

Botulinum toxin in motor disorders

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Advances in the clinical use of botulinum neurotoxins continue. Of interest to the neurologist is the advanced practice in the treatment of focal dystonia and the new developments on other dyskinesias and on autonomic control of smooth muscle motility. New toxin serotypes are now being tested; their availability will improve clinical practice and will possibly lead to combined treatments. Indications in spasticity and in juvenile cerebral palsy are now under scrutiny. The combination of focal chemodenervation with specific rehabilitation procedures enables new development in this field. *Curr Opin Neurol* 12:447–456. © 1999 Lippincott Williams & Wilkins.

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Abbreviations

BTX botulinum neurotoxin
EMG electromyography

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Introduction

The possibility to control or modulate muscle contraction in a specific body district is a recent achievement. The treatment of dyskinesias has provided the first neurological indication of this type of treatment, which has soon extended to autonomic motor control before spreading out to non-neurological indications.

Botulinum neurotoxins

The neuromuscular effect of *Clostridium botulinum* has been known since the last century, but only recently has the use of its toxins gained a therapeutic status. Botulinum neurotoxins (seven serotypes, abbreviated BTX-A to -G) cause a sustained inhibition of neurotransmitter release at cholinergic terminals. They bind specifically at the cholinergic membrane and enter the cytosol of the nerve terminal. Here they cleave different proteins, which are essential components of the neuroexocytosis machinery (Table 1) [1]. At least three different groups of presynaptic BTX binding sites with different serotype specificity are present at nerve terminals. These are for BTX-A, for BTX-B and for BTX-C and -D; the binding site for BTX-E partially overlaps that of BTX-A. The molecular identity of these toxin receptors is not known, nor is their distribution among the various peripheral neuronal terminals characterized by different neurotransmitters [2].

Botulinum toxin-A is the serotype that invariably has been used in the therapy of human dyskinesias, such as focal dystonia or hemifacial spasm. During the last decade, BTX has emerged as a very flexible drug and probably the one with the most versatile spectrum of indications (Table 2). Its beneficial effects are currently being extended to a variety of diseases, not all of which are due to hyperactivity of cholinergic terminals. Two limitations of the use of BTX-A have emerged: the

Table 1. Endocellular targets of different botulinum toxin serotypes

Serotype	Endocellular target
A	SNAP-25
B	VAMP-synaptobrevin
C	SNAP-25
	Syntaxin
D	Cellubrevin
	VAMP-synaptobrevin
E	SNAP-25
F	Cellubrevin
	VAMP-synaptobrevin
G	VAMP-synaptobrevin

Table 2. Expanding indications for the use of botulinum toxin

Date	Serotype	Therapeutic indication in man	Reference
1980	A	Strabismus	[3]
1984	A	Blepharospasm and hemifacial spasm	[4]
1985	A	Cervical dystonia	[5]
1986	A	Spasmodic adductor dysphonia	[6]
1988	A	Pelvic floor dysfunction	[7]
1989	A	Oromandibular dystonia	[8]
1989	A	Post-stroke spasticity	[9]
1990	A	Leg adductor spasticity	[10]
1990	A	Detrusor hyperreflexia	[11]
1991	A	Head or upper limb tremor	[12]
1992	A	Spasmodic abductor dysphonia	[13]
1992	F	Cranial-cervical dystonia, stuttering	[14]
1992	A	Spastic drop foot	[15]
1992	A	Upper limb dystonia	[16]
1993	A	Palatal myoclonus	[17]
1993	F	Cervical dystonia	[18]
1993	A	Hyperfunctional facial lines	[19]
1993	A	Achalasia	[20]
1994	A	Juvenile cerebral palsy	[21]
1994	A	Chronic myofascial pain	[22]
1994	A	Motor tics	[23]
1994	A	Tension headache	[24]
1994	A	Sphincter of Oddi dysfunction	[25]
1994	A	Cricopharyngeal dysphagia	[26]
1994	A	Chronic anal fissure	[27]
1995	F	Blepharospasm	[28]
1995	A	Frey's syndrome	[29]
1995	B	Cervical dystonia	[30]
1996	A	Axillary hyperhidrosis	[31]
1997	A	Vaginismus	[32]
1997	C	Blepharospasm and hemifacial spasm	[33]
1997	A	Palmar hyperhidrosis	[34]

development of an immune response following successive treatments of large muscles with relatively high doses of toxin (secondary nonresponse) and the existence of patients who are unresponsive to BTX-A from the first injection (primary nonresponse). These problems can be overcome with the use of different serotypes that bind to different presynaptic receptors.

