Botulinum toxin and the eye

Ian B Marsh

Botulinum toxin in ophthalmology is used to reduce the function of the eyelid muscles in spasms or therapeutically. Therapeutic and diagnostic use in strabismus is also discussed, along with the controversial treatment of nystagmus.

Alan Scott, an ophthalmologist in San Francisco, published the first work on botulinum toxin type A (BTXA) in medicine. Scott's interest was in finding a compound that could realign the visual axes in cases of squint (strabismus). Various types of chemical, including local anaesthetic and other toxins, were tried before it appeared that BTXA worked well (Scott et al, 1973; Scott, 1980, 1981).

Most of the first applications for BTXA were in ophthalmology or neuro-ophthalmology before the indications for treatment expanded into other areas.

Currently BTXA treatment in ophthalmology is in three areas:

1. Lids/ocular adnexial structures
2. Strabismus
3. Nystagmus.

LIDS/OCULAR ADNEXIAL STRUCTURES

Induced ptosis

Three processes, reduction of corneal sensation, corneal infections and reduced blink reflex, can damage the cornea, which before the introduction of BTXA had been difficult to manage.

Corneal health and clarity depend upon an intact nerve supply from the trigeminal nerve. A cornea that has lost its sensory nerve is prone to the development of neuropathic ulceration. These are very difficult to heal by the instillation of topical medication and before the introduction of BTXA were often treated by a central surgical closure of the upper and lower eyelids (central tarsorrhaphy). This promoted corneal healing but with the disadvantage that examination of the cornea was difficult or impossible and that the time to reverse the tarsorrhaphy could not be determined easily. Injection of BTXA into the levator palpebrae superioris causes a complete or relatively complete ptosis in 2–3 days, which promotes corneal healing. The advantage of BTXA over tarsorrhaphy is the ability to lift the upper lid to examine the cornea (Adams et al, 1987; Kirkness et al, 1988).

Ulceration of the cornea can also occur with infective agents especially the herpes simplex virus. If these are unresponsive or poorly responsive to topical treatment then chemical tarsorrhaphy may hasten their resolution.

Corneal health also depends on an intact blink reflex that spreads the tears evenly and protects the cornea from foreign bodies and injury. The blink reflex can be compromised by either a primary or secondary facial palsy. Most cases of facial palsy with intact corneal sensation can be managed with topical lubricants and taping the lids closed at night until resolution occurs. Some cases with extreme exposure and reduced sensation require a more active management. BTXA may play a role along with lubrication.

Injection into the levator palpebrae superioris delivers a relatively large dose of BTXA to other adjacent structures including the superior rectus muscle. There is a risk of inducing a vertical strabismus, as the dose of BTXA is five to ten times greater than that required for an extraocular muscle (Heyworth and Lee, 1994).

Blepharospasm

Blepharospasm is part of the dystonia syndrome, which is characterized by repeated involuntary muscle spasms affecting either limited muscle groups or more generalized throughout the body. Females are more affected than males and it tends to be a disease of the 5th or 6th decade. Treatment of the spasm within the orbicularis oculi muscles is by BTXA injections. Occasionally patients require other systemic therapy. Some need surgical removal of the orbicularis muscle or section of the facial nerve to control the

Mr Ian B Marsh is Consultant Ophthalmic Surgeon, University Hospital Aintree, Walton Hospital, Liverpool L9 1AE

symptoms. BTXA is the mainstay of the treatment of this difficult condition (Elston and Ross Russell, 1985; Scott et al, 1985; Mauriello et al, 1987; Dutton and Buckley, 1988; Elston, 1988).

Hemifacial spasm

Hemifacial spasm is the result of stimulation of the facial nerve on one side, probably by an aberrant vessel as the nerve exits the intracranial area (Janetta et al, 1997). Investigation and surgery are rarely undertaken, as control of the condition is made possible with BTXA injections into the overstimulated orbicularis oculi muscle (Mauriello, 1985; Savino et al, 1985; Geller et al, 1989; Elston 1986, 1992).

The side effects of the treatment of blepharospasm and hemifacial spasm are all local and resolve with time. Diplopia and ptosis are the major complications.

STRABISMUS

The use of BTXA in strabismus is either diagnostic or therapeutic. Injection of an extraocular muscle requires electromyographic control to ensure accurate placement of the toxin.

BTXA usage in strabismus can be considered under the following headings:

- Postoperative diplopia testing
- Sixth nerve palsy
- Repeated use in place of surgery
- Congenital/early onset convergent squint (esotropia)
- Thyroid eye disease
- Decompensated small angle strabismus
- Third nerve palsy.

