American Medical Directors Association 22nd Annual Symposium
March 4-7, 1999 - Orlando, Florida

Pediatrics Workshop

(P2) Pediatric Long Term Care: Management of Spasticity and Survival Rates

Friday, March 5, 1999

1:30 pm - 3:00 pm

Walt Disney Dolphin Hotel

Faculty:
Sayeed Hussain, MD
Audrius Plioplys, MD, CMD

Objectives:

- Describe the pathophysiology of spasticity seen in cerebral palsy and clinically define the phenotypes of cerebral palsy
- Evaluate the effectiveness of systemic medications, botulinum toxin injections, intrathical infusions, and surgical procedures for the treatment of spasticity
- Define the clinical subsets of physical and neurologic disabilities in children
- List the factors that predict improved survival rates in children with severe neurologic disabilities

CEREBRAL PALSY

MANAGEMENT OF SPASTICITY

Audrius V. Plioplys MD, FRCPC, FAAP, CMD

Alden Village, Genesis House, Little Angels,
Marklund, and Philip Rock Center

Chicago, Illinois

CEREBRAL PALSY

SIGMUND FREUD, 1897

Die Infantile Cerebrallahmung

In S. Nothnagel (editor), Specielle Pathologie und Therapie. Vienna: Holder, 1897; 1-327.

Infantile Cerebral Paralysis. L. A. Russin (translator), Coral Gables, Florida: Univ. of Miami Press, 1968.

CEREBRAL PALSY

Spastic

- Diplegia
- Hemiplegia
- Quadriplegia

Dyskinetic

- Dystonic
- Athetoid

Ataxic

Atonic

Mixed

CEREBRAL PALSY

PREVALENCE:

2.5 per 1,000

CEREBRAL PALSY

CAUSES:

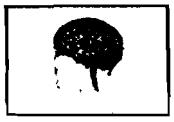
ALL OF CHILD NEUROLOGY

CEREBRAL PALSY

ASSOCIATED DISORDERS:

Mental Retardation
Epilepsy
Incontinence
Feeding
Respiratory

Pathophysiology of Spasticity of Cerebral Origin



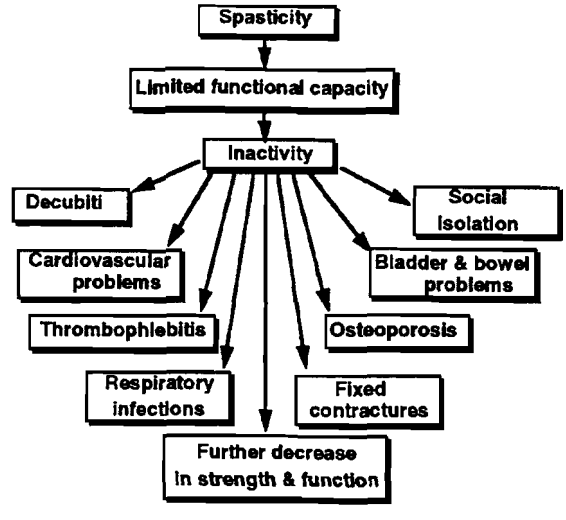
Brain delivers inhibitory neural signals to the spinal cord.

Damaged brain fails to generate or send inadequate inhibitory signals.

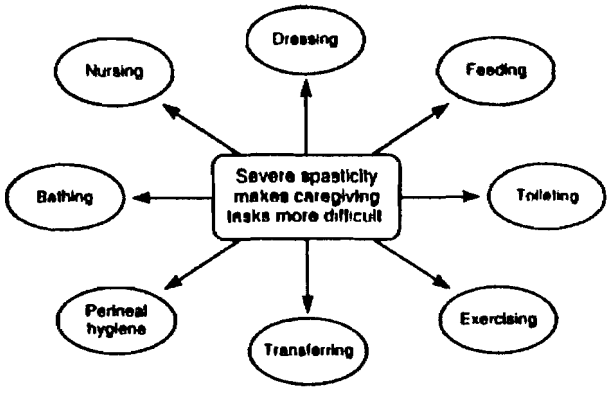
Inhibitory signals modulate reflex signals–tone remains normal.