Manufactured products

Botulinum toxin-A is marketed for clinical use under the trade names of Botox (Allergan, Irvine, USA) and Dysport (Ipsen, Paris, France, manufactured in the UK) and is registered in different countries for a number of indications, which include blepharospasm, strabismus, cerebral palsy, cervical dystonia, focal dystonia, hemifacial spasm. Off-label use has become an inevitable clinical practice, due to the continuous disclosure of new indications (Table 2). There is no evidence of differences in the clinical use of the two BTX-A formulations, which differ in manufacture (including the buffer, the stabilizer, the ratio toxin/hemoagglutinin), storage conditions and units of measure. The strength per molecular weight and the labelled LD₅₀ mouse units differ as well: 1 ng of Botox toxin-hemoagglutinin complex contains 2.5 Botox units, whereas 1 ng of Dysport toxin-hemagglutinin complex (equivalent to 0.16 ng of purified neurotox-

in) contains 40 Dysport units. In clinical practice it can be approximated that 1 Botox unit (U) is grossly equivalent to 3–5 Dysport U [35,36•]. The equivalence ratio is subject to several variables. We consider that 1:4 is most appropriate when common dilutions (e.g., 25–50 Botox U/ml, or 200 Dysport U/ml) are compared. BTX-B (Neurobloc, Élan, USA) has been evaluated in North America and Europe. At variance with BTX-A preparations, Neurobloc will be available as a solution, contained in vials or in pre-filled syringes and labelled in Neurobloc units. BTX-C and BTX-F formulations have also been tried in selected patients.

Recent clinical experience has confirmed that BTX-A is well tolerated. Two notable complications have been reported, one of necrotizing fasciitis [37] and the other the occurrence of a myasthenic crisis [38]. Previous annotations of periocular depigmentation following repeated BTX-A treatments have not been confirmed in an African American cohort [39]. There is no direct neural toxicity, as the intraneuronal injection of BTX-A does not damage the rat sciatic nerve [40•].

Mechanism of action

The main effect of BTX is to produce a chemical denervation of cholinergic nerve terminals, resulting in weakness and atrophy of the striated muscles. Recent clinical evidence has also indicated that BTX-A is efficacious on autonomic terminals to smooth muscles [41•]. BTX injected in the periphery is also capable of interfering with central mechanisms in two ways. First, BTX may chemically denervate gamma motor neurones to intrafusal fibres and reduce spindle afferent input to the spinal cord [42,43,44•]. Second, BTX may cause remodelling of central sensorimotor pathways, by altering sensory feedback from the injected region. The two mechanisms may well be interrelated and may contribute to the efficacy of BTX in dystonia, whereas the action on intrafusal fibres primarily contributes to the correction of spasticity.

Studies support BTX-induced central remodelling. In patients with writer's cramp alterations in the topography of the cortical motor projection to the hand and forearm muscles consisted in a medial displacement of the motor evoked potential representation of forelimb muscles; BTX-A injections into the same muscles could temporarily reverse the changes in the map [45••]. In patients with cervical dystonia, the mean side-to-side ratio of the precentral P22/N30 component of median nerve somatosensory evoked potentials was significantly higher before treatment compared with after treatment and also compared with a control group [46•]. Such plastic changes have not been evidenced by positron emission tomography studies. In writer's cramp, BTX treatment resulted in enhanced activation of parietal cortex and

motor accessory areas, but failed to normalize the impaired activation of primary motor cortex [47].

