

The current status and use of botulinum toxins

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Botulinum toxin is now widely used in neurology for the treatment of disorders involving muscle hyperactivity. Focal dystonia is the primary indication, and the key to effective treatment of dystonia is tailoring the treatment to the individual's pattern of muscle involvement; even complex and generalized dystonias are treated as a collection of focal disorders. The dystonias known to respond to botulinum-toxin therapy include cervical dystonia, blepharospasm, laryngeal dystonia, writer's cramp and anismus. Spasticity is another, growing, indication for the toxins. The treatment of these disorders with botulinum toxins is reviewed here.

Introduction

There are seven different serotypes of botulinum toxin available for study. Each serotype binds to receptor proteins at cholinergic terminals, although there may be different receptor proteins for different serotypes, and each produces a blockade of cholinergic neurotransmission in striated muscle (Martin, 1997; Schiavo *et al.*, 1992; Blasi *et al.*, 1993). The toxins also affect gamma motor neurones serving intrafusal fibres within muscle, thus influencing central neurotransmission (Filippi *et al.*, 1993; Rosales *et al.*, 1996; Modugno *et al.*, 1998), and affecting autonomic terminals on smooth muscles (Albanese *et al.*, 1995). Therefore there are, potentially, a large number of uses for these toxins. The main current uses for the botulinum toxins are reviewed here.

Mechanism of action

In dystonia and spasticity, to some extent, clinical benefit of the toxin parallels the muscle weakness produced by chemical denervation. However, it is also clear that this benefit may outweigh the muscle weakness produced. In addition, significant spasticity may remain, despite muscle weakness. Therefore peripheral weakening of the muscle does not explain all the effects of the toxin: there must be some other mechanism that contributes to its efficacy. To some extent, this is explained by the fact that efficacy is improved by increased uptake during increased muscle activity. Another possible factor is reduced alpha-motor neurone drive, caused by diminished muscle-spindle out-

put. Recently, it has also been shown that intracortical and reciprocal inhibition are normalized in dystonia, probably in the aftermath of an alteration in sensory input from the injected region. Thus, a peripheral action of the toxin is capable of changing the action of the brain in pathological states.

Treatment of dystonia

The direct cause of dystonia may be an overactivity in the supplementary motor area, and a resulting cortical overflow. Focal dystonia is the primary indication for botulinum toxin in neurology. For patients with segmental or generalized dystonia, treatment is approached as a collection of focal dystonias. Effective treatment is therefore dependent on tailoring injections according to the clinical presentation of a particular patient. There are several key issues to be resolved in the use of botulinum toxin to treat dystonia. The most important current issues include the variability of clinical presentation and severity of disease in different patients; and variations in patients' perception of the disease, which may explain some dissatisfaction at the outcome of treatment (Lindeboom *et al.*, 1998). There is also a pressing need for validated scales that will allow the assessment of treatment efficacy in different parts of the body, as this cannot be defined precisely at present.

The key strategy in treating focal dystonia is to treat the symptoms, not the aetiology of the disorder. Thus, many different types of dystonia (for example, tardive, primary, post-traumatic and peripherally induced dystonia) all respond well to botulinum toxin treatment (Brashear *et al.*, 1998; Molho *et al.*, 1998; Comella *et al.*, 1998; Sankhla *et al.*, 1998). Patients suffering from any of these conditions can simply be treated according to their clinical pattern of disease presentation, rather than the cause of their disorder.

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Blepharospasm

Botulinum toxin is the first-choice treatment for blepharospasm. The classical orbital injection is an effective therapy, although that efficacy can be improved in many patients by using, instead, a pretarsal injection (Aramideh *et al.*, 1995; Albanese *et al.*, 1996). Combined therapy with other procedures has also been proposed as a means of improving efficacy. Eyelid protractor myectomy (Chapman *et al.*, 1999) or injection of doxorubicin into the eyelid (Wirtschafter and McLoon, 1998) are two such procedures that may enhance treatment effects. Nevertheless, even without adjunctive treatment, botulinum toxin therapy is highly effective in this indication.

