Botulinum toxin preparations and how they work: Principles of clinical use

Carlo Colosimo
Introduction to neurotoxins

- Neurotoxins:
  - Poison nerves
  - Have general or localised effects
  - Are chemical or biological agents
  - Examples of biological neurotoxins include:
    - Venoms (snake, spider and bee)
    - Conus snail, pufferfish and cane toad toxins
    - Bacterial toxins (e.g. Clostridium botulinum, Clostridium tetani, diphtheria, cholera, pertussis, shigella, anthrax)
Discovery of *Clostridium botulinum*

1895
*Clostridium botulinum* first identified by Emile Pierre van Ermengem

1920–30s
Researchers isolated BoNT and identified different serotypes

1940
BoNT A first crystallised and its composition described

1947
A.S.V Burgen discovered that BoNT blocks neurotransmitter release at the neuromuscular junction
First therapeutic use of BoNT A

• Alan Scott:
  • Early 1970s, used BoNT A in animal experiments
  • 1977, first human treated successfully with BoNT A for strabismus; subsequently used in blepharospasm and hemifacial spasm
  • Late 1970s, set up Oculinum Inc to exploit the treatment potential of BoNT A

• BoNT A uses today:
  • Several neurological and ophthalmological conditions
  • Smooth muscle hyperactivity conditions
  • Autonomic dysfunction
## Botulinum neurotoxins

<table>
<thead>
<tr>
<th>Year</th>
<th>Ser.</th>
<th>Therapeutic indication in man</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>A</td>
<td>Strabismus</td>
</tr>
<tr>
<td>1984</td>
<td>A</td>
<td>Blepharospasm and hemifacial spasm</td>
</tr>
<tr>
<td>1985</td>
<td>A</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td>1986</td>
<td>A</td>
<td>Spasmodic adductor dysphonia</td>
</tr>
<tr>
<td>1989</td>
<td>A</td>
<td>Oromandibular dystonia</td>
</tr>
<tr>
<td>1992</td>
<td>A</td>
<td>Spasmodic abductor dysphonia</td>
</tr>
<tr>
<td>1992</td>
<td>F</td>
<td>Cranial-cervical dystonia, stuttering</td>
</tr>
<tr>
<td>1993</td>
<td>A</td>
<td>Upper limb dystonia</td>
</tr>
<tr>
<td>1993</td>
<td>F</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td>1995</td>
<td>F</td>
<td>Blepharospasm</td>
</tr>
<tr>
<td>1995</td>
<td>B</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td>1997</td>
<td>C</td>
<td>Blepharospasm and hemifacial spasm</td>
</tr>
</tbody>
</table>
Neurotoxin structure and function

- Neurotoxins generally have two sub units, or chains, joined by a disulphide bond (S-S)

- The chains have different functions:
  - The light chain contains the catalytic domain
  - The heavy chain is responsible for binding
Mode of action of BoNT (1)

- BoNT is very potent
- It acts presynaptically by blocking the release of acetylcholine (ACh)
- This process involves four stages:
  - Binding of BoNT to the presynaptic membrane
  - Internalization of BoNT into the nerve ending
  - Inhibition of ACh release
  - Recovery by neuronal plasticity
Mode of action of BoNT (2)

1. Binding to the presynaptic membrane

2. Internalization into the nerve ending (1)

3. Internalization into the nerve ending (2)

4. Inhibition of ACh release
Dose equivalence

• The units of BoNT-A preparations are not the same
  • Doses are specific to each preparation and are not interchangeable with each other or with other preparations of botulinum toxin

• Difference in the units of BoNT-A preparations is due to differences in assay methodology, specifically the diluent
# Commercial development of BoNT-A and B

<table>
<thead>
<tr>
<th></th>
<th><strong>Dysport®</strong> (AbobotulinumtoxinA)</th>
<th><strong>Botox®</strong> (OnabotulinumtoxinA)</th>
<th><strong>Xeomin®</strong> (IncobotulinumtoxinA)</th>
<th><strong>Neurobloc®/Myobloc®</strong> (RimabotulinumtoxinB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Units per vial</strong></td>
<td>300 U Speywood</td>
<td>50, 100, 200 U</td>
<td>50, 100 U</td>
<td>2 500, 5 000 or 10 000 U</td>
</tr>
<tr>
<td><strong>Company</strong></td>
<td>IPSEN Pharma</td>
<td>Allergan</td>
<td>Merz</td>
<td>Eisai</td>
</tr>
<tr>
<td><strong>Active substance</strong></td>
<td>Toxin Type A complex</td>
<td>Toxin Type A complex</td>
<td>Toxin Type A complex</td>
<td>Toxin Type B complex</td>
</tr>
</tbody>
</table>
| **Therapeutic Indications** | **Adult** | - Cranioervical dystonia  
- Focal spasticity / Upper limb and lower limb (for some EU countries) |  |  |
|                      | **Children** | - Cerebral palsy (older than 2 years)  
- +/- Equinus foot |  |  |
|                      | **Other indications** | - Urology  
- Pain |  |  |

**RIMABOTLINUMTOXINB is a second choice drug!**
General considerations for BoNT treatment

- Key treatment determinant is the identification of a specific therapeutic goal that may be achieved with the help of BoNT.
- The disability must be focal, and dynamic in nature i.e. reversible muscle hyperactivity if any functional gain is to be attained.
- Must be a coordinated program of adjuvant treatment approaches to maximize the window of opportunity.
- The success depends upon:
  - The dose used.
  - The specific sites in the muscles where the product is injected.
  - The experience of the physician giving the injection.
  - Clear communication between physician and patient, so that both parties understand and agree on the specific symptoms that are being treated and what can be expected as a result of an injection.
Focal denervation with BoNT-A

• Benefits of BoNT-A therapy in focal dystonia
  • A targeted, local treatment
  • Generally well tolerated
  • Short lived side effects
  • Lasts for up to 12 weeks after injections
  • Long term safety proven over many years
  • Benefits in craniocervical dystonia:
    • Blepharospasm: highly effective, offering sustained improvement rates of 90–95% and a good safety profile
    • Cervical dystonia: good and sustained response, even after 15 years treatment, in 70-80 % of the cases

*Colosimo et al. European Journal of Neurology 2010, 17: 15–21
## Local and systemic (rare) adverse events

<table>
<thead>
<tr>
<th>Disorder(s)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Diarrhoea, vomiting</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue</strong></td>
<td>Muscle weakness, brachial neuritis</td>
</tr>
<tr>
<td><strong>Renal and urinary</strong></td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Abnormal gait</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>Accidental injury due to falling</td>
</tr>
<tr>
<td><strong>Procedure-related complications</strong></td>
<td>Pain, soreness at the injection site, tenderness, swelling, bruising, bleeding, and injury to surrounding structures</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Headache, flu-like symptoms, blurred vision, dry mouth, upper respiratory infections, reduced sweating, constipation, postural hypotension</td>
</tr>
</tbody>
</table>

**Contraindications:** allergy to one of the components of BoNT, infection at the proposed injection site, pregnancy and lactating women (potential contraindication)¹