The selectivity of action of BTX has provided insights into the functional organization of the neuromuscular system. Ocular movements have been analysed in three patients who suffered from diplopia following orbital BTX injections [48•]. Static eye alignment was altered, but the range of movement and the speed of saccades were within normal limits. This dissociation was not observed in a patient affected by systemic botulism, in whom all parameters were altered. The observation may indicate that orbital muscle fibres innervated individually provide precise alignment and that the effects of BTX are greatest on these fibres, particularly when the BTX dose is small.

Dystonia

Focal dystonia stands as the primary indication for the use of BTX in neurology. Segmental or generalized dystonia is approached as a collection of focal treatments. The indications for the use of BTX and its efficacy in dystonia have been established. However, several treatment options remain unsettled, particularly due to the variability of clinical presentation and severity of dystonia, and to variations in the patient's perception of the disease [49•], and the need of validated dystonia scales for many body regions. When a restricted number of muscles are involved (for example, blepharospasm or laryngeal dystonia) the treatment is straightforward in most patients. By contrast, when dystonia affects regions with a richness of motility patterns (for example, the neck or the upper limb) a thorough selection of patients and variations of the treatment schema with time are required. The clinical presentation, not the aetiology of dystonia, is the clue for BTX treatment. Tardive or idiopathic forms respond as well to BTX applications [50•,51•,52], and patients with peripherally induced oromandibular dystonia have also been successfully treated [53•].

Focal presentations

Botulinum toxin-A is considered the first choice treatment for blepharospasm. In several countries BTX-A is licensed for this application and numerous studies have confirmed a response in 90–95% of patients [54]. Injecting BTX-A in the pretarsal rather than the orbital portion of the orbicularis muscle [55,56] may increase the success rate. In spite of the excellent results achieved in a high number of treated patients, the occurrence of response failures fosters the quest for alternative approaches. When BTX-A injections are combined with eyelid protractor myectomy, subjective benefit is more pronounced and the number of repeated injections are reduced in about 50% of patients [57•]. An alternative chemodenervation technique is provided by the injection

of doxorubicin in the eyelid [58•], which has produced prolonged benefit after repeated injections in a small patient series.

Botulinum toxin-A is considered the first choice treatment for adductor laryngeal dystonia. Two approaches are used to reach the thyroarytenoid muscle: electromyography (EMG)-guided percutaneous injection or a transoral injection under direct laryngoscope control. In either case, BTX treatment can be performed unilaterally or bilaterally. Long-term experience in the treatment of laryngeal dystonia with percutaneous injections of BTX-A has been recently reviewed in a large series of patients [59•]. The maximal follow-up time was 13 years for adductor dystonia and eight years for the abductor type. Patients with adductor laryngeal dystonia regained approximately 90% of normal function after bilateral injections in the thyroarytenoid muscles; the duration of benefit lasted on average for 15 weeks. Patients with abductor laryngeal dystonia regained approximately two thirds of normal function after a unilateral injection in the cricoarytenoid muscle; clinical benefit lasted for 10 weeks on average. No major side-effects were reported and no decrease of efficacy occurred with repeated injections. The occurrence of primary or secondary nonresponders was not mentioned. In a series of 29 patients with adductor laryngeal dystonia, the transoral approach was reported to be efficacious in 100% of sessions, while percutaneous injections were helpful in 80% of cases [60•]. No differences in doses, duration or occurrence of side-effects were observed. In a series of 23 patients with adductor laryngeal dystonia, the unilateral treatment did not provide sizeable advantages over bilateral injections, but the majority of patients elected bilateral injections as the most convenient choice for them [61•]. These data are at odds with a previous report that unilateral injections provide better and longer lasting outcome [62]. Eight patients with adductor laryngeal dystonia were treated with BTX-A injections in the ventricular folds rather than in the thyroarytenoid muscle: the clinical benefit was comparable to that observed following the classical treatment [63•].