Laryngeal dystonia

Botulinum toxin is also the first-choice therapy for the adductor form of laryngeal dystonia (Blitzer *et al.*, 1998). There are two different treatment approaches for reaching the thyroarytenoid muscle in this disorder: electromyography- (EMG-) guided percutaneous injection and transoral injection under laryngoscopic control. Both of these approaches are effective, so their use depends mainly on local treatment preferences.

Cervical dystonia

Cervical dystonia is the most common form of focal dystonia, and botulinum toxin is the first-choice therapy. This is the only form of focal dystonia in which there has been a direct comparison between botulinum toxin and oral treatments. Botulinum toxin has been shown to be more effective than the anticholinergic, triexyphenidyl.

There are currently two, and will soon be three, different botulinum toxins available for the treatment of cervical dystonia. Two of these, Botox® (Allergan) and Dysport® (Ipsen) are type A toxins, whereas NeuroBloc®/MYOBLOC™ (Elan) is a type B toxin. Typical starting doses are: Dysport® 500 U, Botox® 200 U and NeuroBloc®/MYOBLOC™ 10 000 U. These starting doses differ because the toxin units used differ – the amounts of toxin injected are much more similar than the doses suggest. A remarkable difference between these toxins, which has implications for their clinical use, is the fact that Elan's botulinum toxin type B is presented as a liquid formulation, whereas the others are lyophilized or dry-powder formulations and must therefore be reconstituted.

Individualization of therapy

The challenge in treating cervical dystonia is the variety in its clinical presentation. This varies both

between patients and in a single patient over time (Dauer *et al.*, 1998). In addition, the combination of rapid and slow movement abnormalities can produce a great variety of clinical presentations. Thus, treatment must not only be carefully adapted for each individual patient, but the initial treatment pattern of injections must also be adapted over time to follow the changes in patterns of muscle activity. It is important that this is done, because failure to do so may lead to a lack of therapeutic response over time. Muscles are selected for treatment by physical examination; the involvement of certain muscles is likely to result in particular clinical presentations (Table 1). Patients with uncomplicated presentations are then treated clinically by direct inspection of the injection site, without EMG guidance. EMG can, however, be used to allow more precise localization of muscles in uncomplicated dystonia, to detect specific activity in muscles when the presentation is complex, or to locate specific deep muscles that are more difficult to reach without EMG support.

Sub-optimal responses

Large doses of toxin are used to treat cervical dystonia, therefore patients are at risk for the development of antitoxin antibodies. These have been demonstrated in a substantial minority of patients – up to 10% (Green *et al.*, 1994; Borodic *et al.*, 1996; Zuber *et al.*, 1993) – and antibodies can be detected in about 30% of patients who develop secondary non-responsiveness to toxin therapy (Jankovic and Schwartz, 1995). The possibility of antibody production can be ruled out if muscle atrophy is observed in the injected area, or if the frontalis test demonstrates that the frontalis muscle can be paralysed (Brin, 1998; Hanna and Jankovic, 1998). Otherwise, non-responding patients should be investigated for antibody production using biological assays.

In patients who do not respond well to therapy and are not producing neutralizing antibodies, this secondary treatment failure may well result from changes in the pattern of muscle involvement, which, if treatment is not adapted, leads to inadequate efficacy. In

Table 1 Individual muscles responsible for symptoms of cervical dystonia

Presentation	Ipsilateral	Contralateral
Torticollis	Sternocleidomastoid	Splenius capitis
Retrocollis	Splenius capitis Trapezius	Splenius capitis Trapezius
Laterocollis	Splenius capitis Trapezius	Sternocleidomastoid
Anterocollis	Sternocleidomastoid Scalenus	Sternocleidomastoid Scalenus

this case, efficacy can be improved by re-assessing the patient and tailoring toxin injections precisely to their clinical presentation. For patients in whom treatment failure is secondary to antibody production there is now an alternative to their current therapy, which is switching from type A toxin to a different serotype. Positive efficacy has been demonstrated in this indication for serotypes B (Brin *et al.*, 1999), C and F (Houser *et al.*, 1998). Although serotypes C and F remain experimental therapies, serotype B will soon be available as a commercial treatment.

