Dr Stephen Tisch and
Dr Paul Darveniza

Botulinum Toxin Therapy at St Vincent's Hospital

INTRODUCTION

Dystonias remain among the most disabling neurological disorders. Spasmodic dysphonia, for example, profoundly interferes with communication and causes great physical and emotional suffering.

Botulinum toxin (BTX) therapy has revolutionised the management of such dystonias and a range of other neurological and disorders. Therapy with BTX has been used at St Vincent's Hospital since 1991. Large numbers of patients have been successfully treated and form the basis of ongoing clinical research. An overview of BTX therapy and the results of a recent study of patients with spasmodic dysphonia are presented.

Dr Stephen Tisch MBBS
Neurology Registrar,
St Vincent's Hospital
Dr Paul Darveniza MD, FRACP
Consultant Neurologist,
St Vincent's Clinic

BOTULINUM TOXIN

BTX is the exotoxin of Clostridium botulinum and is responsible for the neuromuscular paralysis seen in Botulism. BTX is composed of light and heavy chains enveloped in a protective haemaglutinin. BTX binds to the membrane of presynaptic cholinergic nerve terminals, enters the cytoplasm where the active light chain (a Zn metaloprotein ase) cleaves essential proteins involved in Acetylcholine exocytosis and release. This results in chemical denervation of cholinergic nerve terminals and sustained block in neuromuscular transmission. Other tissues reliant on cholinergic transmission (eg sweat and salivary glands) are also blocked by BTX. The effect is not permanent. The terminal bouton regenerates with recovery of transmission after several months. BTX exists as serotypes A-G, however most therapeutic experience has been with BTX-A which is commercially available.

BTX-A has proved useful in the treatment of a diverse range of conditions. (Table 1)

Therapy involves injection of specific muscles to eliminate unwanted excessive muscle activity. The primary neurological indications are focal dystonias, hemifacial spasm and spasticity. Overactive muscles may be identified using EMG guidance to assist localisation of injection. Dosage is individualised to the size of muscles and previous response. Novel uses of BTX

are control of excessive sweating and oesophageal achalasia. Future uses include treatment of prostatic hyperpasia which may reduce the progression to prostate cancer.

Focal dystonias with selective muscle involvement such as blepharospasm and spasmodic dysphonia respond extremely well to BTX therapy. In both disorders favourable response occurs in over 90% of patients!. Similar results occur in hemifacial spasm.

Spasmodic torticollis and cervical dystonias also respond well to BTX therapy. In general, however, the more diffuse the cervical muscle involvement the less favourable the response to therapy. The majority of patients with spasmodic torticollis experience significant improvement. For refractory cases surgical denervation remains an option.

Treatment of focal limb dystonias with BTX is less successful than the aforementioned groups however it may prove very useful in selected patients.

Treatment of spasticity with BTX is more successful in the lower limb than the upper limb. In the lower limb correction of plantar flexed inverted spastic posturing enables correct heel strike and improvement of gait in ambulatory patients with unilateral or bilateral spasticity. In the upper limb BTX is particularly useful to relieve spastic closure of the hand to facilitate hand hygiene and to relieve painful flexor spasms.

The use of BTX to relieve excessive sweating of idiopathic hyperhydrosis is very successful. Multiple skin injections are performed in affected areas and beneficial effects may last as long as 12 months. Parotid pain due to excessive secretion has been effectively treated in one patient treated at St Vincent's Hospital.

BTX is effective in eliminating facial wrinkles. This can be achieved without any noticeable weakness of facial muscles. BTX, for example, will abolish laugh lines around the eyes (crows feet). Failure of injection to do this is used to clinically detect the development of neutralising antibodies. Cosmetic BTX therapy is offered at St Vincent's Clinic.

Worldwide experience has established BTX-A as safe therapy with a very low incidence of serious adverse events. Allergic reactions with anaphylaxis have not been reported however some patients develop flu like symptoms for a few days after treatment. Unwanted excessive weakness of injected muscles occasionally occurs but always recovers fully. Isolated cases of necrotising fasciitis1 and myasthenic crisis2 have been reported following BTX injection. Small numbers of patients develop neutralising antibodies which diminish or abolish the therapeutic effect of BTX.

