Botulinum Toxin
treatment
in Dystonia

Silvia Lori
s.lori@meyer.it
Clinica di Neurologia Pediatrica  Meyer
Università di Firenze

Dystonic Child, Lecco 6-7 giugno 2008
Background

- **Dystonia,** defined as “a neurological syndrome characterised by involuntary patterned, sustained, or repetitive muscle contractions of opposing muscles, causing twisting movements and abnormal postures”.  
  
  *(Fahn, Bressman & Marsden, 1998)*

- Is one of the most disabling movement disorders.

- Although pathogenesis-targeted treatment is still elusive, the currently available symptomatic treatment strategies are quite effective for some types of dystonia in:

  - relieving involuntary movements,
  - correcting abnormal posture,
  - preventing contractures,
  - reducing pain,
  - improving function and quality of life
**Distonia treatment**

- **Oral Medications**
  - Levodopa
  - Anticholinergics
  - Baclofen
  - Benzodiazepines
  - Tizanidine

- **Chemodenervation**
  - Botulinum Toxin A
  - Botulinum Toxin B

- **Other Modalities**
  - Immobilization and Splinting
  - Physical and Occupational Therapy

- **Surgical Therapies**
  - Peripheral Surgeries
    - Selective Peripheral Denervation
  - Central Surgeries
    - Pallidotomy
  - Myectomy
  - Deep Brain Stimulation (Globus Pallidus)
Rationale to use Botulinum Toxin

- Neuromuscular blockade via injection of botulinum toxin reduces the tone of overactive muscles in order to restore the appropriate balance between agonists and antagonists.

Botulinum Toxin (BTX), purified forms of Clostridium botulinum exotoxins:

Seven Serotype

Human Botulism
**Mechanism of Action**

BTX are injected directly into muscle, where they cleave one or more vesicle fusion proteins, thus blocking release of acetylcholine at the neuromuscular junction.
• Levels of Action

• Alpha Motor ending
• Gamma Motor ending
• Cholinergic Autonomic ending
• Central Nervous System
BTX has a clinical onset of action approximately 12 to 72 hours after injection, with a peak effect at 1 to 3 weeks.

Effects then plateau for 1 to 2 months.

“timing recovery”
✓ Neuromuscular function: 3-5 month
✓ Autonomic function: > 5 month

…”snare” protein disattivation
Murine Endplate Response to Intramuscular BoNT-A

Sprouting

Recovery

Source: dePaiva et al. PNAS 1999, 96:3200
Four commercial products:
three of serotype A

Botox® 100 U
Dysport® 500 U

Xeomin® 100 U

and one serotype B

Neurobloc® 5000-10000 U

Each differs in its unit potency, duration of action and side effects.

Side effects may include local discomfort at the site of the injection and excessive weakness of the injected or nearby muscles.
<table>
<thead>
<tr>
<th>Serotype / Target</th>
<th>Molec. Weight (kDa)</th>
<th>Excipients</th>
<th>Final Formulation</th>
<th>Unit / Vial Protein / Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox® (1989)</td>
<td>900 kDa</td>
<td>NaCl, Sero-albumin</td>
<td>Dried vacuum-packed pH: ~7</td>
<td>100U ~5ng</td>
</tr>
<tr>
<td>Neurobloc™ (2000)</td>
<td>700 kDa#</td>
<td>NaCl, Sero-albumin Succinate Na</td>
<td>Solution pH: 5.6</td>
<td>5000, 10,000 50/100ng</td>
</tr>
<tr>
<td>Dysport® (1991)</td>
<td>500 kDa</td>
<td>Lactose Sero-albumin</td>
<td>Lyophilized pH: ~7</td>
<td>500U 12.5ng</td>
</tr>
</tbody>
</table>

#Elan PI data states as 700kDa; literature reports largest complex for B is 500 kDa and largest complex for A is 900 kDa.
**Management of Spasticity with Botulinum Toxin Type A (botox®)**

