The use of botulinum toxin in ophthalmology

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As the diversity of clinical applications for the botulinum neurotoxin continues to grow, exciting developments are occurring in its use around the eye, where indeed its benefits were first recognized. These include use to treat strabismus, eyelid disorders and a number of other ocular conditions.

The bacterium *Clostridium botulinum*, a spore-forming Gram-positive obligatory anaerobe, is best known for causing botulism — an acute symmetrical descending paralysis, which may be fatal. It has been shown to produce seven neurotoxins (A–G), of which A, B and E may produce disease in humans. The binding of these toxins to the presynaptic site of cholinergic junctions causes permanent inhibition of acetylcholine release. This can cause 'transmission failure' at neuromuscular junctions (both α-motor neurons and γ-spindle fibres), autonomic ganglia and some post-ganglionic fibres.

In the 1970s, the ophthalmologist Alan Scott pioneered the use of botulinum toxin A in strabismus as an alternative to surgery. He also suggested that it might be of use in dystonic reactions such as blepharospasm (Scott, 1981). Since then, its use has spread to other focal dystonias and to numerous disorders of the head and neck, as recently reviewed in *Hospital Medicine* (Walshe et al, 2001).

STRABISMUS (SQUINT)

The effectiveness of botulinum toxin A in squint depends on accurate injection near the motor end plate of the appropriate rectus muscle. Needle position and effect of toxin may be monitored by electromyogram — the patient can be asked to look in the direction of the treated muscle and the response measured.

In paralytic squint, botulinum toxin has proved a valuable diagnostic tool in assessing muscle function. For example, in an apparently unrecovered sixth nerve palsy, injection (and temporary paresis) of the ipsilateral medial rectus (i.e. the antagonist of the lateral rectus muscle) permits staging of any return of function in the lateral rectus. Additionally, one injection may be all that is required to restore the balance of function, eliminating diplopia and regaining binocular vision (Scott, 1981).

As an adjunct to strabismus surgery, botulinum toxin can be useful in 'fine-tuning' small operative horizontal misalignments.

In vertical strabismus, good results may be obtained from botulinum toxin injected into the inferior rectus; superior rectus injection, however, is not uncommonly complicated by a ptosis.

Interestingly, botulinum toxin has a more long-term effect in childhood strabismus, probably because its use permits binocular vision and prevents amblyopia. In theory, the earlier the intervention, the less likely contracture will develop in the antagonist muscle, but the optimal age of intervention and the relative merits over surgery continue to be controversial (Scott et al, 1990).

The dose required for treatment of squint is tiny — less than 0.01 of the estimated median lethal dose (LD50). While this has precluded systemic effects, local side effects, such as ptosis, are well recognized. Scleral puncture is reported at a rate of 1 in a 1000 procedures, but with no adverse visual outcome. The main limitation of the procedure is that it is temporary, usually requiring repeating at 2–6 months; in cases where fibrosis has occurred (as in thyroid eye disease), improvement is likely to be more limited.

EYELID DISORDERS

Blepharospasm is a dystonic reaction of involuntary bilateral closure of the eyelids. It is relatively common, usually idiopathic (although Parkinson's disease and Wilson's disease should be considered); it is often associated with dry eyes or blepharitis, which, by causing irritation of

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the front of the eye, may induce or exacerbate the blepharospasm. This vicious cycle may be broken by injection of botulinum toxin into the orbicularis oculi muscle at the junction of the orbital and preseptal parts (Taylor et al, 1991). It has replaced the previous drastic procedure of facial nerve stripping and dramatically reduced the practice of myectomy procedures of the orbicularis muscle, although concomitant use of central anticholinergics may be required. There is, however, a risk of ptosis and even temporary vertical strabismus.

In thyroid eye disease and facial nerve palsy, abnormalities of lid position and closure may lead to exposure of the vulnerable cornea. Botulinum toxin injection of levator palpebrae superioris is now an alternative (and adjunct) to surgical lid lowering procedures, where it avoids the risks and permanent changes to lid structure. It may, however, involve superior rectus so causing a vertical strabismus (Adams et al, 1987; Ozkan et al, 1997).