The clinical presentation of cervical dystonia varies among patients and in a single patient with time [64•]. Rapid jerky movements are combined with slow postural abnormalities to move or tilt the head in different directions. In most patients, the initial schema of BTX injections needs to be progressively adapted to follow the changing pattern of muscle activity. Such changes are responsible for a still not quantified percentage of cases of secondary failure. The involvement of previously inactive neck muscles has been considered an aftermath of BTX-induced muscle weakness [65]. It has been recently shown that increased activity of non-injected muscles, and a switch from one most active

muscle to another, occur not only in patients treated with BTX, but also in those treated orally with anticholinergics [66•]. This suggests that the variable pattern of muscle activation is a feature of cervical dystonia unrelated to BTX injections. It has also been observed that, compared to EMG, physical examination has a low predictive value in the detection of the involved muscles [66•]. However, this will probably not change the common clinical practice to choose injection sites based on physical examination, and to confine the use of EMG to patients with unusual or confounding motor patterns or when the detection of deep muscles is required. The choice of the initial dose is often a matter of local tradition: a slow up-titration of BTX doses would delay the benefit, whereas a high starting dose may expose early to the risk of side-effects. A significant improvement of dystonia scores compared to placebo was observed in patients treated with a total starting dose of 500 or 1000 Dysport units, whereas no improvement was observed in patients treated with lower doses [67•]. The occurrence of adverse effects was significantly higher in patients treated with 1000 units. High doses of BTX-A (500-700 Botox units) have been injected into patients with cervical dystonia secondary to cerebral palsy, to prepare them for surgical fixation of the cervical spine [68].

Higher doses of BTX are required to treat cervical dystonia and spasticity than any other condition and the possibility that neutralising antibodies are developed is correspondingly higher. At least 5–10% of treated patients are estimated to present antibodies [69] that are detectable in about one-third of nonresponding patients [70]. In the remaining patients, secondary failure is thought to be due to changes in the pattern of muscle activity or to undetected neutralizing antibodies. Atrophy of the injected muscles is a very good indicator of clinical efficacy. When atrophy is not observed, a test injection in the frontalis muscle or in the extensor digitorum brevis can be performed. Inability to elicit paralysis or failure to observe a marked decrease in motor action potential [71] speak in favour of the existence of neutralizing antibodies. In such patients, two treatments can be envisaged: the use of a different BTX serotype, or the removal of neutralizing antibodies by means of plasma exchange [72•]. Alternative serotypes include BTX-C, which has been used in patients with blepharospasm or hemifacial spasm [33], and BTX-B and BTX-F, which have been used in cervical dystonia. In patients secondarily nonresponsive to the A serotype, BTX-F provided a benefit lasting for 7 to 11 weeks [73•] while BTX-B was efficacious for up to 16 weeks [74]. Similar effects were observed with BTX-B in patients responsive to BTX-A [75]. The longer than expected duration of efficacy of BTX-B and BTX-F is an intriguing observation. It may indicate that some central

mechanism, irrespective of the toxin serotype, is responsible for the symptomatic benefit in cervical dystonia.

Upper limb dystonia stands as a difficult form to treat. Advances in the clinical use of BTX in writer's cramp have been negligible. It has been recently proposed that 30 min of exercise performed immediately after the injection of BTX-A in the forelimb may improve the functional outcome [76•]. Exercise alone may improve upper limb dystonia [77] and the possibility of combining specific muscle exercise with targeted BTX injections is a potentially important development. Extensor trunk dystonia, manifested by involuntary back arching, has also been successfully treated with BTX [52].

Paradoxical contraction of the puborectalis muscle has been considered a form of focal dystonia leading to outlet-type constipation (anismus) [78]. It has been reported that BTX-A injections into the puborectalis muscle (30 Botox units) improve outlet-type constipation in Parkinson's disease [79] and in non-parkinsonian individuals [80].

