USE OF **BOTOX** IN THE CHILD WITH CEREBRAL PALSY

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WHAT IS BOTOX?

- BOTOX is a purified form of Botulinum toxin
- Neurotoxin produced by Clostridium botulinum (A-G)
- Blocks neurotransmission at motor end plate resulting in
- muscle weakness or paralysis
HISTORY

Botox

Not so great aksully
**Historical Note**

**Historical Notes on Botulism, *Clostridium botulinum*, Botulinum Toxin, and the Idea of the Therapeutic Use of the Toxin**

Frank J. Erbguth, MD, PhD*

“*Neue Beobachtungen über die in Württemberg so häufig vorfallenden tödlichen Vergiftungen durch den Genuss geräucherter Würste*” [“New observations on the lethal poisoning occurring so frequently in Württemberg through the consumption of smoked sausages”] (Fig. 2). Kerner summarised the case histories of 76 patients and gave a complete clinical description of what physicians now recognise as botulism.

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*FIG. 1. Justinus Kerner. Oil painting by Alexander Bruckmann, 1844.*

*FIG. 2. Title page of Kerner’s first monograph on sausage poisoning.*
HISTORY

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1895</td>
<td>Discovery anaerobic microorg <em>Bacillus botulinus</em></td>
</tr>
<tr>
<td>1960</td>
<td>Ophthalmologist Scott 1st to work on therapeutic formulation</td>
</tr>
<tr>
<td>1980</td>
<td>1st use of BTX-A in humans to treat strabismus, blepharospasm</td>
</tr>
<tr>
<td>1989</td>
<td>Effect on wrinkles described</td>
</tr>
<tr>
<td>1993</td>
<td>Use in cerebral palsied children</td>
</tr>
<tr>
<td>1994</td>
<td>Licensed in European Union for neuromuscular disorders</td>
</tr>
<tr>
<td>2002</td>
<td>Approved by FDA for cosmetic use</td>
</tr>
</tbody>
</table>
HOW DOES IT WORK?
Neuromuscular Junction

1 Presynaptic terminal
2 Sarcolemma
3 Synaptic vesicle (ACh)
4 Nicotinic acetylcholine receptor
5 Mitochondrion
Mechanism of botulinum toxin
EFFECT of BTX-A

Inhibition of ACh blocks neurotransmission.

Muscle weakness or paralysis; effect lasts 3-6 months.

Degradation of toxin or abnormal snare protein results in full recovery.
HOW IS THIS USEFUL IN CP?
WHAT HAPPENS IN CP?

- UMN lesion results in hypertonia & spasticity
- Muscle shortening & contracture formation
- Limited range of joint movement

IMPAIRED FUNCTION
RESTORING THE BALANCE

Motor function requires balance of agonist & antagonist muscle groups.

BTX:
- reduces tone, allowing for increased stretch (ROM)
- weakens overactive muscle
BTX only helps with dynamic muscle length, not static muscle length
Modified Tardieu Scale*

- **R1** measures the point of resistance to a RAPID velocity stretch, the “catch”

  \[ \text{\textbullet} = \text{DYNAMIC MUSCLE LENGTH} \]

- **R2** the passive joint range of movement with SLOW velocity stretch

  \[ \text{\textbullet} = \text{STATIC MUSCLE LENGTH/ROM} \]

*Boyd RN, Kerr GH; Eur J Neur 1999, 6
R1-R2
Evidence does it work?
Systematic review identified 10 RCT’s

„Successful” treatment defined as improvement in PRS of 2 or more

European Journal of Neurology 2001; 8 (Suppl. 5): 1-20

Current evidence for the use of botulinum toxin type A in the management of children with cerebral palsy: a systematic review

R. N. Boyd†,‡ and R. M. Hays†

†Hugh Williams Gait Laboratory, Royal Children’s Hospital, Parkville, Victoria, Australia; ‡Children’s Hospital & Regional Medical Centre, Seattle, USA; and School of Physiotherapy, La Trobe University, Bandorea, Victoria, Australia
GAIT

Figure 1: Mean gait parameters (joint angles, in °) for botulinum toxin type A (BTX-A) and control group, along with data for a group of 31 normal children aged between 3 and 6 years. Errors are SD.

Desloovere et al, Dev Med; 2006
Interim report on Clinical Study comparing efficacy of Botox injections into calf muscles in 1 – 3 year old children with 5 – 7 year old children with Cerebral Palsy

Drs Van Bever Donker, Sparks and Goldschmidt
Statistical analysis by Sonja Swanevelder, MRC
Cape Town 2005
Figure 3: Median lines for R1-R2 after first Botox up to 9 months

Figure 7: Median lines for OGS on first Botox up to 9 months
Right hemiplegia

Pre BTX

6 weeks post BTX
Fig. 1 Frequency distributions for patients who underwent surgery at different ages

QUALITY OF LIFE?

