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Botulinum Toxin Treatment of Adult Spasticity

A Benefit-Risk Assessment

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Contents

Abstract

Injections of botulinum toxin have revolutionised the treatment of focal spasticity. Before their advent, the medical treatment for focal spasticity involved oral antispasticity drugs, which had decidedly non-focal adverse effects, and phenol injections. Phenol injections could be difficult to perform, could cause sensory complications and had effects that were of uncertain duration and magnitude. Furthermore, few neurologists knew how to perform them as they were mostly the province of rehabilitation specialists. Botulinum toxin can produce focal, controllable muscle weakness of predictable duration, without sensory adverse effects.

Randomised clinical trials (RCTs) involving patients with spasticity resulting from a variety of diseases (mainly stroke and multiple sclerosis) have clearly shown that botulinum toxin type A (Dysport® and Botox®) can temporarily (for

approximately 3 months) reduce spastic hypertonia in the elbow, wrist and finger flexors of the upper limbs, and the hip adductors and ankle plantarflexors in the lower limbs. The clinical benefits from this reduction of neurological impairment are best shown in the upper limb, with less disability of passive function and reduced caregiver burden. In the lower limbs, there is improved perineal hygiene from hip adductor injections. The benefits of reducing ankle plantarflexor tone are less well established. Pain is also reduced, possibly by mechanisms other than muscle weakness. Improved active function has not yet been clearly demonstrated in RCTs, only in open-label trials. The safety of botulinum toxin-A is impressive, with minimal (mainly local) adverse effects.

There are little data on the use of botulinum toxin type B (Myobloc® or Neurobloc®) in spasticity and the only RCT that has examined this did not show tone reduction; dry mouth appeared to be a very common adverse effect. There are also very little data to allow a benefit-risk comparison of phenol and botulinum toxin injections; each have their clinical and technical advantages and disadvantages, and phenol is much less costly than botulinum toxin.

Botulinum toxin is produced by the bacterium, *Clostridium botulinum*. There are seven serotypes, termed types A–G, of which types A, B and F result in human botulism. Botulinum toxin blocks the presynaptic release of acetylcholine from nicotinic (neuromuscular junction) and muscarinic nerves. Pathologically, ingestion of botulinum toxin, usually in contaminated food, or colonisation of wounds by the bacterium, produces the condition of botulism. Botulism is characterised by generalised neuromuscular paralysis and cholinergic autonomic blockade and can be fatal.

Therapeutic injections of botulinum toxin have been in use since the early 1980s. Botulinum toxin was first used by an ophthalmologist in San Francisco, Alan Scott, to correct strabismus.[1] The toxin was chosen for this purpose because of its ability to produce focal, temporary weakness of muscles to a dose-related degree. Typically, the weakness lasts about 3 months.[2] Since then, the indications for therapy with botulinum toxin have expanded to include many neurological, urological, gastroenterological, ophthalmological and cosmetic conditions. Its main uses exploit its blockade of the neuromuscular junction (paralytic) or autonomic cholinergic systems (sweating, salivation). However, there is a growing conviction that it may have analgesic effects separate from these other actions[3] that explain its pronounced effects on pain, including the prevention of migraine.

Therapeutic botulinum toxin is available in two serotypes, type A (botulinum toxin-A) and type B (botulinum toxin-B). There are two formulations of botulinum toxin-A, Botox® [1], which is available worldwide, and Dysport®, which is available worldwide, except for North America. There is only one formulation of botulinum toxin-B, known in the US as Myobloc® and Neurobloc® in Europe, that is produced by Elan Pharmaceuticals. It is important to point out that the two formulations of botulinum toxin-A are not dose equivalent, largely for technical reasons that arise from the bioassay methods used to determine potency, which is measured in mouse units. Similarly, mouse units of botulinum toxin-B are quite different in potency to those of botulinum toxin-A. Although there are many uses for all the formulations, not all are licensed by the regulatory authorities. For example, in North America botulinum toxin-A is only licensed for the treatment of spasmodic torticollis, blepharospasm, hemifacial spasm, strabismus and glabella lines, and botulinum toxin-B is only licensed for the treatment of spasmodic torticollis. However, in some European countries botulinum toxin-A is also licensed to treat spasticity, which is the subject of this review.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