Lack of neural inhibition leads to spasticity.

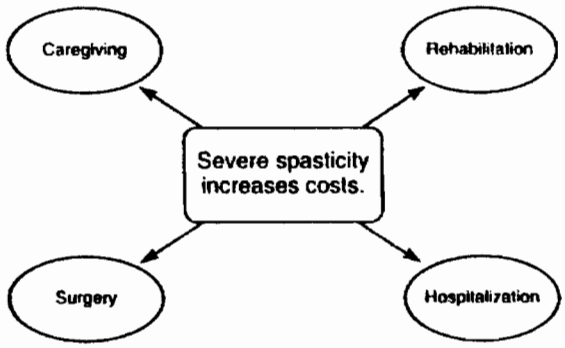
Impact of Spasticity



Consequences of Spasticity for Caregivers



Consequences of Severe Spasticity on Cost of Care



Clinical Presentation and Assessment

Ashworth Scale

Score	Degree of Muscle Tone
1	No increase in tone.
2	Slight increase in tone, giving a "catch" when affected part is moved in flexion or extension.
3	More marked increase in tone, but affected part easily flexed.
4	Considerable increase in tone; passive movement difficult.
5	Affected part rigid in flexion or extension.

Conventional Treatments

- Physical therapy
- Oral antispasticity drugs
- Botulinum toxin
- Nerve blocks
- Orthopedic procedures
- Neuroablative surgery

CEREBRAL PALSY

PHYSICAL THERAPY

CASTING
ORTHOTICS

CEREBRAL PALSY

ORTHOPEDIC SURGERY

Tendon Lengthening
Tendon Transplants
Scoliosis
Hip Dislocation

CEREBRAL PALSY

NEUROSURGERY

Thalamotomy
Cerebellar Dentatotomy
Cerebellar Stimulation

SELECTIVE DORSAL RHIZOTOMY
3 to 6 years old
Reasonable strength, no contractures

CEREBRAL PALSY

PERIPHERAL BLOCKS

Phenol blocks
Alcohol blocks

BOTULINUM TOXIN INJECTIONS
5 to 60 units per muscle
every 3 to 4 months
weakness

Benzodiazepines

- Long-acting and short-acting formulations
- Mechanism of Action (CNS)
  - binds in brain stem and spinal cord
  - post-synaptic site of action
  - potentiates presynaptic effect of GABA
- Clinical Indications: SCI, MS
- Possible Applications: TBI, CP, CVA
- Clinical Effects
  - decreased resistance to passive ROM
  - decrease in hyperreflexia
  - reduction in painful spasms
  - sedation and reduced anxiety

Diazepam

- Recommended Dose
  initial = 2 mg. bid ***(consider starting with single dose at night if nocturnal spasticity is the presenting problem)***
  maximum = 60 mg. daily (20 mg. tid)
  NB: long half-life; active metabolite
- Side Effects: sedation, weakness, hypotension, GI symptoms, memory impairment, incoodination, confusion, depression, ataxia
- Controlled substance with potential for dependency

CEREBRAL PALSY

CHLORAZEPATE

Benzodiazepine
Half-life 2 days
9 to 12 years old: max. start dose 7.5 mg bid
Gradual increase in dose
Max. 60 mg per day divided tid
Available as sustained release (SD)
Side effect: lethargy

Dantrolene Sodium

- Mechanism of Action = peripheral
  - interferes with calcium release
  - uncouples muscle contraction from excitation
  - effects both intrafusal and extrafusal fibers
- Clinical Indications: CVA, CP
- Possible Applications: TBI, SCI, MS
- Clinical Effects
  - decreased resistance to passive ROM
  - decrease in hyperreflexia and tone
  - reduction in spasms and clonus