Clinical Incidations for BTX Therapy

(a) Dystonias

Blephorospasm

Torticollis (cervical dystonia)

Spasmodic dysphonia

Oromandibular dystonia

Focal limb dystonias

(b) Non-dystonic neurological disorders

Hemifacial spasm

Stabismus

Limb spasticity

Palatal myoclonus

Vocal,head or limb tremor

Tics

Bruxism

Stuttering

(c) Non-neurological conditions

Detrusor hyperreflexia

Prostatic hypertrophy

Oesophageal achalasia

Chronic anal fissure

Hyperhydrosis

Sialorrhea

Vaginismus

Protective ptosis

Cosmetic (wrinkles)

Muscle tension headache

De-barking dogs

Table 1

SPASMODIC DYSPHONIA

Spasmodic dysphonia (SD) is a focal laryngeal dystonia characterised by strangled effortful speech with breaks in pitch and phonation. Injection of laryngeal muscles with BTX was first perfomed by Blitzer and Brin in 1984 and has become the treatment of choice in this disorder.

Adductor SD is the most common form and is characterised by overactivity of adductor muscles and strangled speech. For adductor SD, BTX is administered to the thyroaryteniod muscles percutaneously under EMG guidance.

Patients with SD have been evaluated at St Vincent's Hospital since 1983 and treated with BTX since 1991. Comprehensive assessment includes otolaryngological examinations (Dr Ian Cole) and acoustic aerodynamic voice assessments (Helen Brake). This increases diagnostic accuracy and allows separation of SD from disorders that may mimic it such as structural lesions and muscle tension dysphonia. Such examinations are also performed during follow up after injection and provide independent measures of response. Patients are questioned as to the severity of symptoms, treatment benefit and any adverse events at the time of injection using subjective rating scales.

ST VINCENT'S HOSPITAL SPASMODIC DYSPHONIA STUDY

A retrospective study of 169 patients with spasmodic dysphonia seen at St Vincent's between 1983 and 1999 was conducted. The study was designed to determine the clinical features, associated conditions and effects of BTX therapy in the largest Australian series of this disorder.

Of 169 pat ients with SD stud ied 68 per ccnr were fe1nale and 32 per cent tnale. The 1ncan age at diagnosis \Vas 56 yea rs (r a n ge 19 88) . Th e 1nedi a n duration of symptom1s prior to diagnosis \Vas 60 1nonths. The n1ost frequent type of SD was Adductor SD (90 per cent). (Jnly th ree per cent of pat ients had a positive fa,nily history of Sl) or dysronia. A prior history of ncurolcptic exposure before SI) ,vas observed in tv:vo patients. Stridor ,,as presenr in 14 patients (8.3 per cen t) and in seven ,vas the sole 1nanifestation of laryngeal dystonia. The rnost frequent sy1npto1ns in addition to the core syrnpt orns of SI) ,vcrc exacerbation ,vith stress (47 per cent), voca l tre1nor (32 per cent) and exa cerba tion ,vith talk ing on the telephone (29.6 per cent).

The n1os1- freq u en t associ a ted conditions 1,vcrc essential rrc1nor (7.7 per cent) and rnulrifocal dystonia (7.1 per ccnr) . A severe c1not iona l traun1atic event preceded the onset of SL) in 11.2 per cent: of patients by a 1ncdian of three days.

()f the study group of 169 pat ients \,,ith SL\ 144 vvcrc treated 1,vith BTX. R,casons for son1c pa tien ts be ing untreated include asccrt:ainrncnt prior to a vailabilit y of BTX and pa tient preference. In all 1093 treauncnts ,vcrc pcrfonncd bct1,vecn 199l and 1999, The 1nedian dose of BTX injected into each rhyroarytcnoid 1nusclc ,,as nvo units. The 1ncan dura tion of effect was 4.1 1nonths.