1. Definition: Spasticity and the Upper Motor Neuron Syndrome

The term 'spasticity' refers to a specific pathophysiological entity. However, it is used more broadly to refer to many kinds of skeletal muscle overactivity that occur after damage to certain motor pathways in the CNS. Spasticity may be a consequence of CNS injury at any age. In children, it is a common accompaniment of cerebral palsy and there are excellent reviews of treatment with botulinum toxin in this population.[4,5] This review will focus on the use of botulinum toxin for the treatment of spasticity in adults.

Although spasticity may occur after many types of injury to certain motor pathways in the CNS, the most common causes in adults are stroke, multiple sclerosis, head injury, traumatic spinal cord injury and anoxic-ischaemic encephalopathy.[6] In these conditions, damage can occur to a group of motor tracts called the upper motor neuron (UMN) pathways.[7] These pathways originate in the motor cortex and brainstem. The consequences of an injury are divided into the negative, that is, motor underactivity due to a loss of function; and the positive, which represent motor overactivity (table I). Much of the disability that follows damage to the UMN pathways is due to the negative effects (mainly weakness).[8] Additional damage to other areas of the nervous system may contribute to motor impairment through neurological deficits such as sensory loss, apraxia and dystonia.

However, strictly speaking, spasticity refers to a form of hypertonia, i.e. increased resistance to passive stretch at rest, and the accepted definition is that given by Lance:[9]

"Spasticity is a motor disorder characterised by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflexes, as one component of the upper motor neuron syndrome".

As mentioned earlier, several of the 'positive' features of the UMN syndrome are considered to be forms of spasticity; these include true spasticity, spastic dystonia, spastic co-contraction, flexor and extensor spasms, associated reactions and the positive supporting reaction. A further complication is that changes in the soft tissues of the limbs can also increase resistance to passive stretch (hypertonia) and this may be mistaken for spasticity.

Table I. The upper motor neuron syndrome: positive and negative effects

Positive effects
Mediated by spinal reflexes
Exaggerated muscle stretch reflexes
spasticity
deep tendon hyper-reflexia
clonus
Disinhibition of nociceptive (protective) reflexes
flexor spasms (exaggerated flexor withdrawal reflexes)
extensor spasms
Disinhibition of primitive reflexes
extensor plantar response
positive supporting reaction
Spastic movement disorder
Loss of reciprocal inhibition
spastic co-contraction
Other
associated reactions (extra-segmental co-contraction)
mass synergy (loss of selective movement)
Uncertain mechanism
spastic dystonia (tonic supraspinal drive?)
Negative effects
weakness
loss of dexterity (incoordination)
loss of superficial abdominal reflexes

The negative consequences of the UMN syndrome, such as weakness, usually occur immediately after the injury. However, the positive features typically develop after a delay that varies from several days to several weeks. This delay suggests that the positive features arise through neuronal plasticity, some structural or functional rearrangement of the CNS, that takes time. However, once developed there is usually no further progression, provided there is no further CNS injury.

2. Benefit Evaluation

2.1 Epidemiology

It is estimated that 500 000 people in the US are affected by spasticity.[10] Quite apart from the negative effects of the UMN injury, spasticity and the other forms of motor overactivity that comprise the

positive features of the UMN syndrome contribute to substantial morbidity and caregiver burden.[11] Spastic motor overactivity can interfere with the patient's ability to move the affected limbs, a condition that is known as spastic movement disorder. In many patients, the affected limbs are too weak to move, so the patient must use another limb to move the affected limb or rely on someone else to move it. In this situation, spastic motor overactivity at rest can increase tone and reduce the range of movement, leading to abnormal limb postures and making the performance of simple tasks, such as opening a clenched hand for washing, difficult. Tasks that are performed by voluntary movement of the affected limb can be considered tasks of 'active' function and those that are performed by another limb or by another person are considered examples of 'passive function'; spastic motor overactivity can interfere with both.