Dantrolene Sodium

- Recommended Dose:
  obtain baseline serum LFT
  initial dose = 25 mg. bid
  typical = 100-200 mg. daily
  maximum = 400 mg. daily
- Side Effects: weakness (including respiratory muscle weakness), drowsiness, nausea, diarrhea, lethargy, hepatotoxicity (elevated serum transaminases) associated with maximum dose, long-term use especially in women > 30

Oral Baclofen

- Mechanism of Action (CNS)
  - $GABA_b$ selective agonist
  - pre and post-synaptic actions
  - acts on mono and polysynaptic pathways
- Clinical Indications: spasticity of spinal origin (intrathecal baclofen approved for cerebral and spinal spasticity)
- Clinical Effects
  - decreased resistance to passive ROM
  - decrease in hyperreflexia
  - reduction in painful spasms and clonus

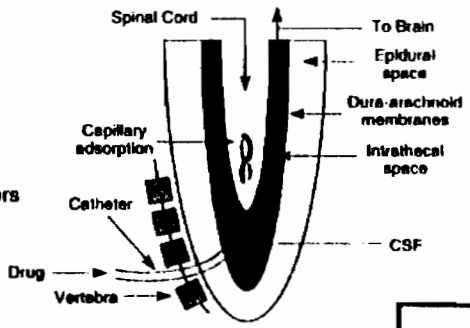
Oral Baclofen

- Recommended Dose
  initial = 5 mg. tid
  maximum = 80 mg. daily (20 mg. qid)
- Side Effects: weakness, sedation, hypotonia, ataxia, confusion, fatigue, nausea, dizziness, lower seizure threshold
- Sudden withdrawal may cause seizures, hallucinations, and rebound spasticity.
- May potentiate effects of antihypertensive agents.

Baclofen: Delivery Makes the Difference

How Does Lioresal® Intrathecal Work?

Drug
- Spinal level
- Excitatory neurotransmitters



Anatomic figure adapted from Krin JS. Intrathecal drug administration: present use and future trends. *Clin Pharmacokinet* 1992 22 319-326

Candidates/Selection Criteria

Step 1: Selection Criteria

Spasticity is:	■ Severe ■ Interfering with care or function ■ Causing complications
Patient is:	■ ≥4 years of age ■ Clinically stable
Family is:	■ Motivated ■ Committed
Goals are:	■ Explicit ■ Collective ■ Realistic

Candidates/Selection Criteria

Step 2: Exclusion Criteria

- Infection
- History of allergy or hypersensitivity

Candidates/Selection Criteria

Step 3: General Clinical Considerations
Three critical issues to be considered:

■ Unique features of ITB Therapy are: – Graduated control of spasticity – Upper extremity treatment – Reversibility	■ Are these features important to this patient?
■ ITB Therapy may decrease trunk and cervical tone.	■ Will this outcome compromise the patient's posture or stability?
■ Successful outcome depends on conscientious follow-up and pump maintenance.	■ Does this patient/family caregiver unit possess the necessary motivation and reliability to maintain the pump?

Candidates/Selection Criteria

Step 4: Screening Trial
Does the patient respond to the 50-, 75-, or 100 µg bolus of ITB Therapy?

If patient responds:	Proceed with implant.
If patient does not respond:	Do not proceed.

Typical Costs Associated With ITB Therapy

- ITB Therapy screening trial
  - Hospital services (observation room and supplies)
  - Physician services (trial procedure and observation)
- SynchroMed® Infusion System implantation
  - Infusion system and drug
  - Hospital services (2- to 3-day minimum inpatient stay)
  - Physician services (surgery, anesthesia)

Costs Associated With ITB Therapy (cont)

- Therapy follow-up and maintenance
  - Physician services (refills, reprogramming, evaluation, management)
  - Medication (baclofen injection)
- Pump replacement (at 3- to 5-year intervals)
- Complications (e.g., catheter kinking)
- Other associated costs (e.g., physical therapy)

Costs and Complications

Possible Treatment Complications

- Equipment malfunctions are possible.
- Unpleasant drug side effects may occur.

