REVIEW

Botulinum toxin in clinical practice

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Botulinum toxin, the most potent biological toxin, has become a powerful therapeutic tool for a growing number of clinical applications. This review draws attention to new findings about the mechanism of action of botulinum toxin and briefly reviews some of its most frequent uses, focusing on evidence based data. Double blind, placebo controlled studies, as well as open label clinical trials, provide evidence that, when appropriate targets and doses are selected, botulinum toxin temporarily ameliorates disorders associated with excessive muscle contraction or autonomic dysfunction. When injected not more often than every three months, the risk of blocking antibodies is slight. Long term experience with this agent suggests that it is an effective and safe treatment not only for approved indications but also for an increasing number of off-label indications.

The potential for a therapeutic use for botulinum toxin was first recognised by Justinus Kerner who in 1817 provided the earliest account of food borne botulism.[1] He correctly recognised that the toxin paralysed skeletal muscles and parasympathetic function, and proposed that botulinum toxin could be used as a therapeutic agent. In 1895, an investigation into an outbreak of food poisoning in Ellezelles, Belgium, led to the discovery of *Clostridium botulinum* and its toxin by van Ermengem.[2] The most potent poison known (it can be lethal at doses as low as 0.05 μg), botulinum toxin has been feared as a possible biological weapon.[3] It was not until the 1981 report of botulinum toxin injections into eye muscles to correct strabismus that the therapeutic potential of this agent became recognised.[4] In 1989, after extensive laboratory and clinical testing of botulinum toxin type A (Botox®, Allergan Inc, Irvine, California, USA), the Food and Drug Administration (FDA) approved it as a therapeutic agent in patients with strabismus, blepharospasm, and other facial nerve disorders, including hemifacial spasm. In 2000, the FDA approved Botox® and botulinum toxin type B (Myobloc™, Elan Pharmaceuticals Inc, Morristown, New Jersey, USA) as treatments for cervical dystonia, and Botox *Cosmetic* for treatment of glabellar (frown) lines. Although its widest application is still in the treatment of disorders manifested by abnormal, excessive, or inappropriate muscle contractions, its use is rapidly expanding to include treatment of a variety of ophthalmological, gastrointestinal, urological, orthopaedic, dermatological, secretory, painful, and cosmetic disorders[5 6] (table 1).

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PHARMACOLOGY AND IMMUNOLOGY OF BOTULINUM TOXIN

Few therapeutic agents have been better understood in terms of their mechanism of action before their clinical application or have had a greater beneficial impact on patients' functioning than botulinum toxin. The therapeutic value of this agent derives from its ability to inhibit the release of acetylcholine from the presynaptic nerve terminal, causing local chemodenervation.[7] There are seven immunologically distinct toxins; types A and B have been studied most intensively and used most widely, but the basic pharmacology and clinical applications of other types of toxins, particularly C, D, and F, are also being explored.[8] Although the seven neurotoxins are antigenically different they contain structurally homologous subunits.[9]

Synthesised as a single chain polypeptide (molecular weight of 150 kDa), botulinum toxin has relatively little potency until it is cleaved by trypsin or bacterial enzymes into a heavy chain (100 kDa) and a light chain (50 kDa). Three dimensional structure shows that the neurotoxins contain a binding domain (heavy chain), a catalytic domain (light chain), and a translocation domain.[10] The action of botulinum toxin involves a four step process: (1) high affinity, serotype specific binding by the heavy chains to acceptors on presynaptic membrane of cholinergic nerve endings; (2) acceptor mediated, energy dependent internalisation of the complex (endocytosis); (3) translocation from the acidic endosome to the cytosol; and (4) enzymatic cleavage by the light chain, a zinc dependent protease, of selected proteins that are critical for fusion of the presynaptic acetylcholine vesicle with the presynaptic membrane, thus preventing release of acetylcholine into the synapse (fig 1).