Spasticity may also cause pain, particularly during muscle spasms and when 'spastic' muscles are stretched, rather than at rest. If spasticity causes muscles to be left in the shortened position for a long time it can promote stiffness of the soft tissues, which aggravates hypertonia and contractures and results in a reduced range of movement.

2.2 Goals of Treatment

Understanding the consequences of spastic motor overactivity and drawing a distinction between active and passive function helps define the goals of treatment of this condition (table II). Where spasticity interferes with voluntary movement (active function) the goal is to reduce the interference so that movement improves. This, of course, makes certain assumptions about the role of the motor overactivity in the movement disorder. Examples might be dynamic spastic ankle plantarflexion during walking or spastic co-contraction of the elbow flexors during attempts at elbow extension.

When there is little or no residual voluntary movement because of severe weakness, spasticity does not contribute to the movement disorder; the spasticity problem is independent of attempted movement and is present at rest (static). The tasks that are affected by this are those of passive function. For example, a tightly clenched fist makes it hard to wash and dry the hand, perform stretching exercises and apply splints. A tightly flexed elbow may interfere with dressing and promote skin breakdown in the antecubital fossa. Hypertonia of the hip adductors may interfere with perineal hygiene and urethral catheterisation.

Table II. Examples of treatment goals in spasticity

Increase patient comfort
Reduce muscle pain
Reduce muscle spasms
Better limb position (cosmetic, improved sleep, improved sexual function)
Ease patient care
Dressing
Hygiene (palm, elbow, shoulder, perineal)
Catheterisation
Positioning in bed or chair
Transfers
Improve patient function
Upper limb – reaching, grasping, releasing
Lower limb – standing and walking
Other
Help with physical therapy – stretching, splinting, wearing orthoses
Delay or avoid orthopedic surgery
Prevent contracture

There may be still other complaints that are not related to function, such as painful spasms, pain during stretching or dissatisfaction with the cosmetic appearance of the limb posture, which could be goals of treatment. Such goals could be viewed as symptomatic.

Finally, treatment could be started to prevent contractures developing or to avoid the need for surgery.

2.3 Assessing Outcome

In evaluating the response to treatment, it is helpful to distinguish between the technical objectives and the clinical objectives just described. In WHO terms, this is the difference between neurological impairment (hypertonia) and disability (function). Patient satisfaction may also be considered.

The most basic technical objective is to reduce the spastic motor overactivity. More advanced technical objectives are to reduce tone and increase passive range of movement, which is hoped will achieve the clinical goals of improved passive func-

tion, and relief of symptomatic complaints, such as cosmetic appearance and pain during stretching. In the case of active function, the advanced technical objective is to reduce spastic co-contraction, dynamic spastic dystonia and other involuntary muscle contractions that interfere with voluntary movement.

Drawing a distinction between the technical outcomes and clinical outcomes of treatment is useful when a clinical goal is not achieved. This could be because of failure of one or more of the technical goals. However, if the technical goal was achieved but the clinical goal was not, it suggests that the spastic motor overactivity was not responsible for the clinical problem. For example, if injections reduced spastic hypertonia in the legs at rest (true spasticity) but failed to improve walking, then perhaps the spasticity was not responsible for the gait disorder. This line of reasoning is particularly important when attempting to improve active function by treating spasticity; the wisdom of doing so has been questioned repeatedly.[12-15]

3. Evidence of Benefit

3.1 Randomised Clinical Trials

There have been 11 randomised controlled trials (RCTs) of the use of botulinum toxin-A in adult spasticity[11,16-25] (table III), 4 with Botox®[16,17,20,24] and 7 with Dysport®.[11,18,19,21-23] There is only one published RCT of botulinum toxin-B in this indication.[26] Most trials involved patients with spasticity due to stroke or multiple sclerosis,[11,16,17,19,21,23-25] but others included patients with spasticity due to CNS trauma and anoxia.[18,20] Six of the botulinum toxin-A studies were of the upper limb, four were of the lower limb, and one was of both the upper and lower limbs. The single botulinum toxin-B study was of poststroke upper limb spasticity.

