Pharmacological spasticity treatment on cerebral palsy

Tratamento farmacológico da espasticidade na paralisia cerebral

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ABSTRACT

Spasticity is a movement disorder characterized by a velocity dependant tonic stretch reflex (muscle tone) increase as a result of the reflex's hyper-excitability and as a component of the Upper Neuron Syndrome, extremely common to in many neuropathological conditions. In this article we will review the physiopathology of espasticidade and the main drugs used in its treatment.

Keywords: Child, Cerebral Palsy, Muscle Spasticity/drug effects, Botulinum Toxin Type A

RESUMO

A espasticidade é uma desordem motora caracterizada por aumento dos reflexos de estiramento tônicos (tônus muscular), velocidade dependente, resultado da hiper excitabilidade deste reflexo, como um componente da Síndrome do Neurônio Superior, extremamente comum a várias condições neuropatológicas. Neste artigo faremos uma revisão da fisiopatologia da espasticidade e dos principais fármacos utilizados no seu tratamento.

Palavras-chave: *Criança, Paralisia Cerebral, Espasticidade Muscular/efeitos de drogas, Toxina Botulínica Tipo A*

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Conflict of Interest Statement
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INTRODUCTION

Spasticity and reflex arch

By definition spasticity is a movement disorder distinguished by a velocity dependant tonic stretch reflex (muscle tone) increase as a result of the reflex's hyper-excitability and as a component of the Upper Neuron Syndrome.[1]

An increase of the stretch reflex may occur due to a hyper-excitability of the alpha motoneurons at a target or due to an increase of the excitatory afferent stimuli triggered by muscle strain or due to both. The motoneurons assemblage is considered hyper-excitable if basic excitatory stimuli are able to trigger an increased threshold and frequency response.[2]

This hyper-excitability may be generalized due to an unbalance between the excitatory and inhibitory impulses on motoneurons. In an upper motoneuron lesion, the inhibitory impulses are diminished causing a hyper-excitability. The exaggerated movement response in a spastic patient comes from changes in how the medullary circuit processes information generated in different sites, including proprioception, extereoception and downward supra-segment stimuli. Spasticity is closely related to stretch reflex arch (Figure1).[2]

Spasticity as a clinical sign needs to be distinguished from spasticity as a contributing factor for Upper Neuron Syndrome movement dysfunction once, in humans, a lesion in the upper motor neuron affects not only the pyramidal tract but also changes movement patrons as the ones involved in the cortico-reticuloespinal tract, leading to an excitability of the alpha motoneurons enhance on a medullar section level and resulting tonus and tendon reflexes responses augmentation.[2]

From a clinical point of view one can observe positive exacerbation signs and negative deficiency signs (Chart 1).

Positive Signs

Spasticty: may be manifested by a tonus increase (tonic activity or sustained tonic stretch reflex), exaggerated tendon reflexes response (phasic tendon reflexes), tendon reflexes phasic phase irradiation in response to tendon percussion, polikinetics tendon reflexes and clonus response. Many of these phenomena may be comprehended on the figure 1 context.

Ia primary afferent fibers that reach muscle intrafusal spindle fibers become excited when the muscle is stretched. These Ia fibers make monosynaptic connections with alpha motoneurons of the origin muscle and their synergistic muscles. These Ia fibers also connect monosynaptically with the inhibitory interneurons that project themselves directly to the alpha-motoneurons of antagonistic muscles.

Pharmacological Spasticity Treatment

The spasticity treatment needs to be individualized to best fulfill the necessities of each patient and his/hers caregivers. The decrease in tonus may be helpful for a patient and not for another with the same clinical situation. Spasticity treatment may include one or all of the following options: oral medicines, chemical blockage (botulinium toxine injection and/or phenol at the hyperactive muscles), intrathecal baclofen pump and surgery,[3] besides physical measures (physiotherapy, occupational therapy, orthesis and plaster caster use)

When handling spasticity one has to avoid and eliminate the triggering factors and the verdict; definitions regarding the therapeutic path to be followed must be made by the entire multidisciplinary team. The options can be to do only medical procedures and interventions, physical therapy or both, depending on the spasticity's characteristics: focal, multi-focal or generalized. A strategy for managing the treatment of spasticity can be seen in Figure 2.

