

SCIENTIFIC CORRESPONDENCE

Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation

David J Keegan, Gerd Geerling, John P Lee, Glen Blake, J Richard Collin, Gordon T Plant

Br J Ophthalmol 2002;**86**:43–46

Aim: To investigate the potential of botulinum toxin A for treating hyperlacrimation.

Methods: Three patients with unilateral symptoms of hyperlacrimation (diagnosed as "crocodile tearing") and one patient with a submandibular salivary gland transplant (SMGT) were studied. Tear production was quantified in the resting and stimulated (chewing or following exercise) state, using Schirmer's test and tear clearance. Lacrimal scintigraphy was used to assess outflow. Intraglandular injections (for patients with "crocodile tears") or periglandular injections (for the SMGT patient) of Dysport were administered in divided doses.

Results: Two of the three eyes with reported gustatory lacrimation had a higher Schirmer test result than their fellow eye following gustatory stimulation. Scintigraphy, with and without stimulation, confirmed a patent drainage system in these patients. The other patient demonstrated a functional obstruction to tear flow. After treatment patients with confirmed gustatory lacrimation and the SMGT patient had a marked reduction in tearing at 2 weeks. This effect lasted 3–4 months. There was no demonstrable improvement in the patient with epiphora secondary to functional obstruction. Two patients who had received intraglandular injections developed a ptosis, which resolved spontaneously.

Conclusions: This study illustrates that gustatory lacrimation is a difficult diagnosis. In post-facial nerve palsy a functional element must always be considered. However, in confirmed hyperlacrimation botulinum toxin treatment is effective but side effects may occur.

Epiphora is a common problem, but can be particularly troublesome in patients where the lacrimal gland is either aberrantly innervated or substituted by a salivary gland transplant (for example, for dry eyes). Following seventh nerve palsy, epiphora may be caused by ectropion, functional canalicular obstruction, or gustatory lacrimation ("crocodile tears"). While ectropion and functional canalicular obstruction result from a reduced function of the paralysed orbicularis muscle, crocodile tearing results from misrouting of regenerating nerve fibres. These are known to be postganglionic parasympathetic secretomotor fibres, and drive the cholinergic component of the lacrimal gland. As a result, excessive secretion of electrolytes and subsequent fluid movements occur when patients chew their food. This problem is analogous to gustatory facial sweating (Frey's syndrome), also an aberrant regeneration phenomenon. Botulinum toxin has been used successfully in Frey's syndrome^{1,2} to modulate the amount of secretion, and other authors have shown that injections around the lacrimal gland are effective in reducing tear secretion.^{3–5}

Recently, submandibular salivary gland autografts have been used to successfully lubricate severely dry eyes.⁶ In this procedure the salivary gland is transposed to the temporal fossa as a free, denervated graft, which becomes revascularised via microanastomoses with the temporal artery and vein. Its secretory duct is inserted through a subcutaneous tunnel into the conjunctival fornix to deliver saliva onto the ocular surface. The amount of secretion from these glands increases over time, suggesting that re-innervation occurs. In about 20% of all grafts this can result in excessive secretion.⁶ Since botulinum toxin has been shown to reduce the secretory output in the salivary glands of an animal model⁷ we evaluated the potential of botulinum toxin to reduce tear production in this situation.

Botulinum toxin, one of the most lethal naturally occurring neurotoxins, is produced by *Clostridium botulinum* bacteria. The toxin acts by rapid and strong binding to presynaptic cholinergic nerve terminals with subsequent internalisation of toxin and reduction in the output of acetylcholine (ACh). This leads to a downregulation of post-junctional ACh receptors. The effect is a weakening of the involved muscle (skeletal or smooth) though this gradually recovers with time.⁸ Botulism has autonomic effects,⁹ especially when caused by *Clostridium botulinum* type B, owing to the alterations in peripheral cholinergic parasympathetic nerves. Since the 1970s it has been known that botulinum toxin may have a role in the treatment of excessive muscular activity such as strabismus, torticollis, dystonias, and blepharospasm.¹⁰

All these findings suggest that botulinum toxin may be a treatment for hypersecretory conditions and this study evaluates its use for patients with gustatory lacrimation or with a salivary gland graft.