3.1.1 Botulinum Toxin Type A

The upper limb studies examined the treatment of elbow, wrist or finger flexor spasticity.[11,17,19,20,22-24] The lower limb studies addressed spasticity of the hip adductors[16,21] or ankle plantarflexors.[18,25] One trial included treatment of a mixture of various upper and lower limb muscles according to the clinical need.[20]

In nearly all of these trials,[11,16-19,21-25] patients with at least moderate or severe spasticity, as measured by the Ashworth Scale[27] or Modified Ashworth Scale (MAS),[28] were recruited and the primary outcome goal was a reduction in spasticity. The Ashworth Scale measures muscle tone, which, as already discussed, may be increased by spasticity (and other forms of spastic motor overactivity) in the UMN syndrome, as well as by biomechanical factors. Thus, muscle tone measured by the Ashworth Scale may not be a true reflection of the presence and magnitude of spasticity. Only one study used electromyography (EMG) to verify the presence of spastic muscle contraction.[20] Thus, it is possible that patients whose hypertonia was more biomechanical than spastic could have been included in these trials. Nonetheless, all trials showed a significant reduction in muscle tone, usually set arbitrarily as a reduction of 1 point on the Ashworth Scale or MAS, with botulinum toxin-A.

These trials often included secondary outcome measures to define the clinical benefit of the tone reduction. The two studies of hip adductor spasticity observed the effect of botulinum toxin-A on adductor muscle spasms,[16,21] and found no change in spasm frequency compared with placebo. Other clinical outcomes tested ranged from symptom reduction (e.g. pain relief, appearance of the limb) to improvement of passive function (dressing, hygiene, caregiver burden) to active function (gait, voluntary arm movement), as well as global measures of function (Barthel index of activities of daily living) [refer to table III]. It is fair to say that essentially the only clinical benefits shown were those of symptom reduction and improvements in passive function.

A study of treatment of poststroke spasticity of the wrist and finger flexors by Brashear and colleagues,[24] in which they recruited 126 subjects, is an example of this. Subjects were treated with 200–240MU of Botox® in a fixed dose and muscle protocol, or the equivalent volume of normal saline. The primary outcome measure was self-reported disability involving four predetermined areas: pain, dressing, hand hygiene and limb position (cosmetic). The degree of disability was scored on a 4-point scale (the Disability Assessment Scale). Each patient chose one of the four areas of disability, of at least moderate severity, to serve as their primary

Table III. Randomised clinical trials of botulinum toxin type A in adult spasticity

Study	Etiology	Area; toxin type; dose injected	Function measure	Improved function?	Other
Snow et al.,[16] 1990	MS	Hip adductors; Botox®; 400MU	None	NA	Improved hygiene score; easier nursing care
Simpson et al.,[17] 1996	Stroke	Elbow, wrist, flexors; Botox®; 75, 150, 300MU	FIM, Fugl-Meyer Scale	No	No change in caregiver dependency scale or pain scale
Burbaud et al.,[18] 1996	Stroke, trauma	Gastrocnemius/soleus, tibialis posterior, flexor digiforum longus; Dysport®; 1000MU	Fugl-Meyer Scale, gait velocity	Yes, Fugl-Meyer	Ankle dorsiflexion
Bakheit et al.,[19] 2000	Stroke	Biceps, wrist and finger flexors; Dysport®; 500, 1000, 1500MU	Rivermead Motor Assessment Scale (arm), Barthel index	No	Subjective caregiving scale – not analysed
Richardson et al.,[20] 2000	Mixed	Upper and lower limb variable; Botox®; 30–500MU	Rivermead Motor Assessment Scale, 9-Hole Peg Test (UL), 10m timed walk	Yes, Rivermead Motor Assessment Scale (lower limb)	
Bhakta et al.,[11] 2000	Stroke	Elbow, wrist, finger flexors; Dysport®; 1000MU	None	NA	Improved disability and caregiver burden scales
Hyman et al.,[21] 2000	MS	Hip adductors; Dysport®; 500, 1000, 1500MU	None	NA	Improved hygiene score. Pain and spasm frequency changes did not differ from placebo
Smith et al.,[22] 2000	Stroke or head injury	Elbow, wrist, finger flexors; Dysport® up to 1500MU	Frenchay Arm Test and upper limb dressing time	No	Patient global assessment score improved
Bakheit et al.,[23] 2001	Stroke	Biceps, wrist and finger flexors; Dysport®; 1000MU	Barthel index, goal attainment scale	No	Subjective rating by patients and physicians favoured improvement; pain rating did not improve
Brashear et al.,[24] 2002	Stroke	Wrist, finger flexors ± thumb flexor; Botox®; 200–240MU	None	NA	Improvements in disability (pain, dressing, hygiene, cosmesis), physician and patient/caregiver global assessment
Pittock et al.,[25] 2003	Stroke	Calf muscles; Dysport®; 500, 1000, 1500MU	Gait assessment	No	Pain reduction and reduced need for walking aids; no change in physician or patient global assessment

