The use of botulinum toxin in otorhinolaryngology

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In recent years, the use of botulinum toxin has become more popular for the treatment of a wide variety of diseases in the head and neck. It offers the possibility of non-invasive treatment of conditions whose aetiology lies in neuromuscular dyskinesis.

Botulinum toxin is an exotoxin produced by the anaerobe *Clostridium botulinum*. Even in minute amounts, this lethal substance can cause botulism, characterized by paralysis and sometimes autonomic nervous system dysfunction.

C. botulinum is spore-forming. The bacterium can cause botulism by infecting wounds or, more commonly, by ingestion of the bacteria or the toxin produced by the bacteria (e.g. in tinned foods). The term botulism is derived from the Latin word for sausage (*botulus*) (Cherington, 1998).

Botulinum toxin binds irreversibly to the neuromuscular junction, causing local weakness and flaccidity when injected into a muscle. Therefore, the toxin lends itself to treatment of conditions in which spasmodic contraction of muscles produces undesirable symptoms.

Botulinum toxin was first used by the ophthalmologist Alan Scott in humans in 1981 (Scott, 1980) to treat strabismus. Subsequently, the Food and Drug Administration approved the use of the toxin in 1989 for specific conditions.

RATIONALE FOR TREATMENT

The skeletal muscles are easily accessible as they are mainly found on the outside of the body, particularly those in the head and neck. When injecting botulinum toxin percutaneously with a fine needle, certain muscle groups can be very specifically targeted, however small they may be.

The toxin inhibits α motor neuron conduction at peripheral motor neuron junctions, leading to weakness and subsequent atrophy of muscles into which it is injected. Therefore, where there is unwanted muscle hyperactivity (e.g. dystonia), selective injection of botulinum toxin into this muscle or muscle group should improve the symptoms. The toxin also inhibits acetylcholine release in the muscle spindle (γ fibres), so reflex hyperactivity can be counteracted by injection into selected muscle groups (Priori et al, 1995).

The autonomic nervous system is also affected by botulinum toxin. It prevents release of acetylcholine in parasympathetic and some sympathetic neurons (cholinergic postganglionic sympathetic neurons), hence its use in oesophageal achalasia.

PHARMACOLOGY

Botulinum toxin is a polypeptide, consistings of a light chain and a heavy chain, with a disulphide bridge between. There are seven serological sub-types, labelled A to G.

After injection into a muscle the toxin binds rapidly to the neuromuscular presynaptic site, thus preventing the release of acetylcholine. The toxin enters the presynaptic terminal via endocytosis. Each botulinum toxin serotype exerts its effect by enzymatic cleavage of one or more proteins: serotypes A, C and E cleave synaptosome-associated protein 25, types B, D, F and G cleave synaptobrevin vesicle-associated membrane protein, and type C cleaves syntaxin (Hallett, 1999).

Botulinum toxin A is the only type available on the market. However, considerable interest has been expressed in types B and F recently, because antibodies develop to the toxins over time.

The dose of botulinum toxin A is expressed in units. One unit is the median lethal dose injected intra-peritoneally into mice under defined conditions. The doses are not the same in the different commercial preparations of botulinum toxin. Doses used range widely, depending on the effect required and the size of the muscle.

SAFETY

Botulinum toxin injections are generally well tolerated. Injections have been associated with a tran-

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sient burning sensation and bruising at the injection site. Where large volumes are injected or where deep injections are required, nearby muscle groups may be affected. These are most commonly seen in the treatment of torticollis with botulinum toxin, where dysphagia can occur as a result of diffusion of the toxin into the oropharyngeal muscles (Committee on Safety of Medicines/Medicines Control Agency, 1993). This may be sufficiently severe to cause pooling of saliva, with risk of aspiration in severely affected patients. Ptosis, lacrimation, photophobia and ocular irritation can occur when there is injection of botulinum toxin A into muscles surrounding the eye, e.g. in the treatment of hemifacial spasm. Angle closure glaucoma has also been reported. There have been occasional reports of hypersensitivity and influenza-like symptoms after injection.

Botulinum toxin A is contraindicated in generalized disorders of muscle activity, such as myasthenia gravis. It is also contraindicated in pregnancy and in breastfeeding.

