

Regular review

Uses of botulinum toxin injection in medicine today

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Botulinum neurotoxin is produced by the anaerobic bacterium *Clostridium botulinum*. It is the most poisonous biological substance known. Very small amounts of botulinum toxin can lead to botulism, a descending paralysis with prominent bulbar symptoms and often affecting the autonomic nervous system. Botulism can occur in two ways. It can result from infection with bacterial spores that produce and release the toxin in the body—as in enteric infectious botulism, when the bacteria grow in the intestine, and in wound botulism, when the wound becomes infected. Alternatively, botulism occurs after ingestion of the toxin (food borne botulism).¹

Botulism has been recognised since the early 19th century, and there was speculation about what caused the condition. In 1822 it was suggested that a “fatty acid” in sausages was the culprit,² and this led to the term botulism (*botulus* being the Latin word for sausage). In 1897, Van Ermengen related botulism to a bacterial toxin.³

The discovery that botulinum toxin blocks neuromuscular transmission⁴ and thereby causes weakness laid the foundation for its development as a therapeutic tool. In 1981, the ophthalmologist Alan Scott pioneered treatment with botulinum toxin when he used it to treat strabismus.⁵ He paved the way for clinical research in many specialities.

Methods

This review was prompted by an increasing number of publications on the therapeutic uses of botulinum neurotoxin. For the literature review we used standard textbooks⁶⁻⁹ and a Medline search for the years 1981 to 1999.

Mode of action

Strains of *Clostridium botulinum* produce seven antigenically distinct neurotoxins designated as serotypes A-G. All seven serotypes have a similar structure and molecular weight, consisting of a heavy (H) chain and a light (L) chain joined by a disulphide bond.¹⁰ They all interfere with neural transmission by blocking the release of acetylcholine (fig 1), which is the principal neurotransmitter at the neuromuscular junction. After synaptic transmission is blocked by botulinum toxin, the muscles become clinically weak and atrophic. The affected nerve terminals do not degenerate, but

Summary points

Botulinum toxin inhibits release of acetylcholine at the neuromuscular junction and in cholinergic sympathetic and parasympathetic neurones

Local injections of toxin weaken overactive muscles and control hypersecretion of glands supplied by cholinergic neurones

Botulinum toxin injections have an established role in some disorders of ocular motility

Botulinum toxin is the treatment of choice for focal dystonias such as torticollis and writer's cramp and for hemifacial spasm and may complement the management of spasticity

Local injections have also been shown to be beneficial in many other conditions including achalasia, chronic anal fissure, and hyperhidrosis

Treatment is usually well tolerated, the main side effect being weakness in adjacent muscles

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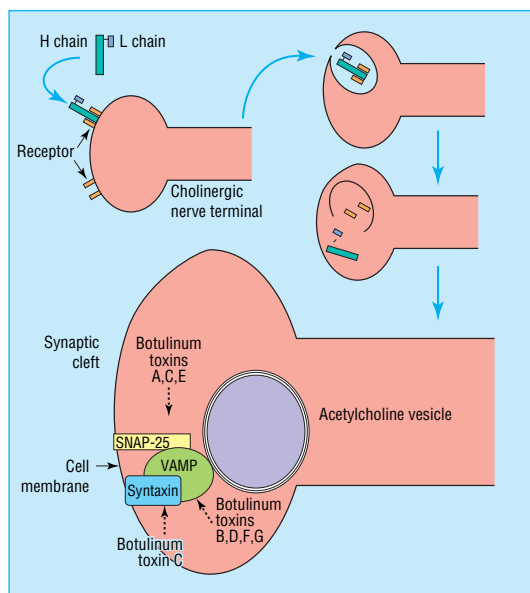
BMJ 2000;320:161-5

the blockage of neurotransmitter release is irreversible. Function can be recovered by the sprouting of nerve terminals and formation of new synaptic contacts; this usually takes two to three months.

Rationale for treatment with botulinum neurotoxin

Botulinum toxin induces weakness of striated muscles by inhibiting transmission of alpha motor neurones at the neuromuscular junction. This has led to its use in conditions with muscular overactivity, such as dystonia. Transmission is also inhibited at gamma neurones in muscle spindles, which may alter reflex overactivity.¹¹

The toxin also inhibits release of acetylcholine in all parasympathetic and cholinergic postganglionic sympathetic neurones. This has fuelled interest in its use as a treatment for overactive smooth muscles (for example, in achalasia) or abnormal activity of glands (for example, hyperhidrosis).