However, overall patient satisfaction is remarkably high.

Estimated Charges for Screening and Implantation

Expense Component	1996 Charges	Frequency/Cost
■ ITB Therapy Trial		Once
– Hospital (outpatient, 2 days)	$ 900	
– Physician	$ 420	
TOTAL	$ 1,320	$ 1,320
■ Implantation		Once
– Drug infusion system[1]	$ 10,200	
– Hospital (inpatient)	$ 4,900	
– Surgeon	$ 2,000	
– Anesthesia	$ 960	
TOTAL	$ 18,060	$ 18,060
TOTAL: Trial & Implant	$ 19,380	$ 19,380

[1]Estimated on the basis of a 30% markup

Estimated Charges for Follow-up and Maintenance

Expense Component	1996 Charges	Frequency/Cost
■ Follow-up and Maintenance		6 per year
– Physician	$ 150	
– Drug and refill kit	$ 460	
TOTAL	$ 610	$3,660/year
■ Pump Replacement		Once/4 years
– Drug infusion system	$ 9,720	
– Hospital	$ 2,000	
– Surgeon	$ 1,800	
– Anesthesia	$ 720	
– Drug	$ 460	
TOTAL	$ 14,700	$14,700/4 years
■ Management of complications (e.g., catheter replacement)	$ 4,200	

CEREBRAL PALSY

CLONIDINE

Alpha-adrenergic agonist
Restores adrenergic inhibition in the spinal cord
Start with 0.05 mg qd
0.1mg qid (usual maximum dose)
PATCH
rebound hypertension
with methylphenidate--deaths

CEREBRAL PALSY

DYSKINETIC SYNDROMES

Trihexyphenidyl
L-Dopa (Sinemet)
Trazodone
(SSRI's may worsen extrapyr. CP)

Tizanidine: Pharmacology and Mechanism of Action

- imidazoline derivative (similar to clonidine but without the same cardiovascular effects)
- alpha-2, noradrenergic receptor agonist
- peak effect occurs 1-2 hours following administration
- half-life = 2.5 hours

Tizanidine

- Mechanism of action (spinal and supraspinal) - decreases facilitory inputs by acting primarily on spinal polysynaptic pathways
- Decreases tone and spasm frequency preferentially in spastic muscles.
- Does not cause muscle weakness.
- Appropriate as first line oral monotherapy; may have utility in polypharmacy program.
- No evidence of dependency, withdrawal, or tolerance effects.

Tizanidine: Clinical Effects

- reduces muscle tone
- reduces spasm frequency
- reduces hyperreflexia
- does not decrease muscle strength
- antinociceptive effects reported in animal studies*

** Coward & Emre, 1988; McCarthy, et al, 1990; Davies & Johnston, 1984; Villanueva et al, 1988*

Tizanidine: Dosage

- Starting dose: 4 mg. at HS
- Optimum dose
  12-36mg. / day in 3 or 4 divided doses
- Daily maximum dose = 36 mg.
- Requires gradual titration to optimal dose in 2-4 mg. steps
- Check liver function tests before and during treatment

Serious Adverse Events in Patients Receiving Tizanidine*

- hallucinations (3% of subjects)
- elevated LFT's (5% of subjects)
- increased risk of hypotension when given with clonidine

** from three placebo-controlled trials*

Tizanidine: Side Effects

- Most frequent side effects include:
  - drowsiness, dry mouth, tiredness, dizziness (as with other anti-spasticity agents, side effects are dose related and may be mitigated by dosage titration)
- Literature suggests that tizanidine may be better tolerated in general than other anti-spasticity agents, as measured by 'global tolerance rating scale'*

** Lataste X, et al., 1994*

CEREBRAL PALSY

OTHER MEDICINES

Clonazepam
Vigabatrin
Meprobamate

CEREBRAL PALSY

PHARMACOTHERAPY

Many possible medicines
Clinical trials of different agents
Functional capacity, range of motion
Use best agent
Formal studies are necessary