Other dystonia indications

In writer's cramp, the approach to treatment is similar to that used in clinical dystonia. The affected muscles are identified by physical examination. However, EMG guidance is always used to target the injection. Anismus is also a form of focal dystonia (of the puborectalis muscle) in which botulinum toxin is effective. Anismus may be a primary condition or an 'off'-type dystonia of Parkinson's disease. Both primary (Maria *et al.*, 2000) and secondary (Albanese *et al.*, 1997) forms of the condition respond well to botulinum-toxin therapy.

Treatment of spasticity

Spasticity is a form of hypertonia, which is the resistance felt when moving a limb passively. Spasticity is defined as a velocity-dependent increase of the tonic stretch reflex, with exaggerated tendon jerks. Other features that contribute significantly to the resistance to passive movements include co-contraction and biomechanical changes. Together, these combine to form the clinical picture of spastic paresis. The diagnosis of spastic paresis is different from that of dystonia, as there are not only positive signs (flexor spasm, increased tendon reflexes, spasticity) but also negative signs (weakness, lack of dexterity, paresis) of the disorder. Botulinum toxin is effective in treating the positive signs but not the negative ones. Therefore a therapeutic strategy should be selected and designed to correct positive signs without exacerbating the negative signs of the disease.

Limb spasticity in adults

Several open trials and four double-blind trials of botulinum toxin in adults have shown that this therapy is effective in reducing resistance to passive movements in both the upper and lower limbs. There are also reports that other sequelae of spasticity that are significant to the patients (for example, pain, need for

care, the resting posture of the limb) have been improved by toxin therapy. Thus, all the signs commonly associated with spastic paresis that are difficult for the patient to cope with are improved by treatment with botulinum toxin. Nevertheless, the practical consequences of therapy are less clear, as there is little conclusive evidence that the reduction in hypertonia produced by botulinum toxin treatment results in an improvement in active functional movements.

Cerebral palsy

Several studies of botulinum toxin have been performed in this indication, generally in children (Corry *et al.*, 1997, 1998; Thompson *et al.*, 1998; Wissel *et al.*, 1999). Improvements in several aspects of the disorder have been demonstrated following this therapy (Table 2). The goals of treatment for cerebral palsy are varied, and include: the treatment of focal dystonia; reduction of spasticity; modifications of early patterns of axial asymmetry that may impair later development of the spine and hips; modification of the effects of spasticity on soft tissue and bone; mimicking the effects of later surgery; providing a therapeutic window for physical interventions (Russman *et al.*, 1997). Thus, cerebral palsy comprises a complex set of indications that require a goal-directed strategy.

Combination therapies

In both spasticity and cerebral palsy, botulinum toxin is not a therapy that is given in isolation. It can and should be combined with other strategies, such as casting, electrical stimulation, ongoing physiotherapy, orthoses and continuing oral medication.

Conclusions

Chemical denervation with botulinum toxin is widely used in the clinic to correct movement disorders asso-

Table 2 Improvements demonstrated in the treatment of cerebral palsy with botulinum toxin

Clinical issue	Improvement	Reference
Dynamic deformities	Gait Spasticity	Koman <i>et al.</i> (1994); (2000)
Dynamic contracture of lower limb	Clinical examination Gait analysis	Cosgrove <i>et al.</i> (1994)
Dynamic deformities of hand and foot	Skilled hand movements Foot posture	Denislac and Meh (1995)
Spasticity and athetosis of limbs	Pain Ease of care	Gooch and Sandell (1996)

ciated with dystonia and spasticity. In addition, it can be used to treat hyperhidrosis, facial lines and anal fissure. There are many other possible indications for this therapy, such that the field continues to grow.

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