Action of botulinum toxin at cholinergic nerve terminals. The heavy (H) chain of the toxin binds selectively and irreversibly to high affinity receptors at the presynaptic surface of cholinergic neurones, and the toxin-receptor complex is taken up into the cell by endocytosis. The disulphide bond between the two chains is cleaved (by an unknown mechanism), and the toxin escapes into the cytoplasm. The light (L) chains of the seven serotypes interact with different proteins (synaptosomal associated protein (SNAP) 25, vesicle associated membrane protein (VAMP) and syntaxin) in the nerve terminals to prevent fusion of acetylcholine vesicles with the cell membrane and thereby impede its release. (Adapted from Moore,⁶ with permission)

Preparations of botulinum neurotoxin

Serotype A is the only one commercially available for clinical use, although experience is emerging with serotypes B, C, and F.¹² Two preparations exist: Dysport, which is most widely used in the United Kingdom, and Botox, which is used in the United States and elsewhere. Unfortunately, there has been much confusion over the doses and units of potency of the two preparations. Although doses are quoted in mouse units (which is the amount of toxin that kills 50% of a group of 18-20 g female Swiss-Webster mice), implying some standardisation, Botox seems to be more potent. A recent study comparing the two preparations found that a unit of Botox is three times as potent as a unit of Dysport.¹³

Practical aspects of botulinum toxin injection treatment

Botulinum toxin has to be injected into affected muscles or glands. Doses have to be tailored according to the mode of use and individual patients. Generally, the effective dose depends on the mass of muscle being injected: the larger the muscle the higher the dose required. However, susceptibility to the toxin varies. Lower doses may be required in patients with pre-existing weakness and in women and lighter patients.

Overactive muscles are identified by muscular hypertrophy, stiffness, tenderness, and visible abnormal muscular activity. In addition, clinical observation of abnormal movements or postures may help identify an overactive muscle. Electromyography can also be useful—for example, in writer's cramp. Hollow Teflon coated needles are used to target toxin injections into affected muscles. In conditions with very localised

muscle overactivity in delicate places, such as strabismus, the injections are usually guided by electromyography.

The weakness induced by injection with botulinum toxin A usually lasts about three months. Patients will then need further injections at regular intervals, although the interval varies widely depending on the dose and individual susceptibility. Patients usually experience relief after each injection and then gradually deteriorate to a point where further injections are required. Response after the injections should be assessed both by using patient reported benefit in terms of pain relief and improvement of disability, and by objective measures on clinical examination.

Most patients treated with botulinum toxin require repeated injections over many years. Some patients who respond well initially develop tolerance to the injections. This can be caused by the development of neutralising antibodies to the toxin. Patients who receive higher individual doses or frequent booster injections seem to have a higher risk of developing antibodies. Injections should therefore be given at the lowest effective dose and as infrequently as possible.

Several types of antibody assay are available.¹⁴ The most widely used is the *in vivo* mouse neutralisation assay. In clinical trials patients resistant to botulinum A have benefited from injections with other serotypes, including B, C, and F. The duration of effect may differ widely with different serotypes—for example, the effect of botulinum F toxin lasts for only about two months in patients with torticollis, even when higher doses are used.¹⁵

Side effects

Injections with botulinum toxin are generally well tolerated. After injection the toxin diffuses into the muscles and other tissues. Its effect diminishes with increasing distance from the injection site, but spread to nearby muscles is possible, particularly when high volumes are injected. Patients receiving injections into the neck muscles for torticollis may therefore develop dysphagia because of diffusion of the toxin into the oropharynx. Distant effects shown by specialised electromyographic tests can also occur, but weakness of distant muscles or generalised weakness, possibly due to the toxin spreading in the blood, is very rare.^{16 17} However, botulinum toxin should be used only under close supervision in patients with disturbed neuromuscular transmission—for example, in myasthenia gravis or Lambert-Eaton myasthenic syndrome¹⁸ or during treatment with aminoglycosides. Other systemic side effects include an influenza-like illness and, rarely, brachial plexopathy, which may be immune mediated.¹⁹ No severe allergic reactions have been reported. Gallbladder dysfunction attributed to autonomic side effects of the toxin and a case of necrotising fasciitis in an 80 year old immunosuppressed woman with blepharospasm have been noted.^{20 21} Botulinum toxin is contraindicated in pregnancy and while breast feeding. Careful monitoring is important when the toxin is used in children as it might alter cell functions such as axonal growth.⁶

Indications for treatment

Over the past 15 years botulinum toxin has been shown to be useful in many conditions, especially strabismus and various movement disorders (box).