### Suggested Pediatric Botox® Dosing

<table>
<thead>
<tr>
<th>Clinical Pattern</th>
<th>Potential Muscles Involved</th>
<th>BOTOX® Dose® Units/Kg</th>
<th>Number of Injection Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper Limbs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adducted/Internally Rotated Shoulder</td>
<td>pectoralis major, latissimus dorsi, teres major, subscapularis</td>
<td>2</td>
<td>1–2</td>
</tr>
<tr>
<td>Flexed Elbow</td>
<td>biceps/triceps</td>
<td>1–2</td>
<td>1</td>
</tr>
<tr>
<td>Pronated Forearm</td>
<td>pronator quadratus, pronator teres</td>
<td>0.5–1</td>
<td>1</td>
</tr>
<tr>
<td>Flexed Wrist</td>
<td>flexor carpi radialis, flexor carpi ulnaris</td>
<td>1–2</td>
<td>1</td>
</tr>
<tr>
<td>Thumbs-in-Palm</td>
<td>flexor pollicis longus, adductor pollicis</td>
<td>0.5–1</td>
<td>1</td>
</tr>
<tr>
<td>Clenched Fist</td>
<td>flexor digitorum profundus, flexor digitorum superficialis</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Intrinsic Plus Hand</td>
<td>lumbricals/interossei</td>
<td>0.5–1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Lower Limbs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexed Hip</td>
<td>iliotibial band, pectoralis minor, rectus femoris</td>
<td>3</td>
<td>1–3</td>
</tr>
<tr>
<td>Flexed Knee</td>
<td>sartorius, gracilis</td>
<td>3–6</td>
<td>2–4</td>
</tr>
<tr>
<td>Adducted Thighs</td>
<td>adductor longus/abductor, biceps/magnus</td>
<td>3–6</td>
<td>1–3</td>
</tr>
<tr>
<td>Stiff (Extended) Knee</td>
<td>quadriceps mechanism</td>
<td>3–6</td>
<td>2–4</td>
</tr>
<tr>
<td>Equinovarus Foot</td>
<td>gastrocnemius medial/lateral, soleus</td>
<td>3–6</td>
<td>1–4</td>
</tr>
<tr>
<td>Striated Toe</td>
<td>extensor hallucis longus</td>
<td>1–2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Dosing Guidelines for Children**

- Total maximum body dose per visit = lesser of 16 Units per kg or 400 Units
- Maximum dose per large muscle per visit = 6 Units per kg
- Maximum dose per small muscle per visit = 1–2 Units per kg
- Maximum dose per injection site = 50 Units
- Maximum volume per site = 1.0 mL, except in select situations
- Dilution: 1–5 mL per vial. More dilute solutions may be more effective in larger muscles.
- Reinjection ≥ 3 months

**Procedure to Treat**

Recommendations:

- Parents' information on the choice/dilution/dose.
- Accurate selection of muscle.
- Re-injection > 4 months

**DOSE MODIFIERS**

<table>
<thead>
<tr>
<th>CLINICAL SITUATION</th>
<th>DOSE PER MUSCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Decrease in Dose</td>
<td>May Be Indicated if</td>
</tr>
<tr>
<td>An Increase in Dose</td>
<td>May Be Indicated if</td>
</tr>
<tr>
<td>Patient weight</td>
<td>Low</td>
</tr>
<tr>
<td>Likely duration of therapy</td>
<td>Chronic</td>
</tr>
<tr>
<td>Muscle bulk</td>
<td>Very small</td>
</tr>
<tr>
<td>Number of muscles being injected simultaneously</td>
<td>Many</td>
</tr>
<tr>
<td>Ashworth score</td>
<td>Low</td>
</tr>
<tr>
<td>Concern that treatment may result in excess weakness</td>
<td>High</td>
</tr>
<tr>
<td>Results of previous therapy</td>
<td>Too much weakness</td>
</tr>
</tbody>
</table>

**Key Points**

- Botox® rarely causes complications or significant adverse effects in the pediatric patient.
- Children may benefit from antispasmodics and/or topical anesthetics before injection.
- Meaningful assessment of treatment outcome depends on careful definition of objectives beforehand.
- The effects of Botox® are seen within several days and last on average for 3–4 months.