The toxin is known to interact with aminoglycoside or spectinomycin. Interaction may also occur with other drugs which have neuromuscular blocking activity, for example polymyxins, tetracyclines and muscle relaxants.

CLINICAL PRACTICE

Two preparations of botulinum toxin exist — Dysport (Ipsen Pharmaceuticals, Maidenhead) and Botox (Allergan, High Wycombe). There is no standardization of dose between the two preparations. Botox seems to be more potent — one study found that one unit of Botox is three times more potent than one unit of Dysport (Odergren et al, 1998). Generally, the larger the muscle, the larger the dose required to give an acceptable effect. Observation of normal movements or postures may help identify which muscle is responsible for the symptoms; electromyography can also help. In delicate areas with small muscles, injections are usually directed by electromyography. One course of treatment with botulinum toxin lasts about 3 months. Further treatment is usually necessary with repeat injections and antibody development can occur (Hambleton et al, 1992). Injections, therefore, are usually given at the lowest dose acceptable to both patient and physician.

Botulinum toxin has multiple uses within the field of otolaryngorhinology (*Figure 1*).

Larynx

Treatment with botulinum toxin A seems particularly effective in patients who have spasmodic dysphonia (Brin et al, 1998) which causes a strangled voice, e.g. in adductor-type dysphonia.

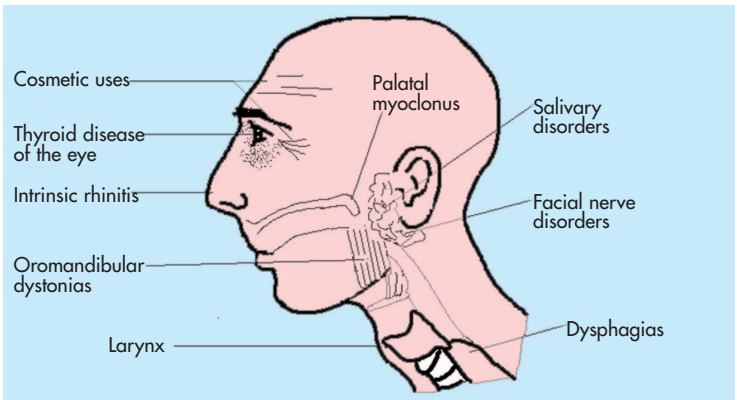

Figure 1. Areas in otorhinolaryngology where botulinum toxin is used.

It is also beneficial in the breathy voice of abductor dysphonia (Ludlow, 1990).

The injection is carried out using a Teflon®-coated needle under electromyographic guidance (*Figure 2*). The patient is requested to say 'eeee' for a prolonged period, during which time an oscilloscope will indicate the proximity of the needle to the muscles of the larynx. Mild aspiration of liquids and transient hoarseness have been reported after injection of the toxin. Use of botulinum toxin in the larynx may also lead to temporary paralysis of the vocal cords, allowing granulomas and, in theory, vocal cord nodules to recover.

Dysphagia

Botulinum toxin has been used in trials for the treatment of cricopharyngeal dysphagia, is well documented in the treatment of oesophageal achalasia (Vantrappen, 1997) and in theory can be used to close the larynx in chronic aspiration. Its use in oesophageal achalasia has an advantage in cases where Heller's operation (a form of surgical myotomy) and dilation of the oesophagus is not possible because the patient is unfit for general anaesthesia. The procedure can be carried out via flexible oesophagoscopy.

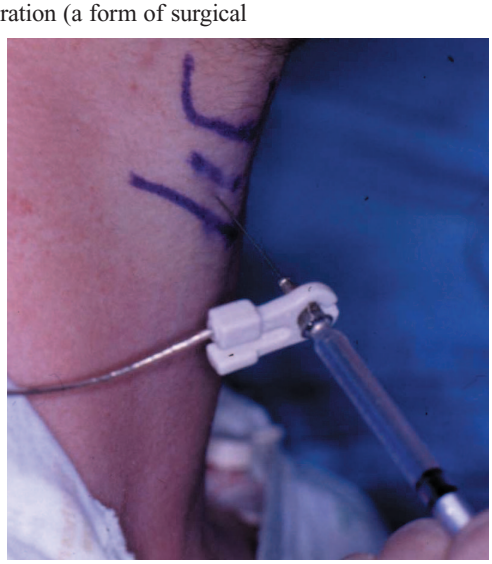

Figure 2. Injection of botulinum toxin into the larynx for spasmodic dysphonia.