The term generalized spasticity is used with clinical connotation when, from a practical standpoint, more than four major muscle groups are involved in the spastic framework.[5]

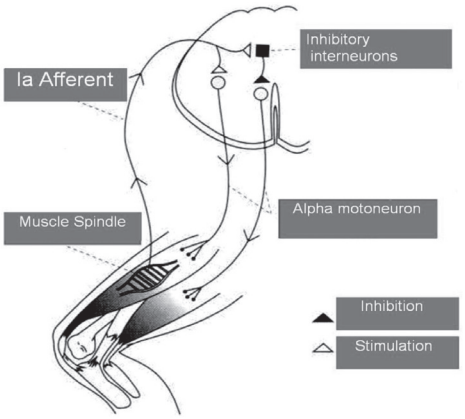

Figure 1 - Stretch reflex arch

The prevention and removal of the causative factors is the first step to be followed. Triggering factors such as infection of any kind (but often urinary), ingrown toenails, poorly fitted orthoses and shoes, tight clothing, posture changes (including bad posture in a wheelchair) etc..; greatly influence the spasticity levels. So to have the real notion of the clinical situation to be addressed, these factors

Chart 1 - Clinical Signs of the Upper Neuron Syndrome movement dysfunction

Positive Signs	
1. Spasticity	Tonus enhance
	Tendon Hyper-reflexes
	Stretch reflex spreads to the extensor muscle.
	Polysynaptic responses on stretch reflexes and clonus
2. Altered flexor reflexes	Babinsky response
	Mass synergic patrons

Negative Signs	
1. Dexterity fingers loss	
2. Muscle Weakness	Inadequate strength
	Slow movements
	Selective movement control loss at the members segment

Spastic muscle rheological changes	
	Shortenings
	Contractures
	Fibrosis
	Atrophy

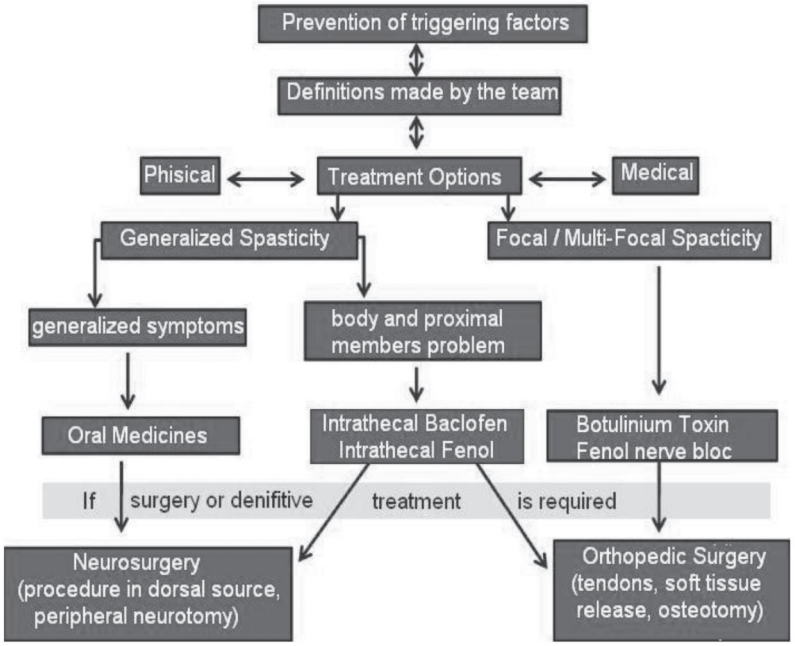

Figure 2 - Management strategy proposition for the spasticity treatment

should be eliminated. Other determinant factors are: stress, fatigue, fever, systemic diseases, sleep disturbances, constipation, diarrhea, immobility and hormonal changes.[6] Then the multidisciplinary team should discuss the need for treatment, its goals and feasibility.