- Paucity of literature looking at QOL or functional outcome
- Upper limb may be more beneficial, as dysfunction is deemed more debilitating
- Wallen et al 2007 showed significant improvement in perception of role fulfillment with OT & BTX combined (upper limb)
COST EFFECTIVE?

- AUSTRALIA: More expensive but deemed worth it
- USA: Not much difference to individual patient
- GERMANY: Cheaper
LONG TERM USE

- Benefit persists
- No permanent effect on muscle

Naumann et al, Eur J Neuro 2006
Mean follow up 3.7 years

Reduction in tone persisted

Reduced gastrocnemius length in long term

Lack of control group
"Honey, let's lay off the Botox for a while, shall we?"
<table>
<thead>
<tr>
<th>Substance</th>
<th>Route</th>
<th>Species</th>
<th>Lethal Dose (ng/kg)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC (main psychoactive substance in Cannabis)</td>
<td>rat, oral</td>
<td>(males)</td>
<td>730,000,000 ng/kg</td>
<td>[13]</td>
</tr>
<tr>
<td>Metallic Arsenic</td>
<td>rat, oral</td>
<td>(females)</td>
<td>763,000,000 ng/kg</td>
<td>[14]</td>
</tr>
<tr>
<td>Coumarin (benzopyrone, from Cinnamomum</td>
<td>rat, oral</td>
<td></td>
<td>293,000,000 ng/kg</td>
<td>[15]</td>
</tr>
<tr>
<td>aromanticum and other plants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (acetylsalicylic acid)</td>
<td>rat, oral</td>
<td></td>
<td>200,000,000 ng/kg</td>
<td>[16]</td>
</tr>
<tr>
<td>Caffeine</td>
<td>rat, oral</td>
<td></td>
<td>192,000,000 ng/kg</td>
<td>[17]</td>
</tr>
<tr>
<td>Arsenic trisulfide</td>
<td>rat, oral</td>
<td></td>
<td>165,000,000 ng/kg</td>
<td></td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>rat, oral</td>
<td></td>
<td>180,000,000 ng/kg</td>
<td>[19]</td>
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<tr>
<td>Cobalt(II) chloride</td>
<td>rat, oral</td>
<td></td>
<td>80,000,000 ng/kg</td>
<td>[20]</td>
</tr>
<tr>
<td>Cadmium oxide</td>
<td>rat, oral</td>
<td></td>
<td>72,000,000 ng/kg</td>
<td>[21]</td>
</tr>
<tr>
<td>Nicotine</td>
<td>rat, oral</td>
<td></td>
<td>50,000,000 ng/kg</td>
<td>[22]</td>
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<tr>
<td>Lysergic acid diethylamide (LSD)</td>
<td>rat, intravenous</td>
<td></td>
<td>16,500,000 ng/kg</td>
<td>[23]</td>
</tr>
<tr>
<td>Strychnine</td>
<td>rat, oral</td>
<td></td>
<td>16,000,000 ng/kg</td>
<td>[24]</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>rat, oral</td>
<td></td>
<td>14,000,000 ng/kg</td>
<td>[25]</td>
</tr>
<tr>
<td>Metallic Arsenic</td>
<td>rat, intraperitoneal</td>
<td></td>
<td>13,000,000 ng/kg</td>
<td>[26]</td>
</tr>
<tr>
<td>Sodium cyanide</td>
<td>rat, oral</td>
<td></td>
<td>6,400,000 ng/kg</td>
<td>[27]</td>
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<tr>
<td>White phosphorus</td>
<td>rat, oral</td>
<td></td>
<td>3,030,000 ng/kg</td>
<td>[28]</td>
</tr>
<tr>
<td>Mercury(II) chloride</td>
<td>rat, oral</td>
<td></td>
<td>1,000,000 ng/kg</td>
<td>[29]</td>
</tr>
<tr>
<td>Beryllium oxide</td>
<td>rat, oral</td>
<td></td>
<td>500,000 ng/kg</td>
<td>[30]</td>
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<tr>
<td>Aflatoxin B1 (from Aspergillus flavus)</td>
<td>rat, oral</td>
<td></td>
<td>480,000 ng/kg</td>
<td>[31]</td>
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<tr>
<td>Venom of the Inland taipan (Australian snake)</td>
<td>rat, subcutaneous</td>
<td></td>
<td>25,000 ng/kg</td>
<td>[32]</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>rat, oral</td>
<td></td>
<td>20,000 ng/kg</td>
<td>[33]</td>
</tr>
<tr>
<td>VX (nerve agent)</td>
<td>human, oral, inhalation, absorption through skin/eyes</td>
<td></td>
<td>2,300 ng/kg (estimated)</td>
<td>[34]</td>
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<tr>
<td>Batrachotoxin (from poison dart frog)</td>
<td>human, sub-cutaneous injection</td>
<td></td>
<td>2,000-7,000 ng/kg (estimated)</td>
<td>[35]</td>
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<tr>
<td>Maitotoxin</td>
<td>mouse, intraperitoneal</td>
<td></td>
<td>130 ng/kg</td>
<td>[36]</td>
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<tr>
<td>Polonium-210</td>
<td>human, inhalation</td>
<td></td>
<td>10 ng/kg (estimated)</td>
<td>[37]</td>
</tr>
<tr>
<td>Botulinum toxin (Botox)</td>
<td>human, oral, injection, inhalation</td>
<td></td>
<td>1 ng/kg (estimated)</td>
<td>[38]</td>
</tr>
</tbody>
</table>
ADVERSE EFFECTS

