents
- Body-size and mass dependent
- Realistic patient/caregiver goals for treatment
- Family committed to intrathecal baclofen as a treatment option


Intrathecal Baclofen: Exclusion Criteria

- Exclusion criteria
  - Infection, history of allergy, or hypersensitivity to baclofen
  - Potential for pregnancy or active breast-feeding


Intrathecal Baclofen: Screening

50-100 µg intrathecal bolus

- Peak response 2-4 hours
- Improvement of function or no deterioration
- No response
- Select other treatment
- Candidate
**Intrathecal Baclofen: Infusion System**

- Implanted in subcutaneous fat or subfascial of the external obliques
- Drug reservoir (10 mL or 18 mL) and pump connected to catheter
- Battery
- External radiotelemetry wand to control pump

**Intrathecal Baclofen: Implantation**

- Tip of catheter usually placed intrathecally from the high cervical spine to the lower thoracic region
- Pump is implanted into a subcutaneous pocket in the abdomen

**Intrathecal Baclofen: Follow-up**

- Postimplantation
  - Titrate dose to ensure balance, stability, and postural control
  - Instruct patient and caregiver about refill schedule, management of complications and potential adverse effects
  - Refills, assessments, and possible dose adjustments are done at ITB therapy center at 4 to 12 week intervals
  - Replace pump after 5 to 7 years

**Intrathecal Baclofen: Complications**

- Local
  - Seroma
  - Hematoma
  - Erosion
  - Infection
- Systemic
  - Withdrawal
  - Drug toxicity
  - Meningitis
  - Urinary retention/constipation
  - Dysphagia
  - Aspiration
  - Possible progression of scoliosis
- Catheter-related
  - Migration
  - Breakage
  - Puncture/rupture
  - Dislodgment
  - Disconnection
  - CSF leaks

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Albright AL. J Child Neurol 1996;11(suppl 1):S29-S35.
Intrathecal Baclofen for Dystonia in Cerebral Palsy

Dystonia is a hyperkinetic movement disorder characterized by sustained muscle contractions that cause twisting or repetitive movements and abnormal postures or positions.

Dystonia Classification

Primary-hereditary
Secondary-most common (CP, TBI)
- Generalized
- Hemidystonia
- Focal
- Segmental
Primary plus Heredito-degenerative

Treatment Options for Dystonia

1. Non-Surgical- oral medications (baclofen, clonazepam, artane, Sinemet -levo-dopa)
2. Surgical
   - Thalamotomies/Pallidotomies
   - Deep Brain Stimulation
   - Intrathecal Baclofen

Intrathecal Baclofen for Dystonia

First reported in early 90’s for generalized dystonia.
Ten additional studies reported aggregate improvement in 28 of 38 total patients
Recent studies have demonstrated improvement in the degree of dystonia, increased comfort, ADL management and improved function and quality of life in individuals previously refractory to other treatments.
Intrathecal Baclofen in Dystonic Storm

Integrated Treatment Approach in the Child with Spasticity

Role of Deep Brain Stimulation in Cerebral Palsy

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  - American Academy for Cerebral Palsy and Developmental Medicine
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