All spasticity treatments have advantages and disadvantages and the final decision rest with the physician supported by the professional staff.[4] The anti-spastic treatment can have several indications as Chart 2 shows.

In this paper we will describe the issues related to the pharmacological treatment of spasticity in children with cerebral palsy.

Age influence on treatment options

When thinking in children with cerebral palsy age is of great importance since there is a growth and development going on in parallel. Depending on the present age and motor development treatment strategies may change. Chart 3 shows these relations.

Methods of Treatment – Oral Medications

Oral medications can influence tone via modulation of afferent or efferent signals from multiple sites within or outside the Central Nervous System, including superior cortical centers, the basal glia, cerebellum, spinal cord and muscles. Neurons and interneurons are influenced by drugs uses that influence a varied range of neurotransmitters including epinephrine, norepinephrine, serotonin, GABA, glutamate, glutamine, dopamine, substance P and others. The descending pathways that may be influenced by antispasmodic drugs are described in Chart 4.[8]

FREQUENTLY USED ANTI-SPASTIC DRUGS

Oral Baclofen[3]

Baclofen: it is a GABA analog, GABAb pre and post synaptic agonist, leading to an inhibition of mono and polysynaptic spinal reflexes.[9] It is the antispastic of choice in spasticity cases with spinal origin in adults.[10]

Standart dose: Adults: 40-80 mg/day in 3-4 doses (Maximum 20mg 4X/day). Children ≥ 12 years: initiate with 2,5mg/day and increase to 5mg each 8/8hs for 3 days (if necessary increase 5mg/dose each 3 days) until maximum of 20-60mg/day. The usual dose is 40-80mg/day, but the effective dose may exceed the maximum daily dose of 80mg/day (20mg 4X/day). Due to renal elimination dose should be reduced if renal function is compromised.

Contraindication: Use with caution in patients with pre-existing psychiatric illness, which may worsen. Transaminases elevation, alkaline phosphatase and blood glucose have been reported. High doses can affect gait and lower motor functions.

Main drug interactions: may potentiate the antihypertensive effects in the course of the use of monoamine oxidase inhibitors. Interferes with tricyclic antidepressants action. Effects on the CNS may be potentiated with the addition of alcohol or other drugs that depress the CNS functions.

Main side effects: Excessive sedation, confusion and hallucinations. Rises levels of liver function tests and blood glucose. Careful monitoring is recommended and use should be withdrawn gradually.[10]

Special notes: Avoid abrupt discontinuation; reduce dose slowly over 1-2 weeks. The dosage should be adjusted according to benefits shown. Excessive doses can cause a decrease in functional gains. The relaxation produced by baclofen improves active and passive mobility.[10] Baclofen has poor lipid solubility which prevents its passage through the blood brain barrier, thus more than 90% of the drug absorbed remains in the bloodstream. As a result, high doses may be needed to achieve effectiveness and consequently the side effects are dose dependent.[11]

Tizanidine[3]

Tizanidine: it is an imidazole derivative, alpha 2-adrenergic agonists, acting on alpha 2 adrenergic and imidazole reptors of the spinal cord. Decreases polysynaptic reflexes (tonic stretch) probably by decreasing the release of presynaptic excitatory neurotransmitters.[9]

Standart dose: Adults – initial dose: 4 mg single dose each 6-8hs increasing the dose in 2-4mg until achieve the optimal effect. The usual dose is 8 mg every 6-8hs to a maximum of three doses in 24 hours or 36mg/day. Children ≥ 12 years: The pediatric dose is not determined. A study in children using 6mg/day reported improvement in motor skill confirmed by electromyography.[12]

Contraindication: Do not use in patients with pre-existing orthostatic hypotension or liver disease. Use with caution in patients with kidney disease and in the elderly.

Main drug interactions: The effects are potentiated by concomitant use of fluvoxamine, ciprofloxacin, CYP1A2 inhibitors, and oral contraceptives. Can result in hypotension. Use with caution in combination with antihypertensive drugs. Avoid concomitant use with oral contraceptives.