Disorders caused by overactivity of muscles for which treatment with botulinum toxin A is established

Ophthalmological disorders

Concomitant misalignment
 Primary or secondary esotropia or exotropia
 Nonconcomitant misalignment
 Paralytic strabismus (III, IV, VI nerve palsy, internuclear ophthalmoplegia, skew deviation)
 Duane's syndrome
 Restrictive or myogenic strabismus

Movement disorders

Idiopathic focal dystonias
 Craniocervical (torticollis and isolated head tremor, blepharospasm, oromandibular dystonia, lingual dystonia, laryngeal dystonia)
 Other focal dystonias (writer's cramp, occupational cramps such as musician's cramp)
 Tardive dystonia
 Hemifacial spasm/post-facial nerve palsy synkinesis

Encouraging clinical reports have generated an abundance of ideas for other uses, but many of these observations are anecdotal. Nevertheless, its potency, relative safety, and the reversibility of its effects have made botulinum toxin an attractive option for some chronic conditions that respond only partially to medical treatment. Sometimes it can be used as an alternative to surgical intervention. In the following section we will focus on established indications of botulinum toxin.

Strabismus and other ocular motility disorders

The idea behind using botulinum toxin A in disorders of ocular motility is to shorten the non-injected antagonist muscle in order to align the visual axes.⁵ In patients with concomitant strabismus, who have compromised or absent binocular fusion, treatment is cosmetic as permanent ocular realignment cannot be expected. In secondary strabismus resulting from transient monocular vision loss (such as posttraumatic cataract), toxin injections can help to establish whether binocular cooperation is still present. If so, the patient would be a candidate for surgery to restore ocular function. Botulinum toxin has also proved useful when surgery has over or under corrected strabismus.²²

Paralytic strabismus is due to weakness of extraocular muscles—for example, the lateral rectus in abducens nerve palsy. Injections into the ipsilateral antagonist (medial rectus) can prevent contracture of this muscle. In restrictive causes of strabismus, for instance in dysthyroid eye disease, botulinum toxin can help to realign the eye before more definitive surgery. Complications include transient ptosis, subconjunctival haemorrhage, and transient vertical deviations of the globe.

Movement disorders

The effectiveness of botulinum toxin A in spasmodic torticollis was first shown in 1986,²³ and it is now the treatment of choice for this condition. Some improvement in pain relief, head position, and disability occurs in 90% of patients, and about three quarters achieve considerable improvement.²⁴ Injections are given into neck muscles, depending on the muscular activity and head position. Patients with severely restricted head movements usually respond less well to the injections.

The most common side effect (occurring in 5-9% of patients) is dysphagia, but this is usually transient.

Botulinum toxin is also the treatment of choice for primary blepharospasm (involuntary eye closure). Injections are given bilaterally into the overactive orbicularis oculi muscle. Possible side effects are partial ptosis or, rarely, double vision. A variant of blepharospasm in which eyelid opening is inhibited sometimes improves after injections into the pretarsal portion of the orbicularis oculi.²⁵

In oromandibular dystonia, injections are given into the masseter, temporalis, and internal pterygoid muscles for predominant jaw closing and into the digastric and external pterygoids for jaw opening spasms. Injections of the pterygoid muscles need electromyographic guidance. Symptoms are reduced in about 70% of patients, and treatment may prevent dental complications and temporomandibular joint dysfunction.⁵

In a large series of patients with laryngeal dystonia, treatment with botulinum toxin A resulted in normal or

Examples of overactive muscle conditions for which treatment with botulinum toxin A has been tried

Ophthalmic disorders

Disorders of ocular motility (nystagmus and oscillopsia)
 Thyroid disease (upper eyelid retraction, glabellar furrowing)
 Therapeutic ptosis for corneal protection

