Treating Blepharospasm

Medical Options

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Goals

- Understand Benign Essential Blepharospasm in a historical context
- Historical aspects of BEB therapy
- Medical treatments for BEB
- Historical aspects of Botulism
- Introduction to botulinum toxins
- Mechanism of Action of botulinum toxins
- Using botulinum toxins in BEB
- The 4 toxins
Taking your Therapy Pulse

1) How many of you have been on Artane?
2) How many of you have been on Klonopin?
3) How many of you have been on a botulinum toxin?
4) Anyone heard of Rabellon?
Blepharospasm History

- Brueghel 16th Century
- Meige 1910
- Henderson 1950’s
- BEBRF (1981)
- Botulinum Toxin ?1982
orders of the basal ganglia.

In the series of 135 patients whose cases were studied, 73 (a few more than half) were treated with various drugs. Over the thirty-year period of this study the following drugs were employed: Rabellon (8 cases); hyoscine (2 cases); stramonium (9 cases); Artane (22 cases); Benadryl (6 cases); Benzedrine (10 cases); amphetamine (3 cases); phenobarbital (8 cases); and tincture of opium, Empirin Compound, quinine, Tolserol, and Elixir of Alurate (1 case each).

The psychiatric status of these hallucinators of the 1950s will be
Essential Blepharospasm

COLES, WILLIAM HENRY MD

Abstract

Essential blepharospasm is a severe, progressive bilateral facial spasm affecting older individuals. Its cause is unknown. As the disease becomes severely disabling, a trial of medical therapy (l-dopa) is justified. This often is not successful; if not, the preferred treatment is bilateral differential nerve resection with avulsion of the nerve branches. Although the response to surgical therapy is variable, it is presently the best treatment for the incapacitated patient who fails to respond to medical treatment.

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Table 4. Results of Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Marked (&gt; Three Months) Improvement</th>
<th>Mild (&lt; Three Months) Improvement</th>
<th>No Improvement or Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrabenazine (TBZ)</td>
<td>8 (2, 2, 5, 7, 19, 25, 31, 39, 52)</td>
<td>18 (1, 5, 7, 12, 12, 18, 19, 20, 21, 31, 33, 39, 52, 61, 63, 68, 76, 83, 83, 91)</td>
<td>5 (11, 15, 29, 63, 87)</td>
</tr>
<tr>
<td>Trihexyphenidyl (THP)</td>
<td>9 (1, 4, 5, 23, 40, 42, 49, 52, 54)</td>
<td>5 (19, 52, 61, 84, 92)</td>
<td>10 (2, 10, 16, 53, 63, 65, 84, 85, 87, 91)</td>
</tr>
<tr>
<td>Lithium (LI)</td>
<td>9 (2, 7, 11, 13, 19, 31, 42, 43, 52)</td>
<td>17 (5, 7, 12, 15, 18, 29, 34, 37, 39, 57, 63, 68, 76, 77, 80, 83, 83, 84)</td>
<td>8 (18, 25, 40, 49, 53, 63, 71, 87)</td>
</tr>
<tr>
<td>Sinemet (SI)</td>
<td>3 (1, 7, 23)</td>
<td>6 (3, 5, 17, 37, 40, 80)</td>
<td>10 (12, 13, 16, 21, 29, 31, 43, 61, 63, 67)</td>
</tr>
<tr>
<td>(Carbidopa + levodopa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam (CL)</td>
<td>5 (29, 35, 37, 44, 80)</td>
<td>26 (5, 6, 10, 15, 16, 19, 19, 20, 22, 23, 25, 28, 31, 33, 34, 34, 41, 45, 46, 47, 57, 57, 58, 76, 79, 80, 80, 82, 89, 92)</td>
<td>15 (7, 11, 14, 18, 38, 39, 40, 43, 63, 71, 77, 81, 85, 87, 97)</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>72</td>
<td>48</td>
</tr>
</tbody>
</table>
# Medications for BEB

## Table 1. Oral Medications for Blepharospasm and Other Cranial Dystonias

<table>
<thead>
<tr>
<th>CLASS</th>
<th>GENERIC (BRAND) NAMES</th>
<th>MECHANISM(S) OF ACTION</th>
<th>POSSIBLE SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>trihexyphenidyl (ARTANE), benztrapine (COGENTIN)</td>
<td>block acetylcholine receptors</td>
<td>dry mouth, constipation, blurred vision, mild memory impairment</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>clonazepam (KLONOPIN), lorzepam (ATIVAN), diazepam (VALIUM)</td>
<td>potentiate the effects of GABA on GABA_A receptors</td>
<td>drowsiness, disequilibrium</td>
</tr>
<tr>
<td>GABA_B Receptor Agonist</td>
<td>baclofen (Lioresal)</td>
<td>stimulates GABA_B receptors</td>
<td>drowsiness, disequilibrium, weakness</td>
</tr>
<tr>
<td>Dopamine Receptor Agonist</td>
<td>bromocriptine (Parlodel)</td>
<td>stimulates D_2 dopamine receptors, 5-HT_2 antagonist</td>
<td>nausea, lightheadness, drowsiness</td>
</tr>
</tbody>
</table>
## Medications for BEB