FOCAL
local weakening beyond therapy goal*
distant adverse events (eg. bladder dysfunction)*

GENERALISED*

PROCEDURAL

* Occurs when dosage and dilution guidelines not adhered to
36 studies
No severe adverse events
Moderate adverse events 25% (BTX-A) vs 15% (controls)
Focal weakness significantly more
Results: For localized/segmental spasticity, botulinum toxin type A is established as an effective treatment to reduce spasticity in the upper and lower extremities. There is conflicting evidence regarding functional improvement. Botulinum toxin type A was found to be generally safe in children with cerebral palsy; however, the Food and Drug Administration is presently investigating isolated cases of generalized weakness resulting in poor outcomes. No studies that met criteria are available on the use of phenol, alcohol, or botulinum toxin type B injections. For generalized spasticity, diazepam is probably effective in reducing spasticity, but there are insufficient data on its effect on motor function and its side-effect profile. Tizanidine is possibly effective, but there are insufficient data on its effect on function and its side-effect profile. There were insufficient data on the use of dantrolene, oral baclofen, and intrathecal baclofen, and toxicity was frequently reported.

Recommendations: For localized/segmental spasticity that warrants treatment, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A). There are insufficient data to support or refute the use of phenol, alcohol, or botulinum toxin type B (Level U). For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment (Level B), and tizanidine may be considered (Level C). There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen (Level U).
WHO IS IT FOR?

Indications for use
INDICATIONS

- blepharospasm, hemifacial spasm, associated focal dystonia
- idiopathic rotational cervical dystonia (spasmodic torticollis)
- Focal spasticity
  - dynamic equinus foot deformity in ambulant paediatric cerebral palsy patients >2 years
  - wrist & hand in adult post stroke patients
General principles

❖ BTX is never an isolated treatment
❖ Integrated within rehab programme
❖ Can be combined with all other treatment modalities (therapy, casting, splinting, orthoses, pharmacotherapy)

Review article

The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy
General principles

- Experienced practitioners (rehab team) essential to clearly identify patients, sites of injection, goals of therapy
- Post op care & intensive physio is crucial
- Young children respond better
Goals of therapy

❖ GMFCS 1-3

❖ Spastic hemiplegics/diplegics with equinus deformity

❖ Delay need for orthopaedic surgery or decrease number of operations

❖ Improved orthoses tolerance
Goals of therapy

- **GMFCS 4-5**
  - Generally less beneficial
  - Simplified care (ease of ADL’s eg. transfers, dressings, bathing)
  - Reduce secondary musculoskeletal deformity (dislocated hips)
  - Decrease pain
PRACTICAL CONSIDERATIONS
COST

- R2700 per vial (100 units)
- 1-3 vials pp
- Related: 1/2 day admission, theatre
- Red Cross has 16 vials/month
Dosage

- Max 16u/kg TBW
- Calf 4u/kg
- Hams 4u/kg
Acknowledgements

❖ Special thanks to:

❖ Dr Kirsty Donald
❖ Dr Fieke Van Bever Donker
❖ Dr Louis Sparks
❖ Red Cross Neurology Department
❖ Red Cross Physiotherapy Department
THANK YOU
Assessing the child with CP
Assessment tools

- Ashworth scales (tone)
- Tardieu scale (spasticity)
- GMFCS, PEDI (function)
- Physician rating scale, Observational gait scale
- Selective Motor Control
- MACS, QUEST (upper limb function)
- Video (Kinematics, gait analysis)
Reasons for non response to BTX-A

- Inaccurate muscle injection
- Muscle fibrosis
- Formation of antibodies
CONCLUSIONS

❖ Preliminary analysis (9 month follow up)
❖ Significant differences shown in
  ❖ Selective Motor Control @ 6 weeks
  ❖ Observational Gait Scale @ 18 w & 6m
❖ Problem of bias due to small numbers in older group
❖ Couldn’t assess upper limb due to inadequate numbers
Selective motor control

- Measures active dorsiflexion
- Helps predict foot function in gait post BTX

*Boyd RN, Kerr GH; Eur J Neur 1999
Observational gait scale

- 7 subscales, scored 0-3, max score 21
  - Knee pos mid stance
  - Initial foot contact
  - Foot contact mid stance
  - Timing heel rise
  - Hindfoot at mid stance
  - Base of support
  - Gait assistive devices
Fig. 2 Kaplan-Meier survival curves, with the occurrence of the first surgical procedure as the end point, for all 424 patients
