The current uses of botulinum toxin

Botulinum toxin is an extremely powerful neurotoxin that is a product of the anaerobic bacterium *Clostridium botulinum* and is responsible for the condition botulism. Public awareness of the toxin has recently been raised by its development as a weapon for biological warfare and its facial cosmetic effects. However, the acute paralytic illness after some forms of food poisoning had been recognized for many years and an association with a neurotoxin was demonstrated over a century ago.

HOW DOES BOTULINUM TOXIN WORK?

The toxin is created as an inactive single protein chain that is cleaved by proteolysis to form an active light and heavy chain bound by a disulphide bridge. The heavy chain binds to receptors on the nerve ending and facilitates the translocation of the toxin into the neurone. The light chain then prevents the normal release of acetylcholine from the neurone into the synapse. Thus, all of the effects of the toxin are a result of its anticholinergic properties.

When used in small controlled quantities botulinum toxin causes muscle paresis rather than paralysis. Once the toxin has affected a neurone, the effect is temporary but long lasting and recovery can take several months. This property has facilitated the application of the toxin in various therapeutic situations and is also advantageous if a complication arises from injecting an excessive dose of toxin.

WHAT TYPES OF TOXINS ARE THERE?

There are seven antigenically distinct serotypes of toxin labelled ABCDEF and G, each having a unique protein chain that has a different site of activity within the neurone but the same end result. The most potent is type A toxin-haemaglutinin complex. This was the initial toxin that was applied clinically by Scott, an ophthalmologist in San Francisco, to weaken specific ocular muscles in patients with strabismus. In 1989 the US Food and Drug Administration approved botulinum toxin type A in the USA and Allergan (High Wycombe) marketed it as Botox in vials containing 100 units. A similar type A toxin was developed in the UK at Porton Down laboratories and this was subsequently marketed as Dysport, initially by Speywood and later by Ipsen Biopharm Ltd (Slough) in vials containing 500 units of toxin.

Recently type B toxin (Neurobloc, Elan Pharma Ltd, Stevenage) has been developed and used therapeutically for cervical dystonias and adductor spasmodic dysphonia (Adler et al, 2002).

Type A toxin is lyophilized powder that requires reconstitution with 0.9% sodium chloride and can be stored for only 8 hours in a refrigerator before it needs to be discarded. Neurobloc preparations are already in solution and each vial (0.5 ml, 1 ml, 2 ml) contains a standard concentration of 5000 units/ml so wastage should be limited. An advantage of this new toxin is that it will still be effective in patients who have become resistant to type A toxin.

WHAT ARE THE CLINICAL APPLICATIONS OF BOTULINUM TOXIN?

The articles included in the symposium in this issue clearly describe the applications and experience of experts in the field, and although each article is expansive in its own right, it has not been possible to cover all of the current indications within this issue. Dystonia affecting the head and neck region or the limbs remains the single most important clinical condition for botulinum toxin injections. However, perhaps the most frequent use for botulinum toxin injections within Western populations is facial cosmesis.

Autonomic symptoms are well recognized in botulism and this can lead to misinterpretation of symptoms and misleading diagnoses (Critchley et al, 1989). However, this characteristic has led to innovative indications to control autonomic symptoms with botulinum toxin, such as axillary or palmar hyperhidrosis, hypersalivation, drooling, Frey's syndrome and crocodile tears. The use in axillary hyperhidrosis has circumvented the need for more radical treatments such as excision of the local skin, surgical dennervation and cervical sympathectomy. There have even been reports investigating the effect of nasal mucosal injections of botulinum toxin in the management of rhinitis (Rohrbach et al, 2001).

Other therapeutic applications include chronic anal fissure, achalasia, and relief of spasticity in children with cerebral palsy. There have been some publications describing a therapeutic effect from treating tension-type headache, migraine and fibromyalgia with botulinum toxin. However, the level of evidence to support these applications is low. Initial enthusiasm for developing new applications should therefore be accompanied by proper therapeutic evaluation in multicentre randomized control trials.

The current high cost of botulinum toxin, increasing number of therapeutic applications and the need for recurrent long-term injections are all important issues to be considered when setting up a service and planning health-care resources. Development of an effective service needs not only commitment from the clinician involved in delivering the service but also support from health service managers responsible for providing adequate resources and for negotiating the health-care contracts. However, once this succeeds, the benefits to patients are considerable.

CONCLUSIONS

There are now a multitude of conditions that have been effectively managed by injections of botulinum toxin and the list seems to expand as time goes on. Naturally, these disorders cross many specialties. The practitioners administering this treatment are often the innovators in the methods of using the toxin.

Once a new use or technique is discovered there is a need and responsibility to dissipate this knowledge among other interested specialists for the benefit of patient care. If dissipation of such knowledge were left strictly to publication of research work, information would either spread far too slowly or may not even be published at all, and the subtleties of techniques and experience would be lost. The internet does undoubtedly provide a valuable source of information for both patients and medical staff alike, but this information is selective, not peer-reviewed and may be biased. However, one particularly useful site is www.wemove.org. Perhaps the most effective method of transferring 'state-of-the-art' information is at nationally arranged cross-specialty meetings. The presentations and discussions could then be published, as was the case for the round table discussion held at the Royal Society of Medicine in 2001 (Lees, 2002). HM

KEY POINTS

- Botulinum toxin is a neurotoxin that prevents the release of acetylcholine and paralyses striated muscle and modifies autonomic responses.
- Type A toxin is the most potent but doses are dependant on the manufacturer.
- Type B toxin is now available and may be helpful in patients who develop resistance to type A toxin.
- Nationally arranged meetings should be arranged at regular intervals to facilitate the spread of information from experts in various specialty sub-groups.

Andrew Swift
Consultant Ear, Nose and Throat Surgeon
Department of Otorhinolaryngology/
Head and Neck Surgery
University Hospital Aintree
Liverpool L9 7AL

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