© WE HOME® [REVISED AUGUST 2005 | EDITION 1.0]  *Adult dosing recommendations should be substituted for children heavier than 60 kg.* 
© WE HOME® [REVISED AUGUST 2005 | EDITION 1.0]  *
Dosing tables are web viewable and downloadable at [www.mindus.org](http://www.mindus.org)*
failure – no responder

- Error of muscle(s) evaluation
- Error of BTX preparation and/or conservation
- Joints structuration
- Antibody formation against BTX

Switching serotypes may be effective, at least temporarily.

For better response may to use more serotype of BTX.
BTX in Dystonia

Elective to treat **Focal Dystonia** (little muscles): blepharospasmus, spasmodic dystonia (torticollis..)

Good/partial/variable results in **Segmental Dystonia**, because localisation, number and muscles size (limb dystonia)

“Add-on” in **Generalized Dystonia**
Treatment of dystonia.

Therapeutic options must be tailored to the needs of individual patients and include chemodenervation with BTX injections for patients with focal or segmental dystonia, and medical treatments or deep brain stimulation for patients with generalised dystonia.
Treatment of recalcitrant idiopathic muscular torticollis in infants with botulinum toxin type a.

Botulinum toxin type a in the treatment of children with congenital muscular torticollis.

Botulinum toxin injection for congenital muscular torticollis presenting in children and adults.
Collins A,. Neurology. 2006 Sep 26;67(6):1083-5

BTXA may be a safe and effective treatment option for children with congenital muscular torticollis who are unresponsive to only traditional regimen of physical therapy and a home program. It may obviate the need for surgical release of a tight non fibrotic SCM
Distonia

“There is a caudo-cranial gradient in age of onset and the age of onset increases as the cranial presentation becomes greater”

Bartolomé 2003

Fahn 1988
## Genetica

<table>
<thead>
<tr>
<th>Locus</th>
<th>Clinical Features</th>
<th>Inheritance</th>
<th>Location</th>
<th>Gene Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>Early-onset Generalized</td>
<td>AD</td>
<td>9q34</td>
<td>Torsin A</td>
</tr>
<tr>
<td>DYT2</td>
<td>Early-onset Segmental (Generalized)</td>
<td>AR</td>
<td>14q22.1-2</td>
<td>---</td>
</tr>
<tr>
<td>DYT3</td>
<td>Generalized-Segmental + Parkinsonism</td>
<td>XR</td>
<td>Xq13.1</td>
<td>---</td>
</tr>
<tr>
<td>DYT4</td>
<td>Dysphonia</td>
<td>AD</td>
<td>16p11.2</td>
<td>---</td>
</tr>
<tr>
<td>DYT5</td>
<td>Dopa Responsive</td>
<td>AD</td>
<td>14q22.1-2</td>
<td>GTP cyclohydrolase I</td>
</tr>
<tr>
<td></td>
<td>Dystonia-Parkinsonism</td>
<td>AR</td>
<td>11p15.5</td>
<td>Tyrosin-Hydroxilase</td>
</tr>
<tr>
<td>DYT6</td>
<td>Rapid-onset dystonia + Parkinsonism</td>
<td>AD</td>
<td>16p11.2</td>
<td>---</td>
</tr>
<tr>
<td>DYT7</td>
<td>Adult Focal</td>
<td>AD</td>
<td>18p</td>
<td>---</td>
</tr>
<tr>
<td>DYT8</td>
<td>Paroxysmal choreoathetosis</td>
<td>AD</td>
<td>16p11.2</td>
<td>---</td>
</tr>
<tr>
<td>DYT9</td>
<td>Paroxysmal choreoathetosis + ataxia, spasticity</td>
<td>AD</td>
<td>16p11.2</td>
<td>---</td>
</tr>
<tr>
<td>DYT10</td>
<td>Paroxysmal kinesigenic choreoathetosis</td>
<td>AD</td>
<td>16p11.2</td>
<td>---</td>
</tr>
<tr>
<td>DYT11</td>
<td>Myoclonus-dystonia + parkinsonism</td>
<td>AD</td>
<td>11q23</td>
<td>ε-sarcoglycan (D2 receptor)</td>
</tr>
<tr>
<td>DYT12</td>
<td>Rapid-onset dystonia + parkinsonism</td>
<td>AD</td>
<td>19q</td>
<td>---</td>
</tr>
<tr>
<td>DYT13</td>
<td>Juvenile or early adult Segmental (Cranio-cervical)</td>
<td>AD</td>
<td>1p36</td>
<td>---</td>
</tr>
</tbody>
</table>
# Dystonic Syndromes