The complex of proteins involved in the regulated fusion of the synaptic vesicle with the plasma membrane is referred to as SNARE (soluble NSF, N-ethyl maleimide-sensitive factor, attachment receptors, proteins essential for regulated exocytosis).[11] The complex consists of vesicle associated membrane protein (VAMP), also referred to as v-SNARE or synaptobrevin, and two target (t-SNARE) proteins: plasma membrane synaptosome associated protein (SNAP-25) and syntaxin. The light chains of both botulinum toxin A and E cleave SNAP-25,

Abbreviations: MPA, mouse protection assay; SNAP, synaptosome associated protein; SNARE, soluble NSF, N-ethyl maleimide-sensitive factor, attachment receptors, proteins essential for regulated exocytosis; UBI, unilateral brow injection; VAMP, vesicle associated membrane protein

Table 1 Clinical applications of botulinum toxin

Dystonia
* Blepharospasm and lid apraxia
* Oromandibular-facial-lingual dystonia
* Cervical dystonia (torticollis)
* Laryngeal dystonia (spasmodic dysphonia)
* Limb dystonia
* Task specific dystonia (eg, writer's or other occupational cramps)
* Other focal/segmental dystonias (primary, secondary)

Other involuntary movements
* Hemifacial spasm
* Limb, head, voice, chin tremor
* Palatal myoclonus
* Motor and phonic tics (including coprolalia)
* Nystagmus and oscillopsia
* Myokymia

Inappropriate muscle contractions
* Spasticity (stroke, cerebral palsy, head injury, multiple sclerosis)
* Painful rigidity
* Strabismus
* Bruxism and temporo-mandibular joint syndrome
* Stuttering
* Chronic tension (muscle contraction) headaches
* Lumbosacral strain and back spasms
* Radiculopathy with secondary muscle spasm
* Myofascial pain syndromes
* Achalasia (lower oesophageal sphincter spasm)
* Spasm of the inferior constrictor of the pharynx
* Spasm of the sphincter of Oddi
* Spastic bladder, detrusor sphincter dyssynergia
* Anismus
* Vaginismus

Other applications
* Protective ptosis
* Hyperlachrymation
* Drooling (sialorrhoea)
* Hyperhidrosis
* Gustatory sweating
* Anal fissure
* Constipation
* Obesity (distal stomach)
* Cosmetic (wrinkles, brow furrows, frown lines, ''crow's feet'', platysma lines, facial asymmetry)
* Tennis elbow and other sports injuries

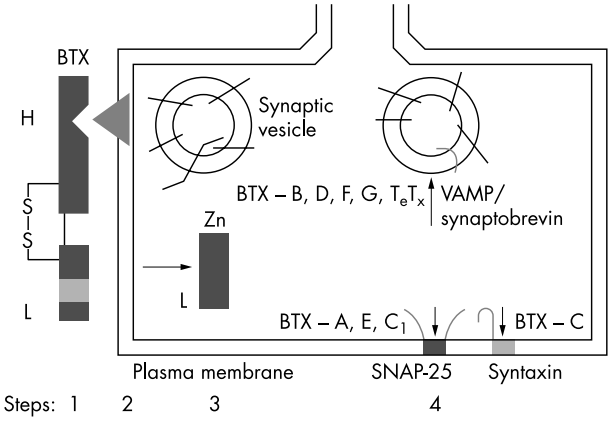

Figure 1 Mechanism of action of botulinum toxin (a four step process). Step 1: after botulinum toxin is activated by proteolytic cleavage of the polypeptide chain into a 100 kDa heavy chain (H) and a 50 kDa light chain (L), linked by a disulphide bond (S-S), the heavy chain (H) domain of the toxin binds to the presynaptic plasma membrane of the motor axon terminal. Step 2: the toxin complex is then internalised by energy dependent endocytosis. Step 3: the light chain (L), a zinc endopeptidase, is released into the cytoplasm. Step 4: the light chain cleaves various components of SNARE (indicated by vertical arrows), including SNAP 25 (botulinum toxin A), VAMP/synaptobrevin (botulinum toxin B), or syntaxin (botulinum toxin C), and thus prevents the fusion of acetylcholine synaptic vesicle with the plasma membrane. This blocks the release of the neurotransmitter into the synaptic cleft, causing local chemodenervation. BTX, botulinum toxin.