FIM = functional independence measure; **MS** = multiple sclerosis; **NA** = not analysed.

disability target. At 6 weeks, the group treated with Botox® showed greater reduction in the primary disability target and significantly more subjects in this group experienced a reduction in the severity of the primary disability target of at least one point. The secondary outcome measure, tone reduction, was significantly greater in the active treatment group. Therefore, this study showed that botulinum toxin-A can reduce tone and improve some symptoms and some deficits of passive function that are associated with spasticity. No measures of active function of the upper limb or of global function were included.

In another study of post-stroke spasticity of the upper limb, Bhakta and colleagues[11] recruited 40 patients with a functionally useless arm and randomised them to receive either 1000MU of Dysport® or the equivalent volume of saline. The elbow, wrist and finger flexors were injected according to a flexible dose and muscle choice protocol, in order to mimic clinical practice. Tone was measured using the MAS. Disability was scored on a five-point Likert scale (from 'no difficulty' to 'cannot do task') and consisted of eight items: cleaning the palm; cutting the fingernails; putting the weak arm through a sleeve; cleaning the armpit; balance while standing; walking balance; cleaning the elbow; and the ability to perform home physiotherapy exercises on the upper limb. From these items, a summary disability score was calculated, ranging from a score of 0 (no disability) to a score of 4 (maximal disability). The caregiver burden scale consisted of four items: cleaning the palm; cutting the fingernails; dressing; and cleaning the armpit. As for disability, a summary caregiver burden score was calculated, which ranged from 0 (no caregiver burden) to 4 (maximal caregiver burden). At 6 weeks, both the disability score and caregiver burden score were significantly reduced in the active treatment group compared with the placebo group. The change in disability was only modest, with a median reduction of 0.5. The reduction of caregiver burden was somewhat better, with a median change of 1.0.

Not all studies have shown a reduction in disability or in caregiver burden, for example the first randomised controlled study of upper limb spasticity reported by Simpson and colleagues[17] in 1996 did not. This was a dose-ranging study, and although spasticity in the elbow and wrist flexors improved in the high-dose Botox® group, measures of global function, upper limb disability and caregiver burden did not. Many possible reasons for this were discussed in the paper, but they included small numbers of patients, a fixed dose and muscle injection protocol, the lack of finger flexor injection and high baseline function. Moreover, it is unreasonable to expect global function measures, such as the Functional Independence Measure, to improve after focal injections in the upper limb. The lessons in study design learnt from this trial allowed subsequent trials to be more successful.

Improvement in active function, that is, function performed by voluntary movement of the affected limb, by botulinum toxin-A has not yet been proven convincingly in randomised clinical trials. This is in contrast to the open-label studies that are discussed later. One RCT showed an improvement in active function of the lower limb, as tested by the Rivermead Motor Assessment Scale[20] and another[18] showed improved voluntary ankle movement: neither study was able to show improvement in direct tests of gait (e.g. 10m timed walk).