Postoperative diplopia testing

The management of childhood strabismus is a complex procedure that takes many years. First, the child's visual acuity and refractive error must be assessed. The appropriate spectacle correction is dispensed followed by further assessment of the vision. If amblyopia ('lazy eye') is present then a regimen of patching of the better seeing eye is instituted. All of this treatment must be undertaken before the age of visual maturation which is complete by the age of 6–7 years. Finally, the eyes are surgically aligned to produce a better appearance.

Some of these patients develop a further misalignment of their visual axes in adulthood. In some of them correction of the angle of strabismus with a prism may show that there is a risk of inducing diplopia with surgery. Patients who have had successful or unsuccessful treatment of amblyopia may be at risk. Diagnostic BTXA injection can temporarily align the eyes and allow the patient to experience whether diplopia would be a problem. A significant number of patients who have been advised against surgery on prism testing may be offered a strabismus procedure (Ketley et al, 1987).

Sixth nerve palsy

Patients who develop a sixth nerve palsy suffer with horizontal diplopia, often of sudden onset, with maximal separation of the images in distance viewing conditions and in the direction of the weak lateral rectus muscle. It is important to identify and treat any underlying condition, especially as a sixth nerve palsy may be a false localizing sign.

In ophthalmic practice the commonest aetiology in the middle-aged or elderly population is small vessel disease. This is often caused by poorly controlled diabetes. Following identification and treatment of the underlying disease, the initial management is observation.

A temporary prism fixed to spectacles or sunglasses relieves diplopia. If the angle of deviation is large then occlusion of the worst seeing eye is used. Alternative patching of the eyes is not required in adults.

An accurate measurement of the angle of deviation is mandatory at the onset of the condition to allow assessment of recovery or progression. This is best performed by an orthoptist. An increasing deviation tends to lead to more urgent investigation.

The vast majority of small vessel disease spontaneously recovers over a 3-month period (Rush and Younge, 1981). Failure of recovery after that time requires more active management.

BTXA injection into the ipsilateral medial rectus muscle can produce a long-standing realignment and may cure the condition. The injection must be made between 3 and 6 months for this to be possible. Denervation of the medial rectus allows the lateral rectus to shorten and leads to permanent change.

If the eye develops a full range of movement after BTXA but then returns to esotropia, a surgical recession of the medial rectus in combination with an lateral rectus resection is required to produce a large central field of binocular single vision.

If the lateral rectus has no action following injection then the eye does not abduct beyond the midline. In these circumstances, a transposition of the superior rectus and inferior rectus temporally may give an area of binocular single vision in the straight ahead direction and to the opposite side of the palsy.

If the palsy is referred beyond 6 months after onset then surgery is often required (Elston and Lee, 1985; Fitzsimons et al, 1988; Metz and Dickey, 1991; Murray, 1991).

Repeated use in place of surgery

Some patients may have undergone one or more operations to align the eyes. In this situation, the patient or surgeon may be unhappy to continue with further surgery. Repeated injections of BTXA at 3-monthly intervals can produce a satisfactory appearance. Toxicity or antibody development does not occur, so this treatment can be continued indefinitely (Lee et al, 1988).

Congenital/early onset esotropia

In congenital esotropia the child starts to develop a convergent squint at approximately 3 months, which is intermittent initially and then becomes constant. The deviation may become very large – up to 30°. Viewing is by cross fixation where the right eye is used in left gaze and vice versa. Each eye is used in turn in the primary position. Visual acuity is equal in both eyes and amblyopia is rare. Cross fixation simulates bilateral sixth nerve palsies, an important differential diagnosis.

The development of binocular single vision is unlikely and the timing of surgery is unresolved.

BTXA has been proposed as a viable alternative to surgery (McNeer et al, 1987; Magoon, 1989; Scott et al, 1990) and sometimes more than one injection is required. Electromyographic monitoring of needle position is impossible in a fully anaesthetized patient. The use of ketamine does not abolish the vestibular ocular reflex (dolls head) and allows accurate injection.

Thyroid eye disease

The features of thyroid eye disease include:

- Proptosis
- Strabismus
- Lid retraction and lag
- Optic nerve compression.

Acute infiltration of the ocular muscles is associated with esotropia and downwards deviation (hypotropia) of the affected eye, as the medial rectus and inferior rectus are the commonest muscles affected. BTXA in this phase may help in reducing the deviation to enable the use of a prism for diplopia resolution.

BTXA in the chronic or 'burnt out' disease is not effective or indicated (Lyons et al, 1990).