but at different sites[12]: the light chains of botulinum toxin B, D, and F cleave synaptobrevin (VAMP),[13] and type C cleaves both SNAP-25 and syntaxin.[8] Within a few days after injection of botulinum toxin A into skeletal muscle, the affected nerve terminals are no longer capable of neurotransmitter exocytosis, but newly formed sprouts release acetylcholine, forming a functional synapse. After about three months, consistent with the return of clinical function of the muscle and a wearing off response from the previous injection, the original terminal resumes exocytosis and the sprouts regress to return the neuromuscular junction to its original state.[14] Using cerebellar neurones, the half life of protease activity based on blockade of transmitter release was estimated to be 31 days for toxin A, 25 days for toxin C1, 10 days for toxin B, two days for toxin F, and 0.8 days for toxin F.[15]

Different commercial preparations have unique properties that account for different potencies and clinical effects. The first commercially available preparation of botulinum toxin was type A botulinum toxin (botulinum toxin A), marketed as Botox® (Allergan Inc). Subsequently, other commercial preparations became clinically available, including another botulinum toxin A called Dysport® (Beaufour-Ipsen, Dreux, France) and botulinum toxin B or Myobloc™, in some countries also referred to as NeuroBloc™ (Elan Pharmaceuticals). In addition, there is a Chinese form of botulinum toxin A, ''Hengli'' (Lanzhou Institute of Biological Products, Lanzhou, China). The standard unit for measuring potency of different preparations is derived from a mouse protection assay (MPA): 1 unit of botulinum toxin is the amount of intraperitoneally injected toxin found to kill 50% (LD_{50}) of a group of mice. Other preparations of botulinum toxin, however, require much higher doses to produce a similar effect. For example, three to five times higher doses of Dysport® and about 50 times higher doses of Myobloc™ are required to produce the same mouse LD_{50}. Although mouse is used for these assays, there are marked differences among species in their sensitivities to the various neurotoxins. It is therefore critically important to recognise that different preparations require different doses, expressed in mouse units, to achieve a similar clinical effect.

While most patients continue to respond to repeat botulinum toxin treatments, some become unresponsive to subsequent treatments as a result of developing neutralising or blocking antibodies.[16 17] The mechanisms of this immunoresistance are still unknown, but studies have shown that the heavy chain (H_C) fragment of the botulinum toxin protein contains epitopes that are recognised by anti-H_C Abs and by H_C primed T lymphocytes.[18] Only those antibodies directed against the 150 kDa neurotoxin complex block the function of the toxin, and not those directed against the light chain or the non-toxin protein components of the complex. There are several methods for detecting botulinum toxin antibodies, but the mouse protection assay (MPA) is considered clinically most relevant because it detects blocking antibodies.[19] Alternatively, clinical immunoresistance is strongly suspected when a unilateral brow injection (UBI) fails to produce paralysis of the injected corrugator or procerus muscle and the patient is still able to frown normally on the injected side one or two weeks later. The presence of blocking antibodies, as determined by the MPA or UBI, means that the patient will no longer respond to the serotype that induced the antibodies, but may respond to an

alternate serotype. However, because of epitope homology between the various serotypes, the cross reactivity may result in immunoresistance to the alternate serotype. In addition to previous immunoresistance to the same or alternate serotype, studies have shown that the following factors increase the risk of developing immunoresistance: ''booster'' injections within less than two to three months of the previous injections; high cumulative dose over a relatively short period of time; and protein loading. The original Botox®, used until 1998, which contained 25 ng of neurotoxin complex protein per 100 units, seemed to be significantly more antigenic than the current Botox® preparation, which contains only 5 ng of the complex protein per 100 units. In a three year follow up study we found a 9.5% frequency of blocking antibodies in patients treated with the original Botox, but there was no evidence of blocking antibodies in patients treated with the current Botox for the same length of time.[19] In a similar study involving Dysport®, 2% of patients developed blocking antibodies after a minimum of six treatment visits.[20] Prevention of immunoresistance—by using preparations of botulinum toxin with the lowest possible antigenicity and by keeping the dose per treatment session as low as possible and the interdose interval as long as possible (at least 2.5 months)—is of paramount importance in maintaining the beneficial response to botulinum toxin injections.

