Volume 3 • Number 6 • 2007

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Botulinum toxin – From WMD to therapeutic agent and cosmetic aid

Botulism has long been known but was first described in the 19th century as a rapidly progressing and fatal paralysis following ingestion of blood sausage. It is most notoriously associated with the early days of the food canning industry in the beginning of the 20th century when many outbreaks occurred particularly in the USA. Food-borne botulism remains to this day a cause of regular outbreaks, but the condition can also arise from wound infection or enteric bacterial overgrowth. The responsible bacterium, *Clostridium botulinum,* was already isolated and identified in the 19th century, but serious research on the purification and crystallization of botulinum toxin type A was carried out only in the cold war era during the search for biological weapons (Schantz and Johnson 1997). Indeed, botulinum toxin became iconic in modern times as one of Iraq's supposed weapons of mass destruction.

Botulinum toxins reduce the presynaptic outflow of the neurotransmitter acetylcholine at the neuromuscular junction, thereby reducing and ultimately totally blocking muscle contraction. The SV2 receptor protein in the presynaptic membrane has been recently identified as the target (Dong et al 2006). Although now notorious as a safe and reliable alternative to certain types of cosmetic surgery, real therapeutic use of botulinum toxin type A dates back to the 1960s when it was first used in ophthalmology to correct strabismus (Scott et al 1973) and subsequently blepharospasm (Scott et al 1985). Indeed, it received FDA approval as long ago as 1989 for the treatment of blepharospasm, strabismus, and facial nerve dysfunction, indications which were followed by approvals for the treatment of cervical dystonia and axillary hyperhidrosis as well as reduction of glabellar lines. In addition to the cosmetic uses (Flynn 2006), there are numerous off-label applications including the treatment of sialorrhea, muscle control disorders such as limb dystonias and spasticity, and painful disorders like low back pain and headache (Cheng et al 2006).

Appearing in this issue of *Neuropsychiatric Disease and Treatment* are two reviews of approved and off-label indications for botulinum toxin type A. Stefan Evers (2007) reviews placebo-controlled randomized controlled trials (RCTs) in tension-type headache and chronic daily headache, and concludes that the majority of trials do not suggest that botulinum toxin type A is efficacious in the treatment of chronic idiopathic headache disorders particularly in chronic tension-type headache. He concedes that it is possible that some subgroups of patients with chronic daily headache may benefit from long-term treatment with botulinum toxin type A – those who are severely impaired and who are not receiving any other type of prophylactic treatment, who constitute about 4% of the total patient group, are most likely to benefit particularly if allodynia is present.

The whole gamut of proven and potential uses of botulinum toxin type A in neurology is reviewed in detail (Ney and Joseph 2007). Clinical uses include the broad categories of facial movement disorders, focal neck and limb dystonias, spasticities, hypersecretory syndromes, and pain. In many of the potential indications only case studies and open label trial are available, but RCTs are becoming the norm as in the case of chronic daily headache. However, botulinum toxin type A has become part of the daily armamentarium of neurologists and other medical specialists treating movement and behavioral disorders. Experimental exploration abounds and perhaps

the most exciting aspect for the neuroscientist is the potential neuroprotective effect of botulinum toxin type A in inhibiting enzymes responsible for hippocampal cell death in rats (Manno et al 2007). From medieval poison to biological weapon to modern therapeutic is quite a transformation, and we await further innovative clinical applications with considerable curiosity and interest.

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