<table>
<thead>
<tr>
<th>Parkinsonism</th>
<th>Neuropathy</th>
<th>Supranuclear oculomotor</th>
<th>Optic/Retinal</th>
<th>Ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia</td>
<td>MLD</td>
<td>Dystonic-lipidoses</td>
<td>GM2</td>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Wilson's</td>
<td>Neuroacanthocytosis</td>
<td>SCA1 and SCA3</td>
<td>HSD</td>
<td>Mitochondrial</td>
</tr>
<tr>
<td>Gangliosidosis</td>
<td>HD</td>
<td>Ataxia-telangiectasia</td>
<td>NCL</td>
<td>SCA1 and SCA3</td>
</tr>
<tr>
<td>HD</td>
<td>SCA1 and SCA3</td>
<td>CBGD</td>
<td>Mitochondrial, including LHON</td>
<td>MLD</td>
</tr>
<tr>
<td>XPD</td>
<td>Mitochondrial</td>
<td>HD</td>
<td>Homocystinuria</td>
<td>Dystonic-lipidoses</td>
</tr>
<tr>
<td>RDP</td>
<td></td>
<td>Pallidal degeneration</td>
<td></td>
<td>NCL</td>
</tr>
<tr>
<td>HSD</td>
<td>Neuroacanthocytosis</td>
<td></td>
<td></td>
<td>Hartnup's</td>
</tr>
<tr>
<td>SCA3</td>
<td>PD</td>
<td></td>
<td></td>
<td>Wilson's</td>
</tr>
<tr>
<td>Neuroacanthocytosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>CBGD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSP</td>
<td>Toxins: manganese, methanol, CS₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBGD</td>
<td>Anoxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcification of BG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemiatrophy/hemiPD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BTX treatment ?!**

**Cerebral Palsy**

**Lesion**
**Dystonia: an update on genetics and treatment**


*Treatment of more severe dystonia has been a difficult area, with only limited success from medical therapies.*

**Botulinum toxin type A treatment in neurogenetic syndromes**


*The use of BTX-A in uncommon neurogenetic syndromes was supported by the majority of families interviewed.*

**Management of movement disorders in glutaryl-CoA dehydrogenase deficiency: anticholinergic drugs and botulinum toxin as additional therapeutic options**


*BTX-A in add-on with anticholinergic drugs*

**Botulinum toxin as a novel treatment for self-mutilation in Lesch-Nyhan syndrome.**


*treatment with BTX-A affects both the central and peripheral nervous systems, resulting in reduced self-abusive behavior in this patient.*
Botulinum toxin as a treatment for infantile cerebral palsy
Pascual-Pascual SI, Rev Neurol. 1997 Sep;25(145):1369-75

BTA is highly effective in the treatment of spastic and/or dystonic CP, and if associate with physiotherapy long and even permanent effect can be achieved.