In the remainder of this review I will focus on the most common clinical applications of botulinum toxin, emphasising results of controlled trials and an evidence based approach to the use of botulinum toxin. Detailed discussion of dosage guidelines and injection techniques, such as the use of electromyography (EMG),[21] is beyond the scope of this review. The most recent references are preferentially cited, but the reader is referred to other, more comprehensive, reviews of the topic.[6 22]

DYSTONIA AND RELATED MOVEMENT DISORDERS

Botulinum toxin first gained clinical acceptance as a result of marked benefits it produced in patients with dystonia, a neurological disorder dominated by repetitive and patterned contractions of muscles producing abnormal movements and postures.[23] While some patients with primary or secondary dystonia improve with levodopa, anticholinergic drugs, baclofen, and muscle relaxants, botulinum toxin injections are now considered the treatment of choice in most patients with focal or segmental dystonia.

Since the initial, double blind, placebo controlled trial of botulinum toxin in patients with cranial-cervical dystonia, including blepharospasm, reported in 1987,[24] several controlled and open label studies have confirmed the efficacy and safety of this treatment in a variety of dystonic disorders.[23] Moderate or marked improvement has been reported in more than 90% of patients with blepharospasm injected into the orbicularis oculi of upper and lower eyelids.[25] The average latency from the time of the injection to the onset of improvement is three to five days and the duration of benefit is usually three to four months. The most frequent side effects, occurring in fewer than 10% of treated patients, include ptosis, blurring of vision, diplopia, tearing, and local haematoma. All these side effects usually resolve in less than two weeks.

Oromandibular dystonia—manifested by involuntary jaw closure and bruxism, jaw opening, or jaw deviation—is among the most challenging forms of focal dystonia to treat. It rarely improves with drug treatment, and there are no surgical treatments. An injection of botulinum toxin into the masseter and temporalis in patients with dystonic jaw closure or the submental muscle complex and lateral pterygoid muscles in patients with jaw opening dystonia often markedly improves the symptoms of temporomandibular joint syndrome and other oral and dental problems, as well as dysarthria and chewing difficulties.[26] A temporary swallowing problem, noted in fewer than 20% of all treatment sessions, was the most common complication.

Hemifacial spasm is another indication for botulinum toxin treatment. In contrast to blepharospasm, a form of facial dystonia, hemifacial spasm is consistently unilateral and is usually caused by compression or irritation of the facial nerve by an aberrant artery or abnormal vasculature around the brain stem or some other local structural pathology. In a study of 110 patients with hemifacial spasm, 95% had moderate or marked improvement in severity and function following botulinum toxin treatment.[27] This is consistent with a 10 year experience with botulinum toxin treatment in 65 patients with hemifacial spasm followed in four Italian centres.[28] In both studies side effects were minimal and consisted chiefly of transient facial weakness.

Cervical dystonia, also called torticollis, is one of the more common primary dystonias. It has been subjected to more open and controlled trials than any other indication for botulinum toxin treatment.[20 29] Optimal results are obtained when, based on a careful neurological evaluation, only the involved muscles are injected with an appropriate dose. As a result of early intervention with botulinum toxin in patients with cervical dystonia, permanent neck contractures are now rare and surgical treatment, such as selective peripheral denervation, is rarely necessary.[30] Neck contractures, wrong selection of muscles or dosage, and previous immunisation with botulinum toxin are probably the most likely reasons for primary non-responsiveness. One long term study showed that 75% of patients continued to benefit for at least five years, 7.5% developed secondary unresponsiveness, and only 1.3% discontinued botulinum toxin treatment because of intolerable side effects.[17] Based on personal experience and a review of published reports, the average per visit total dose for patients with cervical dystonia is about 200 units of Botox®, 500 units of Dysport®, and 10 000 units of Myobloc™. It is important to recognise, however, that the selected dose must be customised for each patient. Most studies in patients with cervical dystonia were conducted with botulinum toxin A preparations, but several studies have subsequently confirmed the efficacy of botulinum toxin B,[31] even in patients who are resistant to botulinum toxin A.[32] The various preparations have relatively similar efficacy, with an average latency from the injection to the onset of clinical effects of about one week and the duration of benefit lasting about three to four months. Transient dysphagia and neck weakness are the most frequent complications with both serotypes. Botulinum toxin B, however, is more likely to produce dryness of the mouth as compared with botulinum toxin A, presumably by exerting a more potent blocking effect on cholinergic release in the postganglionic parasympathetic fibres innervating the salivary glands. Distant and systemic subclinical and clinical effects such as generalised weakness and malaise may occur, possibly as a result of haematogenous spread of the toxin, but this complication is quite rare. These generalised effects, however, are more likely to happen when the total dose per visit is relatively large, such as in treatment for spasticity. Injections into the sternocleidomastoid muscles are most often associated with dysphagia, and when bilateral injections are required, the dose in each muscle must be lowered substantially. Besides types A and B, the other type of botulinum toxin that has undergone clinical testing is type F, but its benefits usually last for only about eight weeks.[33]