Spasticity

Spasticity often accompanies muscle weakness and is associated with an abnormal pattern of muscle activation in the paretic limb. BTX is thought to interfere with the synergy patterns that overcome voluntary muscle control and to improve function in untreated muscles by diffusion. Previous experience on the treatment of spasticity in adults and infants has been recently reviewed [81], and a monographic issue has covered the principles of treatment in spasticity [82]. BTX is a symptomatic remedy in spasticity of the adult, regardless of its aetiology [83]. Its use in the early years of life, however, may influence the development of later motor control and is regarded as a specific indication. Issues related to the treatment of spasticity with BTX include the comparison with other available treatments (e.g., phenol blocks), the definition of the most appropriate BTX doses, and the association with ancillary treatments (for example, electrical stimulation or casting).

The choice of the injection sites is relatively stereotyped in patients with limb spasticity. However, focal forms of spasticity may require targeting specific muscles, such as the lumbrical hand muscles [84]. In proximal regions, focal spasm may produce a dislocation of the shoulder that is difficult to reduce without a previous BTX injection in the pectoralis muscle [85].

BTX doses used to treat limb spasticity in adults are in the high range limits for this type of treatment. The recommended maximum dose of 400 Botox U is easily reached (and may be exceeded) in a single treatment

session [83]. Clinical improvement has also been observed with lower doses. A mean dose of 100 Botox U reduced upper limb flexor spasticity secondary to brain injury in six patients [86]. Improvement of the Ashworth scale has also been observed in 22 patients with chronic hemiparesis, who received 50–100 Botox U in the upper or in the lower limb to treat spasticity [87]. The efficacy of BTX injections can also be enhanced by muscle stretching, a measure comparable to direct muscle activation (see below). In a study of hemiparetic patients with foot inversion, a group of patients received 100 Botox U in the tibialis posterior muscle followed by ankle taping to achieve a continuous stretching of calf muscles. They were compared to a group that received higher doses (190–320 Botox U) distributed in calf muscles, including the tibialis posterior, but no ankle taping [88]. Range of motion in the ankle and other outcome measures improved in the two groups to a similar extent, but the improvement of the Ashworth scale lasted longer in the group treated with higher doses.

It is accepted that the efficacy of BTX is increased when the injected muscles are activated. In a randomized, double-blind, placebo-controlled trial, 24 patients with post-stroke chronic flexor spasticity in the upper limbs were divided into four groups. Available treatments were BTX or placebo, alone or in combination with electrical stimulation. The patients treated with 1000 Dysport units and electrical stimulation had a better outcome than those just treated with the same BTX dose [89]. Surprisingly, the same study also showed improvement in two patients who received electrical stimulation and placebo treatment.

A double-blind randomized study compared the efficacy of BTX-A (400 Botox U in calf muscles) to phenol blockade of the tibialis nerve. Both treatments ameliorated spasticity in patients suffering from post-stroke spastic foot; the outcome of patients treated with BTX-A was better than that of the phenol treated group, especially concerning foot invertor spasticity [90].

Few studies have analysed the long-term efficacy of BTX treatment in spasticity. BTX injections could successfully reduce painful leg spasms in a paraplegic patient, but had to be progressively increased from 100 to 400 Botox U until the initial efficacy waned, possibly due to the development of antibody [91].

Cerebral palsy

Cerebral palsy is a clinically heterogeneous condition presenting with spasticity, dystonia or another dyskinesia in different combinations. It appears early in life and does not result from a recognized progressive or degenerative brain disease. In children, the goals of treatment are to maximise function and minimise the

development of joint contracture and other secondary problems, thereby delaying or preventing surgical intervention [92]. To a large extent, the indications for the use of BTX overlap with those of dystonia and spasticity, which occur in patients with cerebral palsy. However, since the fundamental human motor competence is achieved during the first years of life, early therapeutic interventions influence the development of motor and osteoarticular functions. The most common indications are (1) dynamic *pes equinus*, with the goal to reduce spasticity and to improve gait; (2) adductor spasms, with the aim to reduce scissoring or to improve hygiene; (3) upper limb spasticity, with the aim to attain functional or aesthetic improvements.

Experience on the use of BTX in cerebral palsy is still limited. It has been recently stated that BTX-A is a promising tool for the short-term management, but also questionable on long-term efficacy [93]. Criticism on the scientific evidence collected has been the object of a recent debate [94,95]. The limits to the available studies derive in part from insufficient reliability and validity of the assessing instruments [49,96].