Movement disorders

Secondary dystonia
 Tic disorders (simple tics, Tourette's syndrome, dystonic tics)
 Tremor (essential, primary writing, palatal, cerebellar)
 Painful spinal myoclonus
 Parkinson's disease (freezing of gait, off period dystonia, severe constipation)
 Cephalic tetanus, stiff man syndrome, neuromyotonia
 Muscle stiffness, cramps, spasms

Spasticity

Multiple sclerosis
 Stroke
 Traumatic brain injury
 Cerebral palsy
 Spinal cord injury

Neuromuscular disorders

Myokymia
 Neurogenic tibialis anterior hypertrophy with myalgia
 Benign cramp-fasciculation syndrome

Pain

Headache (tension type, migraine, cervicogenic)
 Backache (neck, lower back)
 Myofascial pain
 Tennis elbow

Ear, nose, and throat disorders

Oromandibular disorders (bruxism, Masseter hypertrophy, temporomandibular joint dysfunction)
 Pharyngeal disorders (cricopharyngeal dysphagia, closure of larynx in chronic aspiration)
 Laryngeal disorders (vocal fold granuloma, ventricular dysphonia, mutational dysphonia)
 Stuttering with glottal blocks

Disorders of pelvic floor

Anismus
 Vaginismus
 Anal fissures
 Detrusor-sphincter dyssynergia

Cosmetic applications

Wrinkles, frown lines
 Rejuvenation of ageing neck

Other disorders for which botulinum toxin A has been tried**Overactivity of smooth muscles**

Oesophageal disorders (achalasia, diffuse oesophageal spasm, oesophageal diverticulosis)

Sustained sphincter of Oddi hypertension

Gastric pyloric spasms

Hypersecretion of glands supplied by cholinergic sympathetic or parasympathetic neurones

Ptyalism

Increased tearing

Hyperhidrosis (axillary, palmar, gustatory)

Intrinsic rhinitis

near normal voice in patients with adductor type (strained or strangled voice) and considerable benefit in patients with abductor type (breathy, whispery voice).²⁶ Injections can be carried out by indirect laryngoscopy or percutaneously with electromyographic guidance. Adverse symptoms are transient hypophonia, hoarseness, and mild aspiration of fluids and sometimes stridor.

Botulinum toxin injections have been shown to provide effective relief for writer's cramp, with pain being generally more improved than motor function.²⁷ The muscles to be injected are usually identified on clinical grounds, but electromyography is used to inject the toxin accurately. Improvement of function is almost invariably associated with some weakness. Other occupational cramps, such as musician's cramp, respond less well to injections as they require very sophisticated neuromuscular performance.

Botulinum toxin is also an effective treatment for hemifacial spasm.²⁸ Before treatment patients should have magnetic resonance imaging of the brain to rule out structural lesions in the cerebello-pontine angle. Nearly all injected patients improve, and the effect can last longer than in patients with dystonia (about five months), possibly because of pre-existing facial weakness. Treatment can be individualised by injecting only those muscles whose contractions are most disturbing to the patient—for example, the orbicularis oculi for involuntary eye closure. Excessive facial weakness is the most common side effect.

Botulinum toxin has been used in several other movement disorders, including tics and various tremor disorders, although the response is usually less than in dystonia, particularly in tremor patients.²⁹

Spasticity

Botulinum toxin has been evaluated in various spastic disorders.³⁰ It was shown to improve gait pattern in patients with cerebral palsy with progressive dynamic equinovarus or equinovalgus foot deformities. Treatment of children with cerebral palsy during the key early years when functional skills in walking are being developed improves the outcome and may help to avoid surgery for contracture and bony torsion.³¹ In multiple sclerosis the toxin can relieve contractions of thigh adductors that interfere with sitting, positioning, cleaning, and urethral catheterisation. It can also reduce muscle tone and increase range of movement in upper extremity spasticity or in spastic foot drop after a stroke. Whether this translates into functional improvement has yet to be substantiated.³²

Other indications

Botulinum toxin has been tried in numerous other conditions (box). The list of possible new indications is rapidly expanding. It seems to be a promising alternative to sphincterotomy in patients with chronic anal fissures³³ and is effective in achalasia.³⁴ Some autonomic disorders resulting in hypersecretion of glands like excessive palmar hyperhidrosis, ptyalism, or gustatory sweating, which often occurs after surgery to the parotid gland, respond well to botulinum toxin.³⁵⁻³⁷ Surprisingly, the response seems to last much longer than in conditions caused by overactivity of striated or smooth muscles.³⁶

Although botulinum toxin has been tried in many conditions, in the United Kingdom it is currently licensed only for blepharospasm, hemifacial spasm, and spasmodic torticollis. In medical practice today botulinum toxin A is probably mostly used for treatment of focal dystonias, hemifacial spasm, and spasticity. Further clinical experience is needed before definitive treatment recommendations in other conditions are made.