Several studies have established the efficacy and safety of botulinum toxin in the treatment of laryngeal dystonia, manifested by spasmodic dysphonia, an effortful and strained voice interrupted by frequent breaks in phonation

and voiceless pauses (adductor spasmodic dysphonia), or a breathy, whispering voice (abductor spasmodic dysphonia). Botulinum toxin is now considered to be the treatment of choice for this disorder.[34] A unilateral or bilateral EMG guided approach or indirect laryngoscopy without EMG has been used to target the thyroarytenoid muscle, involved in the adductor form of spasmodic dysphonia. Irrespective of the technique, most investigators report about 75–95% improvement in voice symptoms. Adverse experiences include transient breathy hypophonia, hoarseness, and rarely dysphagia with aspiration. Outcome assessments clearly show that botulinum toxin injections for spasmodic dysphonia produce measurable improvements in the quality of life.[35] Less consistent improvements have been reported with the laryngeal injections for the treatment of stuttering and voice tremor.[36 37]

Other movement disorders reported to benefit from botulinum toxin injections include task specific focal dystonias, such as writer's or musician's cramps and other occupational dystonias.[38 39] Important insights into the pathophysiology of dystonia and the effects of treatment have been gained from various physiological studies that have shown reorganisational changes in the primary motor cortex in patients with dystonic writer's cramp receiving botulinum toxin injections.[40]

Botulinum toxin injections have been also found to be useful in patients with Parkinson's disease and other neurodegenerative disorders, or stroke related hemiplegia, who occasionally develop secondary ''dystonic clenched fist''.[41] Many of these disorders are also associated with foot dystonia, and botulinum toxin injections into the foot-toe flexors or extensors may not only alleviate the disability, pain, and discomfort often associated with such dystonia, but may also improve gait. Whether botulinum toxin injections will play an important role in the treatment of recurrent painful physiological foot and calf cramps is yet to be determined.

Besides dystonia, botulinum toxin injections are useful in other hyperkinetic movement disorders. Several open label and double blind, placebo controlled studies have also established the beneficial effects of botulinum toxin in the treatment of tremors involving hands[42 43] and head.[44] Although tics associated with Tourette syndrome often improve with antidopaminergic drugs, this treatment is limited because of potential side effects.[45] Several studies have shown that botulinum toxin injections not only improve the motor component of focal tics but also the premonitory sensations that precede both motor and phonic tics.[46 47]

SPASTICITY AND OTHER HYPERTONIC DISORDERS

In addition to involuntary movement disorders, botulinum toxin has been used effectively to treat disorders of muscle tone, including spasticity associated with cerebral palsy, strokes, brain trauma, and multiple sclerosis.[48–51] While clearly effective, botulinum toxin treatment often need to be supplemented by other medical treatments (for example, tizanidine and other muscle relaxants, as well as oral or intrathecal baclofen and phenol injections) and an active physical treatment programme. As a result of botulinum toxin treatment of leg spasticity, children with cerebral palsy may convert from toe walking to normal flat footed gait, thus avoiding surgical lengthening of the heel cord. Furthermore, early institution of botulinum toxin treatment in these children may prevent musculoskeletal deformities and other orthopaedic problems later in life. In one controlled study, 125 patients with cerebral palsy and dynamic equinus spasticity during walking were randomised to receive 10, 20, or 30 mg/kg of botulinum toxin A (Dysport®), or placebo to the gastrocnemius of both legs.[52] There was a statistically significant improvement in all three dose groups, particularly the 20 mg/kg group, compared with placebo in the dynamic component of the gastrocnemius muscle. Other double blind, placebo controlled studies have shown that botulinum toxin injections produced meaningful improvements in wrist and finger spasticity following stroke[53] and also reduced carer burden.[49] In a randomised, double blind trial of 20 patients with post-stroke spasticity, injections of botulinum toxin A to each of the soleus, tibialis posterior, and medial and lateral heads of the gastrocnemius were more effective than percutaneous injection of phenol to the tibial nerve.[54] Several studies have shown meaningful functional improvement and relief of associated pain following botulinum toxin in patients with hip adductor spasticity in multiple sclerosis,[55] rigidity associated with a variety of parkinsonian disorders,[56] and stiff person syndrome.[57] When used early on, botulinum toxin may prevent complications of spasticity such as contractures.[58]