With age, involutional degeneration of the lid retractors may cause disinsertion from the tarsal plates. This results in involutional ptosis in the upper lid and in entropion ('in-turning') of the lower lid (*Figure 1*). Botulinum toxin administration to the orbicularis oculi has been used as a temporary measure in involutional entropion of the lower lid (Steel et al, 1997), where it weakens the rotational in-turning force of the orbicularis oculi. The authors propose that the judicious use of botulinum toxin to the superior portion of orbicularis oculi could restore the balance of tension on the upper lid to provide a non-surgical treatment for involutional ptosis.

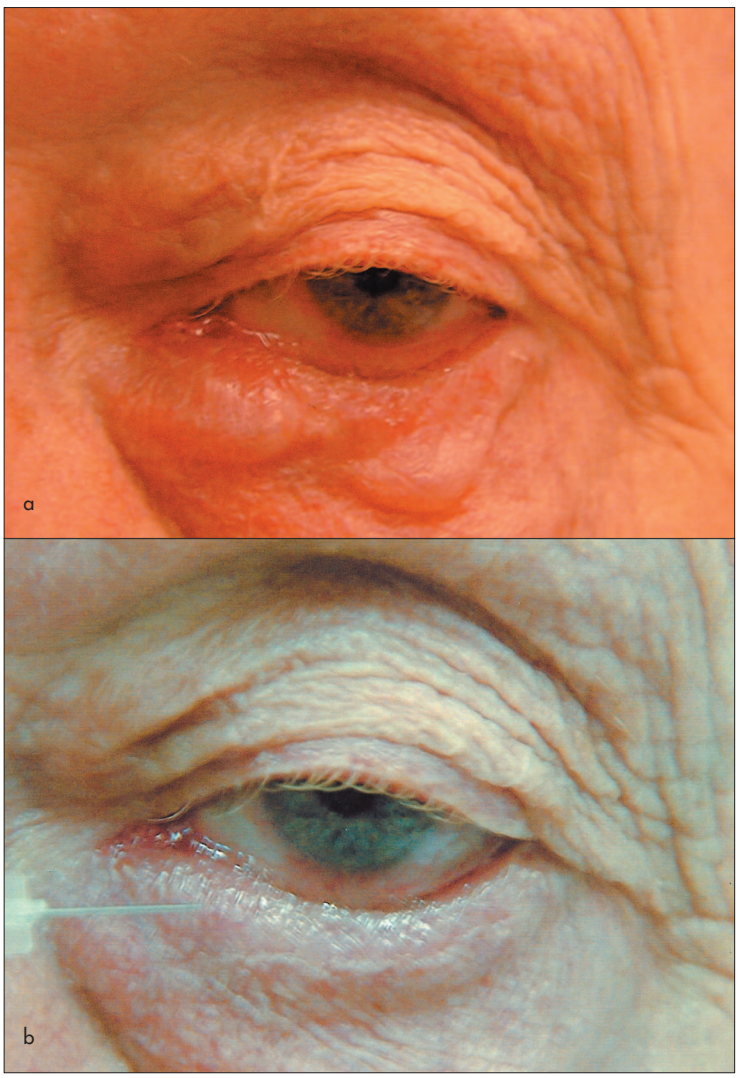

Figure 1. a. Entropion with lashes threatening corneal integrity. b. Being administered botulinum toxin.

AROUND THE EYE

In facial nerve palsy (*Figure 2*), botulinum toxin is used both acutely to induce a protective ptosis and in the longer term to treat the consequences of aberrant regeneration: abnormal movements (synkinesias) and crocodile tears (gustatory epiphora) (Hofmann, 2000). It is also very effective in facial nerve dyskinesias (as in hemifacial spasm) (Taylor et al, 1991).

Correction of brow ptosis (drooping brow) is a longstanding challenge in oculoplastic surgery. Botulinum toxin, as an alternative to unpredictable surgical options, has been found to give a 3–4 mm brow elevation that lifts the natural expression from 'concerned' to 'relaxed' without resulting in 'surprised' (Dyer and Yung, 2000).