Decompensated small angle strabismus

Some children, during their early years, develop an incomplete binocular visual system. This is characterized by mild amblyopia, a small-angle squint of less than 5°, reduced stereoacuity and often a different refractive error between the two eyes.

The vast majority of children do not come to ophthalmologists unless the amblyopia is marked. Occasionally, a precipitating factor, such as intercurrent illness or minor head injury, causes the strabismus to decompensate into a large angle with diplopia.

The first treatment can take the form of fitting prisms into the spectacles, depending on the size of the squint. The second involves the use of BTXA and the third involves surgical realignment. Approximately 50% of BTXA patients will have their strabismus resolved and have no further problems. If one injection is not successful then there is no benefit in giving further BTXA injections. In these cases surgery is required (Marsh, 2000).

Third nerve palsy

Complete third nerve palsy is an almost impossible condition to treat. The ptosis hides a divergent and hypotropic eye with only abduction and mild depression being possible. Any surgery performed is to centralize the eye with a very small field of central binocular single vision.

The only role for BTXA in third nerve palsy is lateral rectus injection to identify if medial rectus function is present (Elston and Lee, 1985; Saad and Lee, 1992). Complete adduction failure after BTXA injection indicates that medial rectus resection will only produce temporary straightening of the eye and that another method of achieving permanent results will be required.

NYSTAGMUS

Nystagmus is either congenital or acquired. True congenital nystagmus is a horizontal type of motion with no vertical component and is not associated with the symptom of oscillopsia.

Oscillopsia is the sensation to the patient of the external world moving and is the hallmark of acquired nystagmus. This symptom is extremely disabling.

There is probably no role for BTXA in the treatment of congenital nystagmus.

In acquired nystagmus the underlying cause should be identified and treated first if possible. The commonest reasons for acquired nystagmus are multiple sclerosis and the Arnold–Chiari malformation. Many treatment modalities are available.

Some authors have advocated the injection of BTXA into the retrobulbar space to weaken all

rectus muscles (Helveston and Pogrebniak, 1988; Leigh et al, 1992; Repka et al, 1994; Ruben et al, 1994; Marsh et al, 1995; Kosmin et al 1996). This can slow the nystagmus and decrease the oscillopsia. The inevitable result will be diplopia, which necessitates occlusion of the uninjected eye. Ptosis may be a side effect. Disruption of the vestibular ocular reflex means that mobility may be affected. If other ocular structures have been involved in the disease process then the effect of BTXA may not be useful (e.g. optic atrophy in multiple sclerosis).

The ideal patient for this form of treatment is therefore wheelchair bound, willing to wear an eye patch and has potentially good visual function. Repeat treatment is necessary if the patient's symptoms are helped. HM

Conflict of interest: none.

Adams GG, Kirkness CM, Lee JP (1987) Botulinum toxin A induced protective ptosis. *Eye* **1**(15): 603–8

Dutton DA, Buckley EG (1988) Long-term results and complications of botulinum A toxin in the treatment of blepharospasm. *Ophthalmology* **95:** 1529–34

Elston JS (1986) Botulinum toxin treatment of hemifacial spasm. *J Neurol Neurosurg Psychiatry* **49**(7): 827–9

Elston JS (1988) Botulinum treatment of blepharospasm. *Adv Neurol* **50:** 579–81

Elston JS (1992) The management of blepharospasm and hemifacial spasm. *J Neurol* **239**(1): 5–8

Elston JS, Lee JP (1985) Paralytic strabismus: the role of botulinum toxin. *Br J Ophthalmol* **69:** 891–6

Elston JS, Ross Russell RX (1985) Effect of treatment with botulinum toxin in neurogenic blepharospasm. *Br Med J* **290:** 1857–9

Fitzsimons R, Lee JP, Elston JS (1988) Treatment of sixth nerve palsy in adults with combined botulinum toxin chemodenervation and surgery. *Ophthalmology* **95**(11): 1535–42

Geller BD, Hallett M, Ravits J (1989) Botulinum toxin therapy in hemifacial spasm. *Muscle Nerve* **12:** 716–22

Helveston EM, Pogrebniak AE (1988) Treatment of acquired nystagmus with botulinum A toxin. *Am J Ophthalmol* **106:** 584–6

Heyworth PL, Lee JP (1994) Persisting hypotropias following protective ptosis induced by botulinum neurotoxin. *Eye* **8**(5): 511–5

Janetta PJ, Abbasy M, Maroon JC, Ramos FM, Albin MS (1977) Etiology and definitive microsurgical treatment of hemifacial spasm. *J Neurosurg* **47:** 321–8