MUSCLE SPASMS AND OTHER PAINFUL DISORDER INCLUDING HEADACHES

One of the most rapidly expanding indications for botulinum toxin is in the treatment of various painful muscle spasms. In a double blind, placebo controlled study using a total of 200 units of Botox® injected at five lumbar paravertebral sites on the side of maximum discomfort, Foster *et al*[59] showed a significant improvement in pain on a visual analogue scale (VAS) and the Oswestry low back pain questionnaire compared with placebo at three and eight weeks after injection. Other disorders causing muscle spasm or muscle tenderness reported to benefit from botulinum toxin injections include fibromyalgia-myofascial pain,[60] temporomandibular joint and orofacial pain (often associated with bruxism),[26] and other musculoskeletal pain and spasm syndromes.[61]

Both muscle contraction headaches and migraines are increasingly treated with botulinum toxin, but there is a remarkable paucity of well designed controlled studies.[62] While some placebo controlled studies of botulinum toxin showed benefits in patients with chronic daily headaches and chronic tension or ''cervicogenic'' headaches, others showed mixed results.[63] Using evidence based medicine criteria, Evers *et al*[64] reviewed published reports of botulinum toxin in the treatment of various headache syndromes and concluded that at present there is ''no sufficient positive evidence for a general treatment of idiopathic and cervicogenic headaches'' with botulinum toxin A. The differences in reported results may reflect differences in patient selection, methods of assessment, dosage of botulinum toxin, and injection techniques. Quantitative sensory testing and measurements of pain thresholds in response to local electrical stimulation showed no statistically significant differences between normal subjects pretreated with subcutaneous injection of botulinum toxin A (Dysport®) or placebo.[65] This suggests that the efficacy of botulinum toxin in various pain syndromes is a result of mechanisms other than a reduction in muscle tone. Other mechanisms proposed to explain the analgesic effects of botulinum toxin include:

- inhibition of release of substances that sensitise muscle nociceptors;
- an effect on spindle afferents favourably altering the firing pattern of supraspinal projections and changing the central sensory processing;
- suppression of neurogenic inflammation;
- inhibition of substance P, glutamate, and other peptides and neurotransmitters involved in mediating pain.

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Botulinum toxin interferes with transmission not only at the neuromuscular junction but also in the cholinergic autonomic parasympathetic and postganglionic sympathetic nervous system. As such it is increasingly found useful in the treatment of various disorders of the autonomic nervous system.[66] Essential focal hyperhidrosis—defined as excessive sweating of the palms, feet, or axillae—affects about 0.5% of the population. Thought to be caused by hypothalamic dysfunction it rarely responds to medical treatment, and sympathectomy can be associated with considerable risk. An intradermal injection of botulinum toxin has provided a highly effective treatment for focal hyperhidrosis, markedly improving the quality of life of the affected individuals.[67 68] In a multicentre placebo controlled trial, axillary injections of botulinum toxin (100 to 200 units of Botox®) in 145 patients with hyperhidrosis reduced axillary sweat production six-fold.[69] In contrast to other conditions treated with botulinum toxin, the duration of benefit in patients treated for hyperhidrosis may last up to one to two years. Botulinum toxin injections into the axillae have been associated with a marked reduction in secretion from the apocrine axillary sweat glands that normally produce a pungent smell when degraded by certain local microbes, and this treatment has led to a reduction in body odour (referred to in Japan as ''wakiga'').[70]

The relatively high frequency of dry mouth following injection of botulinum toxin, particularly botulinum toxin B,[31 32] into the cervical muscles suggests an anticholinergic effect on the salivary glands. Indeed sialorrhoea associated with amyotrophic lateral sclerosis,[71] Parkinson's disease, and other neurodegenerative disorders[72 73] has been treated successfully with botulinum toxin injections. The mechanism of the observed differential effect of the various botulinum toxin serotypes on cholinergic function is unknown, but toxin B may have a greater affinity than toxin A for autonomic nerve terminals, as suggested by more pronounced pupillary involvement with toxin B botulism.