The well-known cosmetic applications of botulinum toxin focus on the reduction of wrinkles (hyperkinetic facial lines) such as glabellar frown lines and 'crows feet'.

WATERING EYES, DRY EYES

An exciting new application of botulinum toxin is based on its capacity to inhibit autonomic as well as neuromuscular transmission. Watering eyes, with consequent visual and social problems, occurs because of a mismatch of tear production by the lacrimal (and accessory) glands and drainage by the lacrimal apparatus. Current surgical options all focus on improving drainage (by widening or bypassing the stenosis). However, the authors are currently investigating the neurodenervation of the lacrimal gland with botulinum toxin with a view to providing an alternative to surgery in this group of patients.

In contrast, botulinum toxin has been recently reported to reduce tear drainage in dry eye conditions by denervating the part of orbicularis oculi that attaches to the lacrimal sac to form the 'lacrimal pump' (Sahlin et al, 2000).

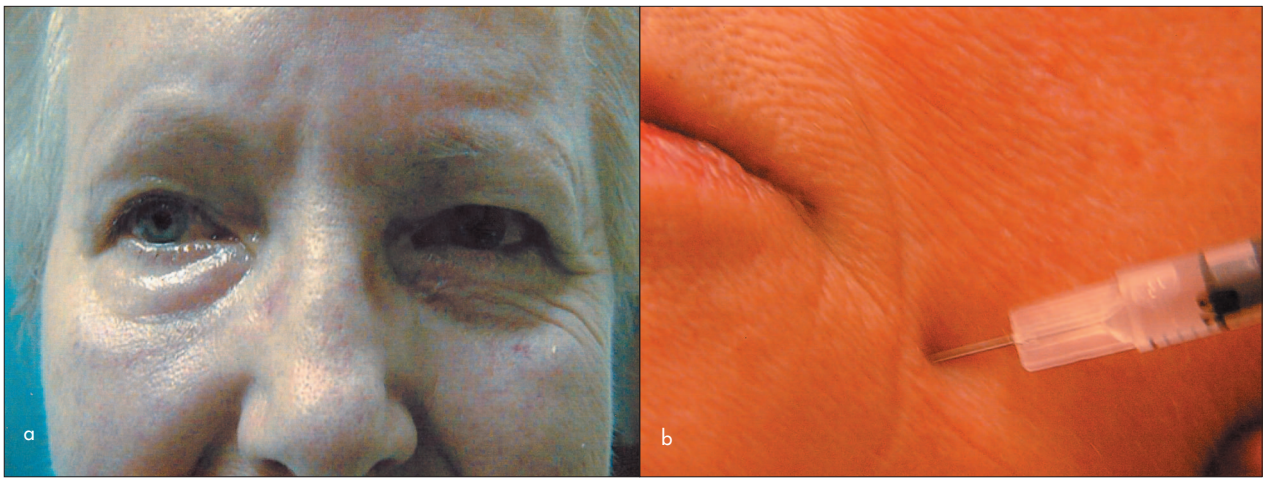

Figure 2. a. Right-sided facial nerve palsy — note loss of facial creases. b. Inappropriate over-activity of the contralateral side may also be inhibited by botulinum toxin improving symmetry.

CONCLUSION

The clinical application of botulinum toxin is remarkable. One observes the most powerful of natural neurotoxins being harnessed for the benefit of patients in a wide range of neuromuscular and autonomic disorders and as an effective alternative to surgery. HM

Conflict of interest: none.

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KEY POINTS

- Botulinum toxin is a powerful inhibitor of acetylcholine release at the neuromuscular junction and cholinergic autonomic junctions.
- Over the last 30 years, botulinum toxin has become an adjunct and alternative to surgery in a wide range of ophthalmic conditions.
- Botulinum toxin is the treatment of choice in blepharospasm, hemifacial spasm and in some cases of strabismus.
- Botulinum toxin has been found to be of benefit in brow ptosis, lid retraction and abnormal closure, dry eye syndromes, entropion and cosmesis.
- Botulinum toxin is being assessed regarding a potential role in watering eyes and lid ptosis.