MATERIALS AND METHOD

Before treatment, all patients were interviewed with a questionnaire and had a clinical examination, including visual acuity, slit lamp microscopy, examination of periocular skin, lid position, extraocular muscle movements, and tear duct syringing. Each patient was asked to score the severity and frequency of tearing in a semiquantified manner from "0" to "4" (severity: none, mild, moderate, severe, and very severe; frequency: never, 1/week, 1/day, >1/day, and constantly). The examination also included Schirmer's testing (following one drop of benoxinate 0.5%) and evaluation of tear clearance, both measured before and after an appropriate stimulus of secretion (either chewing for gustatory lacrimation or exercise for the submandibular gland transplant patient). The latter is a modified Schirmer's test and involves a semiquantitative assessment of the tear drainage by visualising the dilution of 10 μ l of 0.5% fluorescein applied to the fornix by tear secretion.¹¹

In addition, the tear flow was assessed by means of lacrimal scintigraphy. This was performed with the patients sitting erect in front of a large field of view gamma camera. Radionuclide tracer (4 MBq ^{99m}Tc tin colloid) was administered by eye

Table 1 (A) Findings on initial and follow up presentation of patients with gustatory lacrimation

Patient	Age	Diagnosis	Duration of epiphora	Time point	Severity	Freq	Complications	TC
1	58	Ramsay-Hunt	24 months	Pre	3	3	None	01:08 S 01:16
				2 weeks post	2	3		01:04 S 01:08
				4 months post	3	3		01:06 S 01:16
				2 weeks post 2nd injection	2	3		01:04 S 01:04
2	48	Bell's palsy	18 months	Pre	3	3	3 mm ptosis following injection	01:02 S 01:08
				2 weeks post	3	3	Resolved within 3 weeks	01:04 S 01:08
3	45	Bell's palsy	8 months	Pre	3	3+	Complete ptosis (6 mm) Mild superior rectus underaction	01:04 S 01:04
				2 weeks post	1	0	Resolved within 6 weeks	01:04 S 01:04

(B) Findings on initial and follow up attendances after first (4) and second (4b) periglandular botulinum toxin injections in the patient with a submandibular gland transplant

Patient	Age	Diagnosis	Duration of epiphora	Time point	Severity	Freq	Complications	TC
4	20	S-MGT	9 months	Pre	3	3		01:16 S 01:32
				Post 5 mg benzhexol	1	2		01:04 S 01:06
				2 weeks post	1	1		01:08 S 01:04
				1 week post 2nd injection	0	2	Mild dry eye	
4b				4 months post 2nd injection	3	4		01:02 S 01:08

Severity was scored 0–4 (none, very severe). Frequency was scored 0–4 (never to continuous). It demonstrates the reproducible tearing in patients 1 and 3, which was not obvious in patient 2. The stimulus was consuming the food item that they felt stimulated tearing most in each individual patient (1–3). The stimulus used was physical exercise. Tear clearance (TC), stimulated (S), frequency (Freq).

drops simultaneously in each eye and sequential images of 1 minute each acquired for 15 minutes using a 128 × 128 matrix and a zoom factor of two. Scintigraphy is particularly appropriate for identifying functional obstruction to outflow in contrast with a dacryocystogram (DCG).

Gustatory lacrimation patients received injections of Dysport, 20 units (U) in three divided doses, transcutaneously to the lacrimal gland. For the submandibular gland transplant, injections of Dysport were given at a dose of 1000–1200 U subcutaneously around the transplant, sparing the presumed location of the microvascular anastomoses and the secretory duct.

At 2 weeks and 3 months following injection the patients were re-examined and had repeat lacrimal scintigraphy. Patients were specifically examined for subjective and objective reduction in tear production following an appropriate prosecretory stimulus; and for complications of injection such as ptosis, extraocular muscle palsies, and haematoma of the lacrimal or transplanted salivary gland.

RESULTS

In total, four patients were included in the study, three with a diagnosis of gustatory reflex hyperlacrimation (crocodile tearing), and one for severe epiphora following autologous submandibular gland transplantation.

Patient 1, a 58 year old man, developed gustatory lacrimation 1 year after a left Ramsay-Hunt syndrome in 1996. Apart from obvious tearing and a mild left sided ptosis his examination was normal, and upon chewing food a marked increase in unilateral tearing was noted (Table 1A). Lacrimal scintigraphy demonstrated a patent lacrimal system.

He received an injection of 20 U of Dysport to his lacrimal gland in three divided doses. After 2 weeks there was a marked reduction in tearing objectively and subjectively. There were no complications but after three comfortable months post-injection tearing had returned to the pretreatment level and the injection was repeated. Again, he had considerable benefit from the treatment although tear secretion was not reduced by the same amount (Table 2 (patient 1b)).