A randomized double-blind study on flexor upper limb spasticity has confirmed improvement of range of movement and of function following the injection of a total amount of 4–7 Botox U/kg or 8–9 Dysport U/kg in children with dynamic contractures secondary to cerebral palsy [97]. In children with crouch gait, the injection of BTX-A in the hamstrings (maximum doses of 5–8 Botox U/kg or 35 Dysport U/kg) produced muscle lengthening and improved ambulatory function [98]. A randomized prospective comparison of BTX-A treatment and of serial casting in children with spastic *pes equinus* yielded a comparable efficacy, but BTX-A had a more prolonged action and fewer side-effects [99].

Other dyskinesias

Long-term efficacy of BTX-A in hemifacial spasm has been confirmed in large patient series. The success rate was up to 97% over a period of 7 years [100,101]. In post-paralytic spasm, BTX-A reduced facial synkinesias and excessive lacrimation secondary to facial nerve palsy [102].

Botulinum toxin has been used to treat hereditary trembling chin [103], vocal tics [104], stimulus sensitive spinal segmental myoclonus [105], essential palatal myoclonus [106], and neuromyotonia [107,108].

Botulinum toxin-induced muscle relaxation is helpful to alleviate pain of different aetiology, particularly when it is associated to a dyskinesia: whiplash associated neck pain [109], facial pain in cranial dystonia [110], myofascial pain [111] and muscle tension headache [112].

Autonomic motility

The use of BTX injections to control autonomic motility has provided a wealth of new indications, particularly at the gastrointestinal level [41•]. The consensus on the efficacy of BTX for the treatment of achalasia appears less firm than before [113]. In patients with achalasia, a diagnostic trial with BTX may help clarify the indication for definitive therapy [114]. At 1-year follow up it has been observed that pneumatic dilatation has a better outcome than BTX treatment [115]. Oesophageal manometry improves after pneumatic dilatation, but not after BTX treatment [116].

BTX reduces exocrine secretion and is a first line treatment in patients with gustatory sweating [117,118]. The intraglandular injection of BTX-A or BTX-D reduces the production of saliva from the canine submandibular glands [119•]. A randomized, double-blind, placebo-controlled study of patients with severe axillary hyperhidrosis has shown that improvement persists at 13 weeks post treatment without serious side-effects [120]. In vasomotor rhinitis, a disorder characterised by excessive parasympathetic activity, the injection of 4 Botox U diminished the severity of rhinorrhea [121].

Anal fissure stands as the only indication for which BTX treatment is pathogenic, rather than merely symptomatic [122]. A comparison of BTX-A and nitro-glycerine in 50 patients confirmed that BTX is more efficacious [123].

In neurourology practice, BTX-A is an alternative to sphincterotomy in patients with voiding dysfunction due to spinal cord injury [124,125]. Finally, injections of BTX-A may promote prostate involution [126] and ameliorate voiding after prostatitis [127].

Conclusion

Botulinum toxin (BTX) is currently used as a focal muscle relaxant to treat conditions characterized by excessive muscle activity. It is now accepted that the effects of BTX are not restricted to cholinergic terminals and that its selectivity depends on the occurrence of binding sites at presynaptic sites. Activity of BTX-A on smooth muscle innervated by noncholinergic fibres indicates that these autonomic terminals possess still unmapped BTX-A binding sites [41•]. A mapping of the distribution of presynaptic sites binding different BTX serotypes will enable the prediction of new possible clinical indications of BTX. BTX is still regarded as a symptomatic drug for repeated application, but recent data show that central sensorimotor remodelling occurs in patients receiving BTX treatment for dystonia, tremor or spasticity. BTX treatment may thus influence the pathophysiology of central nervous system disease, and new long-term clinical and instrumental follow-up

studies are necessary. The insufficient reliability of some currently available scales has hindered the long-term evaluation of patients treated with botulinum toxin, but the expected improvement of clinical outcome scales will make this goal attainable in the near future.

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