There are many reasons why improvement in active function has not yet been shown, but the main ones relate to study design.[29] Most of the studies performed so far have focused on reducing resting muscle tone and spasticity, rather than trying to improve voluntary movement by reducing spastic muscle overactivity during movement. The problems of reduced passive function, caregiver burden and symptoms such as pain and limb appearance are more directly the result of high resting muscle tone. Therefore, patients have usually been chosen for the trials on the basis of high resting muscle tone and their potential for tone reduction with botulinum toxin, rather than for their potential for improvement of voluntary movement. Furthermore, the outcome measures chosen in the clinical trials were probably not suitable for showing changes in active function. The problems of active function experienced by patients are broad and individual so that generic, standard measures of function may be insensitive to change. For this reason, individualised outcome measures, such as goal attainment scaling, have been advocated.[30]

By way of contrast, greater success has been achieved in cerebral palsy, where RCTs have shown improvements in the active function of the lower limb (gait)[31-33] and the upper limb.[34] The reason that trials in children with cerebral palsy have shown success where the adult trials have not is unclear. The younger brain may be more plastic, or perhaps the outcome measures used were more sensitive.

3.1.2 Botulinum Toxin Type B

In the only RCT of botulinum toxin-B,[26] 15 patients with at least moderate spasticity of the elbow, wrist and finger flexors following stroke were randomised to receive either 10 000 units of botulinum toxin-B (Myobloc®) or placebo. Muscle tone was measured with the Ashworth Scale and there was a subjective measure of improvement, the physician global assessment of change (GAC) scale. In this double-blind study, measurements were made at baseline, and 2, 4, 8, 12 and 16 weeks. At the end of this period, there was a 12-week open-label trial. There was no significant reduction in tone in the treatment group compared with the placebo group during the double-blind phase of the study. In the open-label phase, tone was significantly reduced in the elbow, wrist, finger and thumb flexors at week 4. The lack of tone reduction during the double-blind phase of the study is surprising. Although it is not possible to convert units accurately between the different formulations of botulinum toxin, 10 000 units of Myobloc® would be roughly equivalent to 200 units of Botox®. Treatment with a similar dose of Botox® reduced tone convincingly in one study of wrist and finger flexors;[24] however, the additional treatment of elbow flexors, as in the botulinum toxin-B RCT, could have prevented success due to the dose being too small to provide an effect in this area. On the other hand, the open-label botulinum toxin-B study that preceded this RCT used the same injection protocol and was successful in reducing tone significantly in all three areas.[35] There were few adverse events in the RCT, but eight of the nine patients receiving botulinum toxin-B reported dry mouth[26].

3.1.3 Summary

The results of the RCTs published so far have involved single injections, thus, although there is no reason to doubt that the tone reduction benefits of botulinum toxin-A can be repeated, there are no data to prove it.

The RCTs performed thus far have mostly not been suitable for inclusion in a meta-analysis. Even though many were of single disease entities (stroke or multiple sclerosis), there has been considerable heterogeneity in the doses of botulinum toxin-A used, the injection techniques used, the muscles injected and the outcome measures employed (Ashworth Scale or MAS), as well as in the adjunctive physical therapies or medications. However, two RCTs of poststroke upper limb spasticity,[19,23] performed by the same research group, were sufficiently similar to allow meta-analysis.[36] The purpose was to examine whether reduction of spasticity with botulinum toxin injections produced functional benefit. Patients received 500, 1000 or 1500 units of Dysport®, or equivalent placebo injections. A 'composite functional index' was created for the meta-analysis from objective and subjective measures of passive function. Pooled data from 47 patients showed an inverse relationship between spasticity and arm function in patients treated with the Dysport® 500 or 1000 unit doses, but not placebo or the 1500 unit dose. The 1500 unit group showed marked reduction in spasticity but less improvement in function than the other Dysport® dosage groups, possibly due to overweakening of the muscles or the small number of patients in this group.

3.2 Open-Label Studies

3.2.1 Botulinum Toxin Type A

There have been many open-label studies of botulinum toxin-A for the treatment of adult spasticity of the upper limbs, lower limbs, or both[37-58]. These studies have included patients with spasticity that has resulted from stroke, multiple sclerosis, head injury, spinal cord injury and anoxic ischaemic encephalopathy. In most of the open-label studies the dose and muscle selection were liberal. Doses of Dysport® ranged from 500 to 1500 units and doses of Botox® ranged from 100 to 300 units. Most studies involved injections into the upper limb flexor muscles (elbow, wrist, fingers), lower limb extensor muscles or hip adductors.