Patient 2, a 48 year old man, had a diagnosis of right gustatory lacrimation following a recovered Bell's palsy 2 years before presentation. Apart from a mild excess of tears in the right eye the ocular examination was normal. Lacrimation was not reproducible even though various stimuli were used including chewing and exercise. Scintigraphy demonstrated a functional obstruction to flow. He received an injection of 20 U of Dysport. Some subjective improvement in his condition occurred, but this was not demonstrable with clinical tests. He developed a ptosis of 3 mm, which resolved spontaneously (Table 1A). He did not receive a repeat injection.

Patient 3, a 45 year old man, complained of gustatory lacrimation following resolution of a left Bell's palsy 8 months before presentation (Table 1A). He had a mild (1 mm) left ptosis with obvious pooling of tears, otherwise his ocular examination was normal. On stimulation with food his lacrimal output increased considerably (Table 2). Scintigraphy demonstrated a patent lacrimal system. He received an injection of Dysport. Following the injection he developed a 6 mm ptosis and some underaction of the left superior rectus muscle. These began to resolve within 5 weeks of the injection and by 8 weeks the ptosis and strabismus were fully resolved. At the 2 week visit he had marked resolution of his symptoms with no gustatory lacrimation (Tables 1A and 2).

Table 2 Details of Schirmer's testing (measured in mm) in each of the patients before and after treatment with Dysport, with and without stimulation (food or exercise)

Patient	Unstimulated		Stimulated	
	Pre-injection	Post-injection	Pre-injection	Post-injection
Patient 1a	15	15	80	25
Patient 1b	22	15	58	32
Patient 2	13	9	15	23
Patient 3	22	13	47	18
Patient 4a	23	16	80	16
Patient 4b	20	7	100	Not available

Patient 4, a 20 year old woman, had developed Stevens-Johnson syndrome at age 2. She had multiple lid procedures and developed an absolute tear deficiency (Schirmer test in 5 minutes = 0 mm), which left her in extreme discomfort despite the frequent application of unpreserved pharmaceutical tear substitutes and occlusion of all lacrimal puncti. In April 1998 she received an autologous submandibular gland transplant. Fifteen months later the Schirmer test was 60 mm in 5 minutes. Although her previous discomfort was much relieved she complained of frequent excessive epiphora provoked by exercise and heat.

Tearing could be reduced by the oral administration of 5 ml of the anticholinergic benzhexol (Table 1B). This suggested a cholinergic basis to her hyperlacrimation. Side effects from this treatment precluded its long term use.

She received three periglandular injections of Dysport totalling a dose of 1200 U. One week following her third injection she reported a marked subjective improvement in her hyperlacrimation. She also described an occasional recurrence of the dry eye symptoms she had before the transplantation, which necessitated topical lubricants. Three months after injection she reported increased tearing and Schirmer's test was 12 mm in 5 minutes. Another 2 weeks later she described constant epiphora and received a repeat periglandular toxin injection of 1000 U (Table 1B (patient 4b)). Two weeks after injection her symptoms had again improved. At 3 months following retreatment she began to complain of occasional excessive tearing again. On retesting her post-stimulation Schirmer's test was 100 mm (that is, two strips). Given the nature of her problem and the need for large doses of periglandular toxin she had Lester-Jones tubes inserted to facilitate tear flow.

DISCUSSION

This study demonstrates a positive effect of intraglandular and periglandular injections of botulinum toxin A (Dysport) in patients with gustatory lacrimation and in one case of a submandibular gland transplant complicated by oversecretion. It confirms the reports in previous papers³⁻⁵ of its benefit in gustatory lacrimation and suggests that it is more efficacious in clinically confirmed hyperlacrimation, demonstrated uniquely in this study.

No objective improvement could be demonstrated in a patient solely with subjective complaints of gustatory lacrimation that was subsequently shown to be due to functional obstruction of the lacrimal drainage system rather than hyperlacrimation. Another patient referred to this study was confirmed to have a functional obstruction and he was not treated, following our experience with patient 2.

The onset of effect in treated patients occurred within the first 3-4 days following the injection and lasted for 3 months. There was little effect on unstimulated tear flow (Table 2). The patient with a salivary gland transplant required multiple

injections (three); total dose was 1200 U, to attain the desired effect, which lasted for 3 months. Thus, the duration of action of botulinum toxin A in this study is similar to the findings for squint and blepharospasm,¹⁰ but shorter than reported for Frey's syndrome.²

With regard to the specific mechanism of action of botulinum toxin our results confirm the cholinergically dependent nature of gustatory lacrimation. It also suggests that it is cholinergic activity in submandibular gland transplants that drives their late hypersecretion. This may result from reinnervation either from the surrounding transplanted bed or from any surviving parasympathetic ganglia inside the transplant.¹²

Given that our treatment failure was in a patient who could not reproduce his symptoms in the clinic we would advocate the withholding of treatment for such patients, pending a controlled clinical trial. Functional lacrimal drainage obstruction may be the main cause of the patient's epiphora and must be considered.