Preoperative treatment with botulinum toxin to facilitate cervical fusion in dystonic cerebral palsy. Report of two cases.

Preoperative chemodenervation of selected cervical muscles with injections of high-dose BTX-A eliminated all involuntary neck movements, permitting the patients to tolerate halo fixation and facilitating postoperative spinal fusion.

Injectable neuromuscular blockade in the treatment of spasticity and movement disorders
Tilton AH. J Child Neurol. 2003 Sep;18 Suppl 1:S50-66

The treatment program, in which chemodenervation is only one tool, requires a multidisciplinary evaluation and individualized plan to address the whole patient.

Botulinum toxin type B improves the speed of reaching in children with cerebral palsy and arm dystonia: an open-label, dose-escalation pilot study.

Use of BTX-B as a safe and effective treatment for upper extremity dystonia in children with cerebral palsy. Larger controlled trials are needed to confirm these results.

59 CP pz (29F-30M)

- 13 CP Dystonic
- 46 CP Spastic

56 pz treated with BTX-A

- 5 SUP/INF LIMB
- 2 SUP LIMB
- 49 INF LIMB

Follow-up: 1-3-6-12 month after treatment
54/59 pz

ROM mean/month

Ashworth Mean/month

BAD Scale: segmental mean score

Quality treatment for family

Parents

<table>
<thead>
<tr>
<th>Parents</th>
<th>1 insatisfactory</th>
<th>2 sufficient</th>
<th>3 good</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13/59 pz
BTX and Central Nervous System

On the Question of Permeability of the Blood-Brain Barrier to Botulinum Toxin

Dr. Daniel A. Boroff, Int. Archs Allergy appl. Immun. 48: 495–504 (1975)
Physiological Effects of Botulinum Toxin in Spasticity

Jean-Michel Gracies, MD, PhD

Abstract: There is considerable evidence that injection of botulinum toxin (BTX) into muscles with spastic overactivity reduces resistance to passive movement in joints supplied by the injected muscles. The demonstration of improvement in active performance of the paretic limbs has been only anecdotal to date, and represents the most difficult challenge in research on BTX therapy in spastic paralysis. Data are reviewed that indicate several neurophysiological actions of BTX, other than the blocking of acetylcholine release at the neuromuscular ending: effects on the central nervous system, including retrograde axonal transport, reduced motoneuronal excitability, action on central synapses such as decreased Renshaw inhibition and increased presynaptic inhibition; action on gamma motoneuronal endings; action on most active terminals; spread of BTX to neighboring muscles; spread of BTX effects to remote muscles. Several of these neurophysiological actions are likely to contribute to improvement in active movements, as they may antagonize the primary mechanisms of functional impairment in patients with spastic paralysis: weakness, spastic cocontraction, spastic dystonia, and muscle shortening. We review the evidence for reduction of spastic cocontraction in both the injected muscle and its antagonist, and for improvement of antagonist weakness after BTX injection. The capacity of intramuscular BTX to reduce spastic dystonia and lengthen shortened muscles is also discussed based on prior literature. When injected into the more overactive of a pair of spastic antagonists around a joint, BTX should affect all the main mechanisms impairing active function around the joint. © 2004 Movement Disorder Society
Breakdown of inhibitory mechanisms in dystonia

Motor and SMA cortex

Cortex

Spinal Cord

Brainstem

Nakashima et al. 1989

Berardelli et al. 1995

Ridding et al. 1995
Central Effects of Botulinum Toxin Type A: Evidence and Supposition

A. Currà ET AL.

Movement Disorders
Vol. 19, Suppl. 8, 2004, pp. S60-S64
© 2004 Movement Disorder Society