GASTROINTESTINAL, GENITOURINARY, AND SPHINCTER DISORDERS

Various gastrointestinal disorders such as dysphagia caused by spasm of the cricopharyngeal component of the inferior constrictor of the pharynx,[74] achalasia,[75 76] and other oesophageal spasms,[77] as well as spasm of the sphincter of Oddi,[78] have also been treated successfully with local botulinum toxin injections. Botulinum toxin has been found effective in the treatment of anismus associated with intractable constipation caused by spasm of the rectal sphincter[79] or associated with Parkinson's disease.[80] Chronic anal fissure—a distressing condition causing a split in the lower half of the anal canal associated with spasm of the internal anal sphincter and constipation—has been found to be essentially eliminated by rectal injections of 15 to 20 units of Botox®.[81]

Botulinum toxin is also being increasingly used in the treatment of bladder and other genitourinary disorders. Using a transperineal needle with EMG monitoring, botulinum toxin injection is minimally invasive and an effective method of managing voiding in patients with spastic bladders. In one study of 21 patients with neurogenic incontinence caused by detrusor hyperreflexia, an overall dose of 200 to 300 units of botulinum toxin A was injected at 20 to 30 different sites in the detrusor muscle, sparing the trigone, under cystoscopic and ultrasonographic guidance.[82] At six weeks all but two patients were fully continent and the maximum bladder capacity increased from a mean of 286 ml to 458 ml. Other genitourinary indications for botulinum toxin treatment include voiding dysfunction from prostatitis,[83] prostatic pain,[84] and vaginismus.[85]

OTHER INDICATIONS

The use of botulinum toxin is continuously expanding as clinicians are becoming more familiar with its therapeutic potential. In addition to disorders already mentioned, others successfully treated with botulinum toxin include nystagmus,[86] palatal myoclonus,[87] and stridor.[88] Botulinum toxin also has been found effective in the treatment of co-contractions after birth related brachial plexus lesions,[89] scoliosis,[90] and freezing associated with parkinsonian gait.[91] Botulinum toxin is also increasingly used to reduce unwanted muscle contractions during the perioperative period[92] and to reduce EMG artefacts in the frontotemporal muscles while attempting to localise a seizure discharge on an electroencephalogram.[93]

There is growing interest in the use of botulinum toxin in cosmetic and dermatological applications, such as the correction of wrinkles and frown lines.[94] Injections into the corrugator and the procerus muscles bilaterally have been found to be effective for the treatment of vertical glabellar eyebrow furrows (''frown lines''). Injections at multiple sites in the frontalis muscle eliminate horizontal lines in the forehead, injections into the lateral orbicularis oculi are very effective in treating lateral canthal wrinkles (''crow's feet''), and injections into the platysma muscles often result in marked improvement in the appearance of the age related platysma muscle bands.[95] Inappropriate placement or dose of botulinum toxin, however, may result in loss of facial expression and disfiguring complications.[96] Botulinum toxin has been found useful in correcting facial asymmetry after injection for hemifacial spasm,[97] and in patients who developed synkinesia and hyperlacrimation after facial palsy.[98]

CONCLUSIONS

In summary, I have drawn attention to the expanding new indications of botulinum toxin in the treatment of a variety of neurological and non-neurological disorders (table 1). Despite its proven therapeutic value, there are still many unresolved issues and concerns about this agent. These include lack of standardisation of biological activity of the different preparations, a poor understanding of toxin antigenicity, variations in the methods of injection, and inadequate assays for antibodies. Clinicians interested in using botulinum toxin chemodenervation in their practice must be aware of these concerns and should exercise proper precautions to minimise the potential risks associated with the toxin. Most importantly, they should become thoroughly familiar with the disorders they intend to treat and with the anatomy at the injection site. Besides occasional complications, usually related to local weakness, a major limitation of botulinum toxin treatment is its high cost. However, several studies analysing the cost–effectiveness of treatment with this agent have concluded that the loss of productivity because of untreated dystonia or spasticity and the cost of drugs, physiotherapy, or surgery more than justify the financial expense associated with botulinum toxin treatment.[99] Finally, botulinum toxin has been shown to have a positive effect on health related quality of life.[100]

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