The pretreatment assessments and procedure itself were straightforward to perform. In our study the reported side effects of botulinum toxin injection were a temporary ptosis (n = 2) following intralacrimal injections and temporary dry eye (2 weeks' duration) in the salivary gland transplant patient. One of our patients had marked ptosis and superior rectus underaction secondary to the injection and as with all toxin treatments involving the adnexa we must advise of these potential side effects. Intraglandular or periglandular injections of botulinum toxin A seem to be a safe, reversible, and reliable means of managing this rare condition. It is less invasive than surgical alternatives such as Lester-Jones tube insertion. This is a small group of patients and the future clinical role of botulinum toxin A in treating gustatory lacrimation needs to be formally evaluated with a randomised controlled clinical trial. This study and others provide the necessary information to justify such a trial in appropriate centres. Although submandibular gland transplantation is a rare operation the use of botulinum toxin may be useful as a temporary measure to reduce excessive lubrication until a more permanent measure can be taken.

ACKNOWLEDGMENTS

This study was supported by a grant from the special trustees of Moorfields Eye Hospital. Gerd Geerling was in part supported by grants from the DFG (Ge 895/4-1) and the special trustees of Moorfields Eye Hospital.

.....

Authors' affiliations

D J Keegan, G Geerling, J P Lee, J R Collin, G T Plant, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK
G Blake, Department of Nuclear Medicine, Guy's Hospital, London

Correspondence to: David Keegan, Department of Pathology, Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK; d.keegan@ucl.ac.uk

Accepted for publication 2 July 2001

REFERENCES

- 1 **Drobik D**, Laskawi R. Frey's syndrome: treatment with botulinum toxin. *Acta Otolaryngol* 1995;**115**:459-61.
- 2 **Schulz-Bonhage A**, Schroder M, Ferbert A. Botulinum toxin in the therapy of gustatory sweating. *J Neural* 1996;**243**:143-6.
- 3 **Borojerdi B**, Ferbert A, Schwarz M, et al. Botulinum toxin treatment of synkinesia and hyperlacrimation after facial palsy. *J Neurol Neurosurg Psychiatry* 1998;**65**:111-14.
- 4 **Riemann R**, Pfennigsdorf S, Riemann E, et al. Successful treatment of "crocodile tears" by injection of botulinum toxin into the lacrimal gland: a case report. *Ophthalmology* 1999;**106**:2322-4.
- 5 **Hofmann RJ**. Treatment of Frey's syndrome (gustatory sweating) and 'crocodile tears' (gustatory epiphora) with purified botulinum toxin. *Ophthal Plast Reconstr Surg* 2000;**16**:289-91.
- 6 **Geerling G**, Bastian G-O, Sieg P, et al. Autologous transfer of the submandibular gland as treatment for most severe cases of keratoconjunctivitis sicca. *Ophthalmology* 1998;**105**:327-33.
- 7 **Shaari CM**, Wu BL, Biller HF, et al. Botulinum toxin decreases salivation from canine submandibular glands. *Otolaryngol Head Neck Surg* 1998;**118**:452-7.
- 8 **Melling J**, Hambleton P, Shone CC. Clostridium botulinum toxins: nature and preparation for clinical use. *Eye* 1988;**2**:16-23.
- 9 **Jenzer G**, Mumenthaler M, Ludin HP, et al. Autonomic dysfunction in botulism B: a clinical report. *Neurology* 1975;**25**:150-3.
- 10 **Jankovic J**, Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med* 1991;**324**:1186-94.
- 11 **Xu KP**, Tsubota K. Correlation of tear clearance rate and fluorophotometric assessment of tear turnover. *Br J Ophthalmol* 1995;**79**:1042-9.
- 12 **Garrett JR**, Kyriacou K. "Paralytic" secretion after parasympathectomy of rabbit submandibular glands includes a cholinergic component. *Q J Exp Physiol* 1988;**73**:737-46.



Have your say

eLetters

If you wish to comment on any article published in the *British Journal of Ophthalmology* you can send an eLetter using the eLetters link at the beginning of each article. Your response will be posted on *British Journal of Ophthalmology* online within a few days of receipt (subject to editorial screening).

www.bjophthalmol.com