EDITORIAL

Therapeutic application of botulinum toxin

The neurotoxins produced by the anaerobic spore-forming Clostridium botulinum constitute the most potent group of acute toxins known. The seven serologically distinct toxins (A–G) all exert similar highly specific pharmacological activity acting primarily at the neuromuscular motor synapse by blocking release of the neurotransmitter acetylcholine. This results in a flaccid muscular paralysis that is typical of the rare but often fatal disease botulism. Early symptoms of botulism include nausea, dry mouth and impaired vision but the disease may progress through widespread flaccid neuromuscular paralysis leading ultimately to death from respiratory depression. In man the most common cause of the disease is the ingestion of food containing pre-formed toxin produced by contaminating C. botulinum organisms. Infection with C. botulinum can give rise to other forms of botulism. Wound botulism is a rare form of the disease that results when C. botulinum contaminates, colonises and produces toxin in wounds in a manner analogous to the tetanus disease process. Infant botulism, so called because children of up to c. 35 weeks of age only appear to be susceptible, results from colonisation of the intestinal tract by C. botulinum with consequent secretion of toxin.

There is no known cure for the toxic paralysis of botulism. Therapeutic preparations of antitoxin are available and may form an integral part of the clinical treatment but by the time clinical symptoms present the toxin is irreversibly bound to the nerve terminal and the blockade of neurotransmitter release cannot be reversed. However, antitoxin therapy may improve survival and shorten the clinical course of the disease. Antitoxin therapy may form a useful adjunct to the antibiotic treatment used to eliminate intestinal colonisation in cases of infant botulism. Botulinum toxoid vaccines presently offer the only effective means of preventing the neuroparalytic effects of the botulinum toxins. Although the mortality of botulism has fallen in recent years the lack of any effective cure for the disease still evokes an emotive and fearful view of the disease still evokes an emotive and fearful view of the disease. Recent exciting evidence suggests that the neurotoxins have zinc endopeptidase activity and that the toxins may act by cleaving the specific protein component(s) of synaptic vesicle membranes.

The very characteristics that make botulinum toxin such a potent neuroparalytic agent exquisitely suit the toxin for use as a drug to induce specific muscular weakness. This novel clinical application of botulinum
toxin type A was introduced initially as an alternative to conventional surgical intervention for the treatment of strabismus.29 The therapeutic use of botulinum toxin has extended beyond its initial application to include a variety of neurological disorders associated with involuntary spasmodic contraction of muscles, specifically focal dystonias.31, 32 No specifically treatable causes of dystonia have been identified, hence only symptomatic relief can be offered to patients, but botulinum toxin therapy has proved to be remarkably effective in this context. Toxin therapy has become established as the treatment of choice for benign essential blepharospasm, in which intermittent or sustained involuntary contraction of the orbicularis oculi causes forceful closure of the eyes and is now used in preference to the surgical alternatives of muscle stripping or bilateral avulsion of the facial nerve. The treatment is not a cure, as the development of new motor end plates may restore motor function, but repeat injections usually serve to maintain effective control of the condition.23-25 Symptoms of hemifacial spasm, Meige syndrome, facial synkinesis, oromandibular dystonia and laryngeal dystonia all respond well to toxin therapy.26 Spasmodic torticollis is a dystonia of neck muscles that causes abnormal head movements and posture and which is frequently accompanied by cramp-like pains. Botulinum toxin therapy has proved to be beneficial for torticollis, giving temporary improvements in posture and relieving pain.31, 27, 28

The chemical denervation induced by botulinum toxin is increasingly being used for more complex conditions involving abnormal muscle contraction, including writer's cramp and other task-specific disorders of hand muscles. Motor dysfunction due to abnormally increased muscle tone, such as spasticity, may respond well to toxin therapy. There may also be a role for treating some forms of tremor, which is by far the most common involuntary muscular disorder.23, 29 There appear to be no absolute contra-indications for toxin treatment of involuntary muscular spasms. Generally, side effects are minor, self-limiting and localised and may be minimised by careful selection of dose and placement of injections. The long term effects of continued treatment are not known but there have been no reports of adverse systemic effects in patients who have received long term courses of treatment. Concerns about the possible chronic stimulation of an immune response by repeated injections appear generally not to be valid except for a very few patients with conditions that require the administration of higher doses of toxin. In some rare instances patients may stop responding to toxin and, in a proportion of these cases, the presence of circulating, toxin neutralising, antibodies can be demonstrated.30 Where patients develop antibodies there is no alternative to ceasing treatment, although since the various toxin serotypes do not cross react, the possibility of resuming treatment with another toxin serotype may exist.26

The increasing knowledge of the structure and function of the botulinum toxins31, 12, 14-19 offers the possibility of developing new classes of drugs incorporating various biological activities of these toxins. For example, the highly specific binding of the H1 to the motor end plate may be utilised to target other biologically active molecules to motor nerves. Also, the ability of the L2 component to modulate calcium-dependent excocytoses other than acetylcholine release suggests the possibility of controlling other clinical conditions that result from uncontrolled release of mediator substances. It would seem that the remarkable change in our view of the botulinum toxins arising from their initial clinical application may continue with the advent of further, somewhat unexpected, clinical benefits.

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References
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