

Botulinum Toxin : From Toxin to Therapy

By Erle Lim
Consultant Neurologist
National University of Singapore

■ Introduction

Nowadays, Botulinum toxin is the buzzword *du jour*. Articles about how "Botox", the trade name for the toxin produced by *Allergan* pharmaceuticals and *Dysport*, which is produced in Europe, can take years off your face by means of regular injections, has given much hope to ageing fashion mavens everywhere. Sweating, it is said, is soon to be a thing of the past - with injections to the palms and armpits, we can all say goodbye to sweat stains and mortifying embarrassment forever!

Cosmesis is not, however, the only use to which this drug can be put. The drug, properly administered by a trained physician, can offer hope to patients whose quality of life is diminished by diseases such as dystonia, which is characterised by inappropriate contraction of muscles causing the adoption of oftentimes bizarre and disabling postures. Botulinum toxin can also be used to treat patients who have inappropriate muscle contractions or even contractures due to stroke or cerebral palsy, especially when combined with rehabilitation.

It is interesting that this miracle drug has rather nebulous origins. As the word implies, the substance is a poison - in fact, it is one of the most poisonous substances known to man, with just a few nanograms of the poison being capable of killing a man. The disease is known since ancient times, the clinical symptoms of food-borne botulism being described in the early 19th century. Indeed, it is because this type of food poisoning was often seen after ingestion of spoiled sausages, that it became known as botulism, after the Latin "Botulus", or sausage. The neurotoxin, which produces muscle paralysis, is produced by the bacterium, *Clostridium botulinum*, which proliferate after spores of the bacterium are ingested in improperly preserved foods.

Botulinum toxin in its purified form was developed, not for its potential as a therapeutic drug, but as a biological agent of destruction - ie. in germ warfare. After its molecular structure was determined, techniques were developed to produce the toxin in quantity. Of course, it would not be fair to say that all the research done was for nefarious reasons, but a lot of the research was undertaken under the auspices of the military, not only to produce the toxin, but also to develop interventions in the event of exposure to it.

■ How does Botulinum Toxin act? And why is it safe to use in clinical practice?

There are seven serologically distinct serotypes of Botulinum toxin, labelled A to G. All of them act at the level of the neuromuscular junction. Only serotypes A and B have been approved for clinical use to date, and only Type A is available in Singapore. Botulinum toxin induces a *chemical denervation* of striated muscles by cleaving proteins required for the release of acetylcholine. The different serotypes work by cleaving different proteins. This results in temporary flaccid paralysis of the injected muscles, which lasts approximately three to five months. Muscle function returns when new neuromuscular junctions form. This necessitates repeat injections in order to obtain sustained benefit.

Botulinum toxin is safe for clinical use because the injections of miniscule amounts of the drug are given intramuscularly or subcutaneously rather than intravenously. Each vial of Botox (produced by Allergan), for example, contains 100 units of Botulinum toxin Type A. 1 unit of purified toxin is defined as that amount which is lethal to 50% of female Swiss Webster mice. The lethal dose for humans is estimated to be about 3500 times the lethal dose for mice, or about 35 vials. Typically, only 20-60 units are used in treatment for facial lines and at most 360

units at any one sitting, so there's a very wide margin of safety. In addition, during the injections, care is taken to withdraw the plunger prior to injecting the toxin to ensure that the needle is not within a blood vessel, as injecting Botulinum toxin intravenously might well be disastrous. However, after a decade of therapeutic application of the toxin, no anaphylaxis or deaths attributable to Botulinum toxin have been reported

■ **What adverse effects are possible?**

The obvious adverse effects are due to injection of too high a dose or of diffusion of the toxin to unintended sites. This may take the form of excessive weakness in the injected muscles or of weakness in muscles adjacent to injected muscles, eg dysphagia or dysphonia after injection of neck muscles.

Other side effects may be attributed to a serum sickness-like reaction due to the protein content in the toxin preparation. This may result in malaise, itching, flu-like symptoms or even chest infections and headaches.

Pain at the injection site may well be expected. Rashes rarely occur.

As a rule, the administration of Botulinum toxin is a safe procedure when given by a trained physician. Informed consent is taken by the administering physician prior to the procedure to ensure that the patient understands the potential side effects.

■ **Are there any contraindications to the administration of Botulinum Toxin?**

Obvious relative contraindications to the administration of Botulinum toxin include pregnancy, as the potential teratogenicity of the drug remains unknown. Thus, the drug should not be given to pregnant mothers until the cessation of breastfeeding. Contraindications to botulinum toxin use include a history of hypersensitivity to the toxin, human albumin, or saline and neuromuscular disorders, such as Eaton-Lambert syndrome and myasthenia gravis. Several medications potentiate the effects of botulinum toxin, such as aminoglycosides, penicillamine, quinine, and calcium channel blockers. Toxin injection should not be performed for these patients.

■ **Clinical applications of Botulinum Toxin**

Recognition of the clinical applications of Botulinum toxin is attributed to Scott. He used local injection of minute doses to selectively inactivate muscle spasticity in strabismus. It was found to be a safe and effective therapy without significant local or systemic side effects, and this led to its use in other conditions.

To date, botulinum toxin has been used to selectively paralyse muscles in treating various forms of dystonia and spasticity. Some of the more obvious dystonia conditions which come to mind include task-specific dystonia (such as writer's cramp), torticollis, spasmodic dysphonia (causing either a strangled voice in adductor spasm or a breathy voice in abductor spasm), dysphagia due to cricopharyngeus overactivity in Parkinson's disease and blepharospasm. Botulinum toxin is useful in the treatment of post-stroke spasticity, as well as in the rehabilitation of the child with cerebral palsy. Interestingly, botulinum toxin has been shown to be useful in the treatment of tension headaches and migraines, and a clinical trial, funded by Allergan, is now about to commence in Singapore (including the National University and Alexandra hospitals) to investigate the appropriate doses in Asian patients. Injection of selective muscles can also do much to ameliorate tremors and motor tics.

Less disabling, perhaps, but no less distressing to "sufferers" are the conditions of hyperhidrosis and ageing. Selective application of botulinum toxin to the palms and/or the axillae have been clinically proven to reduce sweating for up to six months. Palmar injections are, however, painful - and this often limits the applicability of the procedure. The cosmetic applications of botulinum

toxin, not only to reduce wrinkling chemically but also to "sculpt" the face by causing atrophy of rather more bulky facial muscles is now commonplace.

Botulinum toxin can also be applied under endoscopic guidance in the treatment of achalasia. Injection of minute amounts (eg 10 units) to the salivary glands can also ameliorate the socially embarrassing problem of sialorrhoea or hypersalivation.

Despite its rather "frivolous" reputation at the moment, where members of the public view Botulinum toxin as the "anti-wrinkling" drug, it can be seen that this toxin has far more uses than as a beauty enhancer.