In the studies of botulinum toxin-A, treatment was generally aimed at tone reduction and was usu-

ally measured by the Ashworth Scale or MAS. Additional measures included limb posture, passive range of movement, pain, and passive function (dressing, hygiene, cutting fingernails, etc.). Some studies employed measures of voluntary movement (ankle, wrist, elbow flexion and extension) or active function, such as the Fugl-Meyer Scale, the Frenchay Arm Test, Rivermead Motor Assessment Scale, gait velocity, step length and other measures of walking. In general, the studies were successful in showing tone reduction and increased passive range of movement. Most often, there was improvement in symptoms, such as pain, as well as in passive function of the upper limbs (e.g. see Bhakta et al.[37]).

The results for active function in open trials of botulinum toxin-A have generally also been favourable, unlike those seen in the RCTs. Several studies have shown improvement in gait parameters after injections into the calf plantarflexors.[38,40-42,48,49] In one study, spastic toe flexors and great toe extensors (hitch-hiker's toe) were injected and showed a reduction in pain and improved gait and stance.[57] Some studies have shown that upper limb function can improve,[51,52,55,56] although in others[45,47,54,58] only a subset of patients improved significantly. In another study there was short-term recovery of active finger extension after injection into spastic finger flexors.[50]

Although there has been no RCT of repeated injections of botulinum toxin reported yet, the unchanging benefit of repeated injections for post-stroke upper limb spasticity has been shown in an open-label study.[45]

Valuable information can be gleaned from open-label studies that can help in the selection of patients, dose, and muscles for injection. For example, EMG examination of the muscles before the injection appears to help predict the success of tone reduction.[59] This seems logical considering the difficulty in distinguishing biomechanical hypertonia from neurological hypertonia (spastic muscle overactivity). Observations from these trials also suggest that improvement in motor performance (voluntary movement and active function) is more likely in patients with mild neurological deficits, mild spasticity, and residual function of agonist and antagonist muscles.[51] This type of information is also useful when designing controlled studies.

3.2.2 Botulinum Toxin Type B

In a published open-label study of botulinum toxin-B (Myobloc®), 10 000 units were injected into the elbow, wrist and finger flexors of ten patients with stable spasticity of at least moderate severity (Ashworth score of 2 or greater) after stroke.[35] Tone was reduced at 4, 8 and 12 weeks afterwards, with a reduction that was statistically significant in all 3 areas at week 4, the elbow and wrist at 8 weeks, and the wrist only at 12 weeks. At week 4, the mean reductions were at least one point on the Ashworth Scale. The physician's global assessment score was also improved at all visits, but the functional measures (Jebsen Hand Test and Nine Hole Peg Test) did not change. Nine of ten patients experienced mouth dryness that was 'moderate' at week 4, 'slightly annoying' at week 8, and that had resolved by week 12. One patient reported pain in the injected biceps, and another complained of heaviness of the injected arm.

In a second study from Europe,[60] hip adductors of four patients with disabling spasticity refractory to conventional methods were injected with doses ranging from 10 000 to 22 000MU of botulinum toxin-B (Neurobloc®). Muscle tone or painful spasms improved in all patients within 2 weeks, associated with an improvement in gait and easier nursing care.

3.3 Other Issues

3.3.1 Pain in Spasticity

Pain is commonly mentioned as a symptom of spasticity. Pain in spastic muscles is uncommon at rest and more often occurs during muscle stretch (active or passive) and muscle spasms (flexor, extensor, hip adductor). Many of the open-label reports and RCTs attest to the pain relieving properties of botulinum toxin in spasticity. Until recently, it had been assumed that the pain-relieving effects of botulinum toxin came about through muscle weakness. However, there is increasing evidence that botulinum toxin has analgesic and anti-inflammatory properties that might account for some of the pain relief.[7]