Ketley MJ, Powell CM, Lee JP, Elston JS (1987) Botulinum toxin adaptation test: The use of botulinum toxin in the investigation of the sensory state in strabismus. Transactions of the 6th Orthoptic Congress, Harrogate: International Orthoptic Society: 289–93

Kirkness CM, Adams GG, Dilly PN, Lee JP (1988) Botulinum toxin A induced protective ptosis in corneal disease. *Ophthalmology* **95**(4): 473–80

Kosmin A, Marsh IB, Batterbury M (1996) The use of botulinum toxin injections in the management of acquired nystagmus and oscillopsia. *Clin Rehabil* **10:** 205–9

Lee JP, Elston JS, Vickers S, Powell C, Ketley MJ, Hogg C (1988) Botulinum toxin therapy for squint. *Eye* **2:** 24–8

Leigh RJ, Tomsak RL, Grant MP et al (1992) Effectiveness of botulinum toxin administered to abolish acquired nystagmus. *Ann Neurol* **32:** 633–42

Lyons CJ, Vickers SF, Lee JP (1990) Botulinum toxin therapy in dysthyroid strabismus. *Eye* **4:** 538–40

Magoon EH (1989) Chemodenervation of strabismic children. A 2 to 5 year follow up study compared with shorter follow up. *Ophthalmology* **96:** 931–4

McNeer KW, Tucker MG, Spencer RF (1997) Botulinum toxin in the management of essential infantile esotropia in children. *Arch Opthalmol* **104:** 1762–7

Marsh IB (2000) Is botulinum toxin treatment useful in decompensated microtropias? In: JT de Faber, ed. *Transactions of the 26th meeting of the European Strabismological Association, Barcelona.* Swets and Zeitlinger, Lisle: 83–5

Marsh IB, Kosmin A, Smyth KL (1995) Use of botulinum toxin in acquired nystagmus. Transactions of the 8th International Orthoptic Congress, Kyoto. Edited by M Louly. International Orthoptic Society: 232–4

Mauriello JA (1985) Blepharospasm, Meige syndrome and hemifacial spasm: treatment with botulinum toxin. *Neurology* **35:** 1499–500

Mauriello JA, Coniaris H, Haupt EJ (1987) Use of botulinum toxin in the treatment of one hundred patients with facial dyskinesias. *Ophthalmology* **94:** 976–9

Metz HS, Dickey CF (1991) Treatment of unilateral sixth nerve palsy with botulinum toxin. *Am J Opthalmol* **112:** 381–4

Murray AND (1991) Early botulinum toxin treatment of acute sixth nerve palsy. *Eye* **5:** 45–7

Repka MX, Savino PJ, Reinecke RD (1994) Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Opthalmol* **112:** 1320–4

Ruben ST, Lee JP, O'Neil D, Dunlop I, Elston JS (1994) The use of botulinum toxin for the treatment of acquired nystagmus and oscillopsia. *Ophthalmology* **101:** 783–7

Rush JA, Younge BR (1981) Paralysis of cranial nerves III, IV and VT. Causes and prognosis in 1,000 cases. *Arch Ophthalmol* **99:** 76–9

Saad N, Lee JP (1992) The role of botulinum toxin in ten consecutive cases of partial third nerve palsy. *Aust NZ J Ophthalmol* **20:** 41–6

Savino PJ, Sergott RC, Bosley TM, Schatz NJ (1985) Hemifacial spasm treated with botulinum A toxin injection. *Arch Ophthalmol* **103:** 1305–6

Scott AB (1980) Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* **87:** 1044–9

Scott AB (1981) Botulinum toxin injection of eye muscles to correct strabismus. *Trans Am Ophthalmol Soc* **LXXIX:** 734–70

Scott AB, Rosenbaum A, Collins CC (1973) Pharmacological weakening of extraocular muscles. *Invest Ophthalmol* **12:** 924–7

Scott AB, Kennedy RA, Stubbs HA (1985) Botulinum toxin as a treatment for blepharospasm. *Arch Ophthalmol* **103:** 347–50

Scott AB, Magoon EH, McNeer KW, Stager DR (1990) Botulinum treatment of childhood strabismus. *Ophthalmology* **97:** 1434–8

KEY POINTS

- Botulinum toxin is the first-line treatment of patients with hemifacial spasm and blepharospasm.
- Induction of ptosis in corneal disease promotes healing and obviates the need for surgical tarsorrhaphy.
- Some patients with acquired nystagmus may benefit from treatment.
- Treatment has minimal side effects and these will all reverse with time.