The incd ian trcattncnt outcornc score 1,vas "cxccllcntn or "very good" in 80 per cen t of pat ien ts and "sat isfactory)) in 10.4 per cent . Only .3.5 per cen t of patients had 1nedian treattnent outcorne scores of "unsatisfactory". Mu ltivariate a na lys is i nd ica ted t ha t grea ter SL) sever ity \Vas assoc i a ted \Vith poorer trcat tncn t: ou t:co1ne (()R.=3.13' c:I [I.49,6.67] p-0.003). Importantly, older age, long d u ra t ion of syrn p t:orns, rnultifocal dyst:onia and essential tre1nor or strid or were not associ a ted \Vi th poorer treattnent outcotne.

Mild to rnoderat:e paralytic dysphonia \Vas observed in 23 per cent of patients. Ho\vever paralytic aphonia \,ith severe loss of voice \Vas rare (12 events in eight pa tients, 1nean d u ra t ion of 32 days) . Techn ical fa i lure occurred in 8.2 per cent of treatrnents. Severe dysphagia \Vas also rare, con1plicating less than 0.6 per cent of treattncnts. Other rare adverse events included local pa in (13 events), bleed ing and flu like sy1npto1ns (one event each).

The results arc cornparable \virh other large published series[3] A. Blirzer[3] reported a 12 year experience of over 900 patients with SD. l n th is study 87 per cent of patients had adductor SI) and achieved average benefit of 90 per cent: norn1al fu nct:ion last ing an a verage of 15.1 \Vecks. A posi t i ve fa tnil y hist ory of dystonia was rnore frequent (12.1 per cent) ho1,vever this tnay reflect the large proportion of Je\\rish pa tients in this series sharing tnu t:ations of the l)TY1 gene. Stridor \\,as less frequent (1 per cent:) hcnvevcr trcannent out:cotne \Vas very sirni lar \Vi th excellen t response. Poorer trea t1nen t outcorne \Vas significantly associated \Vi th rnore severe Sl") i n our study, however it should be appreciated that ((poorer,, was defined as less tha n "excellen t" and tha t tnost pat ien ts \Vi th severe SI) exper i enced satisfactory treat1nent outcorne.

The St Vince n r>s Spastnod ic I)ysphon ia stu dy has a dded to t he existing body of knov.,ledge of SI). The study found BTX to be highly effective and well tolerated in a diverse range of SL) pat ients and confinns the role of BTX as the treatrnent of choice in this d isorder.

REFEREN CE S

1. Bent ivoglin AR, Albanese A. Botulinum toxin in motor disorders. C:urreni ()pinion in Neurology, 1999; 12: 447-456
2. Borodic (;, Myasthenic crisis afrer hmul inurn roxin.Lnncet 1998; .352(914.3): 1832
3. B!iizer A, Brin !vii\ Stewart CF. Botulinum t oxin management (if Spasmodic Dysphonia (Laryngeal Dystonia): a 12-Ycnr experience in more rhan 900 patients. Laryngoscopc 1998; !08:1435-1 441
4. Whurr R, Nye C, Lorch M. Meta-analysis of Botulinum roxin l'reannent· of spasmodic dysphonia: a review of 22 studies. Int J Langu,ige and (}immunical ion Disorders, 1998; 33, 327-331
5. Hallett M. ()ne m,1n's poison,clin ici! applicat ions of Borul inum toxin. N Engl J Med, 1999; 341(2), 118-120
6. Percz-M irand;i M, J imenez JM. Treatment of chronic anal fissure. N Eng! J l\.1ed, 1998; Jl8(23), 1698-1699
7. Jankovic J, ()nnan J. Botulinum A toxin for cranial-cervical dyston ia: a douhlc-blind placebo connol!ed srudy. Ncunilogy 1987;)); 616-623

A CKN OW LEDGEM EN T S

We ackno\vledge the significant contribu tion of l-lelcn Brake) Speech Patho log ist, []r Mathc\\1 La\v, Stat ist ic ian and I)r Ian C:ole, ()tola y n go logist i n the Spas,nod ic L)ysphonia Study.