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Actions/Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptic</td>
<td>pimozide (ORAP), haloperidol (HALDOL)</td>
<td>blocks dopamine receptors ((D_2 &gt; D_3 &gt; D_1 &amp; D_4))</td>
</tr>
<tr>
<td>Monoamine Depleter</td>
<td>tetrabenazine (NITOMAN)</td>
<td>inhibits monoamine transporters in the brain</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>levetiracetam (KEPPRA)</td>
<td>binds to the synaptic vesicle protein SV2A</td>
</tr>
<tr>
<td>Imidazopyridine</td>
<td>zolpidem (AMBIEN)</td>
<td>binds to the benzodiazepine receptor 1</td>
</tr>
<tr>
<td>Atypical Antipsychotic</td>
<td>clozapine (CLOZARIL)</td>
<td>blocks dopamine receptors ((D_4 &gt;&gt; D_1, D_2, D_3, &amp; D_5, partial 5-HT_{1A} agonist, cholinergic and histaminergic antagonist))</td>
</tr>
<tr>
<td>Serotonin Receptor Antagonist</td>
<td>cyproheptadine (PERIACTIN)</td>
<td>5-HT(_2) antagonist, antihistaminic</td>
</tr>
<tr>
<td>Antiarrhythmic Agent</td>
<td>mexiletine (MEXITIL)</td>
<td>inhibits inward sodium currents</td>
</tr>
</tbody>
</table>
ORAL MEDICATION DOES NOT WORK
Introduction to Botulinum Toxins
What was the first FDA approved indication for Botox treatment?

- Wrinkles
- Sweating
- Cervical Dystonia
- Blepharospasm
Test Your Botox Knowledge

Botulinum Toxins come from where?
- Bacteria
- Virus
- Fungus
- Dirty Laundry
- Drs. Ties
First discovered in 1793 as foodborne botulism known by Justinus Kerner, a German physician and Poet.

Associated with spoiled sausage and aptly named botulism after the Latin word for sausage, botulus.
More than 70 years later, Dr. Emile Pierre van Ermengem of Belgium was asked to investigate an outbreak of botulism following a funeral dinner where three people died and 23 were paralyzed.

Van Ermengem was able to make a connection between botulism and a spore-forming bacterium he named Bacillus botulinus (now known as Clostridium botulinum). Many scientific studies followed, and seven strains of botulinum toxin were eventually identified (A-G).
1928: Dr. Herman Sommer at the University of California, San Francisco, isolates botulinum neurotoxin type A (BoNT-A) in purified form

1946: Dr. Edward Schantz, a young US army officer stationed at Fort Detrick, and his colleagues, purify BoNT-A in massive quantities for use in government and educational institutions.

The US Office of Strategic Services (OSS) develops a plan for Chinese prostitutes to assassinate high-ranking Japanese officers using small gelatin capsules containing a lethal dose of botulinum toxin.
1966’s: Dr. Schantz and Dr. Alan B. Scott, of San Francisco's Smith-Kettlewell Eye Research Institute, test BoNT-A in monkeys to determine if it is an effective therapy for strabismus.

1970’s Dr. Scott forms his own company called Oculinum, Inc., to develop BoNT-A as a therapeutic tool for strabismus.
1978: Dr. Scott receives permission from the US Food and Drug Administration (FDA) to test BoNT-A in human volunteers.

The original batch is 150 mg and is used for more than 250,000 injections in humans.

For many years, this was the only batch approved by the FDA, which requires batch approval for biological drugs.
In the early 1980s, he published a number of studies including a 1981 paper in the Transactions of the American Ophthalmological Society that asserted botulinum toxin “appears to be a safe and useful therapy for strabismus.”

Additional research showed the drug’s benefits went beyond ophthalmology, providing patients with temporary relief from facial spasms, neck and shoulder spasms, even vocal cord spasms.
1982: A multicenter clinical trial to test BoNT-A for the treatment of strabismus is organized and enrolls more than 7000 patients.

1984: Multiple reports of use of Oculinum for blepharospasm

1987: Dr. Alastair Curruthers, a Canadian dermatologist, uses BoNT-A to remove wrinkles from the forehead of his receptionist, Cathy Bickerton Swann.

1988: Allergan acquires rights to use BoNT-A from Oculinum, Inc., and begins to conduct clinical trials for other indications, including cervical dystonia.
In 1988, drugmaker Allergan acquired the rights to distribute Scott’s batch of botulinum toxin type A (or Oculinum, as it was then known) and a year later, the FDA approved botulinum toxin type A for the treatment of both strabismus and blepharospasm.

Shortly thereafter, Allergan acquired Scott’s company and changed the drug’s name to “Botox®.”
1989

Allergan receives FDA approval to market BoNT-A (Botox®) in the United States as an orphan drug to treat strabismus, blepharospasm, and hemifacial spasm associated with dystonia in patients 12 years of age and older.
Q and A