Main side effects: May prolong the QT interval. May cause excessive sedation and hallucinations. The depressant effects over the CNS may be exacerbated by alcohol use.

Chart 2 - Indications for anti-spastic treatment[4]

Indication	Examples
Functionality increase	Mobility: velocity pickup, march quality and resistance or the wheelchair propulsion
	Improvement in transfer
	Improves dexterity and object reach
	Improves sexual function conditions
	Enables better hygiene
Symptoms Improvement	Improvement in pain and muscle spasms, allowing the use of orthoses and adaptations.
Posture Improvement	Improves body image
	Prevent contractures
Care necessities decrease	Helps dressing, improves personal care and hygiene.
	Improved positioning for feeding and adjusting orthoses.
Future responses improvement	Prevents the use of drugs or other treatments
	Facilitates therapy
	Postpone or avoid surgery

Chart 3 - Age influence on cerebral palsy treatment options[7]

0-3 years	4 years-puberty	Puberty
Set Goals	Set Goals	Set Goals
Establish aetiology		Review motivation / Evaluate for psychological issues
Start physiotherapy and occupational therapy	Start physiotherapy and occupational therapy	Physiotherapy and occupational therapy involving life activities.
Consider oral medication for spasms, significant spasticity and sleep disturbances.	Consider oral medication for spasms, sleep disorders, contractures in formation.	Consider oral medication for spasms, sleep disorders, contractures in formation.
Botulinum toxin	Botulinum toxin	Botulinum toxin
	Selective dorsal rhizotomy	
	Baclofen pump	Baclofen pump
	Orthopedic Surgery	Orthopedic Surgery

May cause dry mouth, somnolence, asthenia and dizziness. May cause liver damage, so monitoring liver function at the beginning and at 1, 3 and 6 months of treatment is recommended. Retinal degeneration and corneal clouding have been reported. On drug discontinuation, avoid abrupt withdrawal, rebound reaction may develop hypertension, tachycardia, and hypertonia.

Special notes: Monitoring should be made to: hypotension, bradycardia, delirium, dizziness, syncope, liver problems, sedation, hallucinations and psychotic withdrawal symptoms. Patient should take precaution in risky or dangerous tasks. Patients must avoid alcohol and CNS-depressant drugs. There may be changes in food absorption and this can affect the effectiveness of the drug and its levels of adverse effects. Due to the effect of sedation taking the medicine at night may facilitate sleep and diminish tone.[10]

Dantrolene[3]

Dantrolene: it is a derivative of hydantoin. It is the drug of choice for treatment of hyperthermia secondary to abrupt withdrawal of baclofen, in malignant hyperthermia and neuroleptic malignant syndrome.[9] Dandrolene acts within the muscle, inhibiting the calcium release from the sarcomero, causing muscular weakness.[10,11] It is a drug well absorbed between 3-6 hours after ingestion and is metabolized in the liver having its peak effect between 4-8 hours after ingestion.

Standart dose: Adults – initial dose: 25mg/day for 7 days. Increase to 25mg 3X/day for 7 days. Then 50mg 3X/Day for 7 days. Afterwards to 100mg 3X/day. Maximum dose 100mg 4X/day. During titration of doses if the higher doses do not show the desired effect regress to lower doses. Children with 5 years or more: The starting dose is 0.5 mg / kg / day for 7 days. Increase to 0.5 mg / kg, 3X/day for 7 days. Then increase to 1 mg / kg, 3X/ day for 7 days and further increase to 2mg/kg 3x/day. The maximum dose is 100mg 4X/day (12mg/kg/day).[11]

Contraindication: Active liver disease. The use of dantrolene may decrease the function when spasticity is used to control the posture and gait. Caution with pulmonary, cardiac and liver dysfunction. The risk of hepatotoxicity is 1%.[10]

Main drug interactions: Concomitant use with CNS depressants increases the risk of drowsiness and cardiovascular collapse.