**Abstract:** No convincing evidence exists that botulinum toxin type A (BT-A) injected intramuscularly at therapeutic doses in humans acts directly on central nervous system (CNS) structures. Nevertheless, several studies, using various approaches, strongly suggest that BT-A affects the functional organization of the CNS indirectly through peripheral mechanisms. By acting at alpha as well as gamma motor endings, BT-A could alter spindle afferent inflow directed to spinal motoneurons or to the various cortical areas, thereby altering spinal as well as cortical mechanisms. Muscle afferent input is tightly coupled to motor cortical output, so that the afferents from a stretched muscle go to cortical areas where they can excite neurons capable of contracting the same muscle. The BT-A–induced reduction in spindle signals could, therefore, alter the balance between afferent input and motor output, thereby changing cortical excitability. © 2004 Movement Disorder Society
our data suggest that botulinum toxin can transiently alter the excitability of the cortical motor areas by reorganizing the inhibitory and excitatory intracortical circuits. The cortical changes probably originate through peripheral mechanisms.
**Somatosensory Disinhibition in Dystonia**

**E. Frasson et al.***

Movement Disorders
Vol. 16, No. 4, 2001, pp. 674–682
© 2001 Movement Disorder Society
Published by Wiley-Liss, Inc.

**Abstract:** Despite the fact that somatosensory processing is inherently dependent on inhibitory functions, only excitatory aspects of the somatosensory feedback have so far been assessed in dystonic patients. We studied the recovery functions of spinal N13, brainstem P14, parietal N20, P27, and frontal N30 somatosensory evoked potentials (SEPs) after paired median nerve stimulation in 10 patients with dystonia and in 10 normal subjects. The recovery functions were assessed (conditioning stimulus: S1; test stimulus: S2) at interstimulus intervals (ISIs) of 5, 20, and 40 ms. SEPs evoked by S2 were calculated by subtracting the SEPs of the S1 only response from the SEPs of the response to the paired stimuli (S1 + S2), and their amplitudes were compared with those of the control response (S1) at each ISI considered. This ratio, (S2/S1)*100, investigates changes in the excitability of the somatosensory system. No significant difference was found in SEP amplitudes for single stimulus (S1) between dystonic patients and normal subjects. The (S2/S1)*100 ratio at the ISI of 5 ms did not significantly differ between dystonic patients and normal subjects, but at ISIs of 20 and 40 ms, this ratio was significantly higher in patients than in normals for spinal N13 and cortical N20, P27, N30 SEPs.

These findings suggest that in dystonia there is an impaired inhibition at spinal and cortical levels of the somatosensory system which would lead to an abnormal sensory assistance to the ongoing motor programs, ultimately resulting in the motor abnormalities present in this disease. © 2001 Movement Disorder Society.
Conclusions: The results of SEP after BTX-A administration in children with cerebral palsy do not confirm the central action of BTX-A on somatosensory pathways. We did not find any significant changes of SEP latencies associated with clinical reduction of spasticity. It seems that SEP results could support the opinion, that BTX-A does not have any direct central effect on sensory pathways. Remote side effects may be explained by an indirect mechanism due to modification of the central loops of reflexes or to hematogenous spread of BTX-A.
SPINAL CORD INJURY: REVERSING THE INCORRECT CORTICAL MAPS BY INDUCTIVE LABILITY PROCEDURE


BOTULINUM TOXIN: FROM SPASTICITY RELIEVER TO A NEUROMOTOR RE-LEARNING TOOL


RELEARNING TOWARD MOTOR RECOVERY IN STROKE, SPINAL CORD INJURY, AND CEREBRAL PALSY: A COGNITIVE NEURAL SYSTEMS PERSPECTIVE

Conclusion

**BTX is a good tool for:**

- relieving involuntary movements,
- correcting abnormal posture,
- preventing contractures,
- reducing pain,
- improving function and quality of life

**BTX and central effects is a “challenge” for the therapeutic implications**
Thank

Tnfp Katiuscia Romano
FT Monica Martini
FT Silvia Paoli