Facial nerve disorders

Where there is healing of fibres of the facial nerve after an injury, a synkinesis can occur which may cause unwanted muscle groups to fire and contract. Injection of botulinum toxin into affected muscles can

relieve this problem. In much the same way, hemifacial spasm can be treated by injecting botulinum toxin into affected muscles (Elston, 1992). The results can be dramatic.

Ear

Perhaps the most potent use of botulinum toxin for symptoms which manifest themselves in the ear is injection of the agent into the tensor vali palatini in cases of palatal myoclonus. This causes an objective tinnitus of a clicking nature, which is so loud that when an observer's head is placed beside the patient's, it is clearly audible. Very small amounts of the toxin are required and therefore the chance of antibody development is very small indeed.

Oromandibular disorders

Oromandibular dystonia, temperomandibular joint abnormality, bruxism and masseter muscle hypertrophy can all be treated by botulinum toxin. In the case of masseter muscle hypertrophy (*Figure 3*), the cosmetic effects can be so dramatic as to change the shape of a patient's face. The previous treatment for this disorder was surgery, which was associated with considerable risk to the facial nerve and the parotid duct. Use of botulinum toxin means that this is no longer a problem and has the added advantage of leaving no scarring.

Thyroid disease

Injection of botulinum toxin into the upper eyelids relieves the exophthalmos of Grave's disease.

Cosmetic

Wrinkles such as crow's feet, frown lines and enlarged muscles around the face, such as masseteric hypertrophy, can be treated with botulinum toxin.

Salivary abnormalities

Frey's syndrome, seen after parotidectomy, is now treated with botulinum toxin. Hypersecretion of saliva can also be treated by injection of botulinum toxin into the offending gland.

Nose

Intrinsic rhinitis has been successfully treated by the local injection of botulinum toxin, which inhibits the parasympathetic supply to the area.

KEY POINTS

- Botulinum toxin works on peripheral neuromuscular junctions, where it causes selective weakening of muscles into which it is injected.
- Weakening and atrophy occur within 2–20 days, and in 2–4 months, recovery occurs as new terminal axons sprout.
- Botulinum toxin A is the only commercially available product, available as Dysport or Botox. Doses have not been standardized between the different preparations, so doses are specific to each individual preparation.
- Depending on how frequently and how much botulinum toxin is used, antibody-mediated resistance can occur, in which case botulinum toxin B and F may prove alternative treatments.
- Botulinum toxin has a wide range of uses in ear, nose and throat surgery.
- Treatment is well tolerated, the main side-effect is weakness of adjacent muscles.

CONCLUSIONS

Botulinum toxin is now used as first-line treatment in many disorders of the head and neck. It should be considered in all diseases which arise from neuromuscular dyskinesis, especially when a patient is unfit for surgical intervention. HM

Conflict of interest: none.

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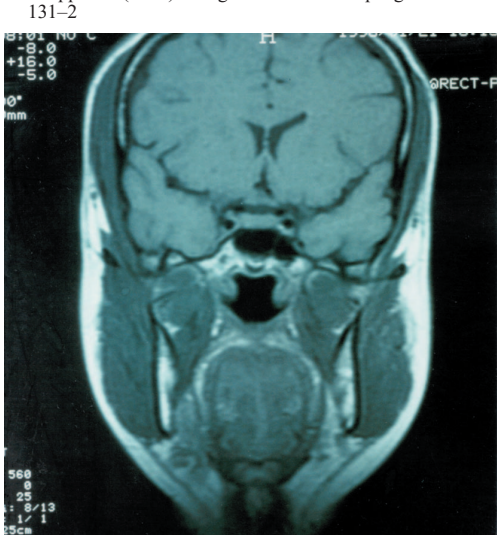

Figure 3. Magnetic resonance image showing massive masseteric hypertrophy.