Main side effects: It may be noted as a side effect mild sedation, nausea, vomiting and diarrhea. Liver monitoring should be done before the start of therapy and periodically thereafter due to increased risk of hepatocellular disease in women and patients over 35 years. Photo sensitivity reaction may occur, sun exposure should be avoided.

Special notes: Medication should be discontinued if after 45 days therapeutic effects are not noticeable. Patients should be warned of risks in hazardous tasks and to avoid prolonged sun exposure. This medicine is little stable on solution, so administration is only possible for children able to swallow capsules.[10]

Diazepan[3]

Diazepan: acts by binding to GABA receptors, which has binding sites for the drug. Exerts a pre-and postsynaptic indirect effect, increasing their affinity to endogenous GABA. Diazepam is the oldest medicine used to treat cerebral and spinal cord spasticity, being widely used. Its antispastic effect is dose dependent. Administered orally, reaches maximum serum level after an hour and its half-life is 20-70 hours. It is metabolized by the liver into two active components: N-desmethyldiazepam (nordiazepam-half-life of 36-96 hrs) and oxazepam, its active metabolite, which is inactive and excreted in urine. Binds itself to serum proteins (98%) and under hypoalbuminemia conditions its side effects are most evident. Its action is mainly supraspinal (cerebral cortex, thalamus, basal ganglia, cerebellum, reticular formation), also acting in polysynaptic spinal pathways.[9] Thus benzodiazepines act at the

Chart 4 - Known or expected effects of neurotransmitters on the structures and pathways of the Central Nervous System

Neurotransmitter →	Excitatory							Inhibitory		
Paths or Structures ↓	Glutamate	Dopamine	Epinephrine	Norepinephrine	Serotonin	Substância P	Exteroceptive sensory signals	GABA	Glycine	α-adrenergic
Cortical	+		+	+				++	+	+
Brainstem		+						++	+	
Corticospinal	+++		+	+				++	+	
Lucus cerulius	+							++	+	++
Reticolospinal				+++	+++			++	+	
Vestibulospinal								++	+	
Spinal Cord	++		+	+		++	++	++	+	++

spinal cord and above.[11]

Standart dose: Adults – initial dose: 2-10mg/3-4Xday. Children aged 6 months or more: the starting dose is 1 to 2.5 mg, 3-4Xday (0.12-0.8mg/kg). The dose may be increased gradually as needed and tolerated.[10]

Contraindication: acute glaucoma and children under 6 months.

Main drug interactions: Interact with phenothiazines, narcotics, barbiturates, monoamine oxidase inhibitors and other antidepressives. Avoid using alcohol and other CNS-depressant substances. Risk of blackouts with the use of flumazenil.

Main side effects: Sedation. Caution with hepatic and renal function. Liver and blood monitoring should be made in prolonged use. Neutropenia and jaundice have been reported. Avoid abrupt withdrawal. Increases the possibility of fainting in epileptic patients.

Special notes: Monitoring of hypersensitivity reactions, rebound or withdrawal symptoms and insomnia. Heart and lung function should be tested. Avoid concomitant use with sedatives and alcohol. Careful in operating machinery or driving a car. Patients should be cautioned against drug abuse, dependence and side effects. For causing sedation it should be taken before bedtime to facilitate sleep.[10,13]

In sum, according to the 2009 European Consensus Review for the use of botulinium toxin in children with cerebral palsy, in relation of oral medicines we have.[14]

Treatment indication: rare, it is a treatment option with limited time for high spasticity levels beginning with GMFCS IV (rarely III), ex: benzodiazepine, oral baclofen (if intrathecal treatment is contraindicated).

Goal: reduced tone, pain relief, facilitate placement and care, treat some acute situations.

Principle: spasticity reduction, GABAergic action.

Limitations and controversies: side effects affecting cognition, sedation, tolerance development.

CONCLUSION

The strategic proposal for the management of spasticity in children with cerebral palsy recommends clear differentiation between situations that require a systemic treatment or a focal treatment. Systemic therapy provides significant improvements, but the side effects associated with oral medications should be seriously considered, because they can impair cognitive aspects that will impact the final functionality.

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