We thank Professor Niall P Quinn and Dr Cathy Chuang for critical review of the manuscript.

Funding: AM was supported by the Ernst Jung-Stiftung für Wissenschaft und Forschung in Hamburg, Germany.

Competing interests: KPB and AM have been supported by Ipsen, the manufacturer of Dysport, to attend an international symposium.

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(Accepted 16 August 1999)

Evidence based case report

Asymptomatic haematuria ... in the doctor

Chris Del Mar

The patient was waiting in the consulting room; everything was nearly ready. The occasion was the examination in general practice for fifth year medical students. We run an objective structured clinical examination. For this part, the student had to measure the patient's blood pressure (the "patient" was actually someone recruited from our general practice), test his urine using a dipstick, and report to the examiner within the five minutes between bells. Just one thing was missing—the midstream sample of normal urine for testing. Because I did not want to disturb the volunteer patient, I collected it from myself. I measured the patient's blood pressure again (this had to be done after every 10th student)—it was stable. And I tested the urine to check it was normal—it was not.

For the next two hours, students either told me (or, in the case of those less skilled at this technique, did not tell me) that there was a trace of blood in the urine. This was not a problem as far as the examination was concerned because the marking was not affected by the test result. But it was a problem for me. What should I do? I tested my urine again a week later, and when I found it was still positive I sent a specimen to the laboratory. The report stated that urine culture was negative but confirmed the presence of normal red cells (30/ml).

Conventional medical teaching had taught me that bleeding must come from somewhere. The model that sprang to mind first is summarised in the table. I then checked with a textbook of surgery.¹ I had forgotten tuberculosis and schistosomiasis as causes of haematuria. A textbook of medicine² suggested further assessments, including checking my blood relatives for urine abnormality and carrying out haemoglobin electrophoresis and 24 hour urinary estimations of urate and calcium excretion. If all these investigations were negative, intravenous urography, cystoscopy, and renal computed tomography were proposed, with indefinite regular follow up thereafter. The essential feature of this model is that identifying the lesion anatomically or physiologically is the key to managing the problem. Early diagnosis of some of the serious causes of

haematuria such as transitional cell carcinoma might affect the outcome favourably by enabling treatment to be given. With other causes such as minimal change glomerulonephritis, early diagnosis is unlikely to affect mortality or morbidity.

I consulted my general practice colleague. His approach was similar. He ensured that I had checked my urine microscopy and culture to establish whether the blood was haemolysed or not, and he measured my blood pressure. He wondered whether my bicycle riding might be the cause, and suggested I recheck the urine after a month or two. If test results were still positive, it looked as if the cascade of likely events would include ultrasonography, urine samples for malignant cells, and then probably referral to a urologist for consideration of cystoscopy and intravenous urography.

"We probably won't find any cause for it," he said. I think this was to reassure me. I had time to think about adopting an evidence based approach.

Formulating the question

The most difficult part of adopting evidence in practice is formulating the question. This involves quite a different way in thinking—away from "patho-anatomical-physiological" questions towards empirical ones. What is the chance of having a serious condition with asymptomatic haematuria? What sort of study did I want? Ideally, it would be huge study of general

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BMJ 2000;320:165-6

Causes and management of haematuria

Site of bleeding	Disease	Management
Generalised	Bleeding diathesis	Check bleeding and coagulation profiles; treat accordingly
Lower renal tract	Prostate hypertrophy or cancer; urethral inflammation; bladder lesion or cancer	Cystoscopy; treat accordingly
Ureteric lesions	Transitional cell carcinoma; ureteric calculi	Ultrasonography or intravenous urography; treat accordingly
Renal lesions	Cancer; calculi; vascular abnormalities; reflux nephropathy; glomerular lesions	Check blood pressure; ultrasonography or intravenous urography; treat accordingly