Noxious stimulation is known to increase spasticity and provoke flexor and extensor spasms. Is it possible that botulinum toxin may partly reduce

these forms of spastic motor overactivity due to its analgesic properties? This will be difficult to prove, especially as there is a purported effect of botulinum toxin on muscle spindle efferents, which could reduce spasticity. On the other hand, flexor spasms are mediated by group II, III, and IV (non-spindle) afferents, known collectively as flexor reflex afferents.[61] In experimental models of myalgia, these nociceptive afferents can be sensitised and stimulated by algesic substances, such as substance P and calcitonin-gene-related peptide.[62] There is experimental evidence that botulinum toxin blocks neural release of substance P as part of its analgesic mechanism.[63] Thus, it is conceivable that botulinum toxin may reduce flexor spasms in part by reducing sensitivity of the flexor reflex afferents, while at the same time reducing the painfulness of these spasms. Similar mechanisms might underlie the reduction in the pain of stretching spastic muscles, which presumably also stimulates nociceptive mechanoreceptors in muscle. Reduced adductor spasm frequency would provide evidence that botulinum toxin may act to reduce painful sensory input, something that might not be expected if its only effect was to reduce muscle strength. However, two RCTs of treatment of hip adductor spasms[16,21] failed to show such an effect.

3.3.2 Preventive Effects of Botulinum Toxin Treatment

One hope when using botulinum toxin in spasticity is that it might prevent contractures if used early. In the only study of its type, patients with severe acute brain injury were randomised to receive standard treatment (controls), casting with saline injections into the ankle plantarflexors, or casting with botulinum toxin injected into the ankle plantarflexors.[64] The purpose of treatment was to prevent ankle plantarflexor contractures. Both treatment groups improved their range of ankle dorsiflexion to a similar extent; controls improved much less. In this study, casting with botulinum toxin conferred no extra benefit over casting alone. The possibility that early treatment with botulinum toxin might prevent spasticity or soft tissue changes from fully developing is worth pursuing.

3.3.3 Ancillary Treatment

Botulinum toxin is usually employed as part of a comprehensive neurorehabilitation effort aimed at restoring function and independence. Spasticity treatment is only one part of rehabilitation and most experts perceive botulinum toxin as an adjunct to other antispasticity measures. Physical treatment usually includes stretches, splinting, casting and positioning. Although it is thought that botulinum toxin injections without such physical treatment are likely to be less beneficial, this has not been tested. Some doctors refuse to inject botulinum toxin unless the patient can receive physical therapy afterwards.

In one previously mentioned study, [64] botulinum toxin injections added extra benefit to casting in the maintenance of ankle range of movement after acute brain injury. In a randomised, single-blind trial, low-dose botulinum toxin combined with ankle taping was compared with standard doses of botulinum toxin alone in the treatment of spastic equinovarus after stroke.[65] Patients received ankle taping and an injection of 100MU of Botox® into the tibialis posterior, or 190–320MU of Botox® into several ankle muscles without taping. Ashworth scores, passive range of movement, gait velocity and step length were similar in the two groups. This study did not directly address the question of whether physical treatment augments botulinum toxin treatment, but it at least shows that it may help to lower the dose of botulinum toxin needed. A single-blinded study suggested that electrical stimulation of lower limb muscle of patients with post-stroke spasticity for several days after injection produced greater benefits on spasticity and gait.[66]

New rehabilitation methods are emerging and it remains to be seen how botulinum toxin treatment will fit into these. One case report suggests that constraint-induced therapy and botulinum toxin might be an effective combination.[67] A pilot study of functional electrical stimulation following botulinum toxin injections into the calves of patients with spastic 'foot drop' resulted in better gait scores than standard physiotherapy alone.[68]

4. Risk Evaluation

4.1 Treatment of Adult Spasticity

Botulinum toxin is the most potent biological toxin known to man, so there are understandable concerns about its safety for therapeutic injection. The adverse effects of botulinum toxin injections can be categorised as in table IV. Most adverse effects of botulinum toxin arise through weakness of the muscles injected or those nearby, which become weak through local spread of the toxin.[69] The specific symptoms that arise depend on the region injected. Injections around the eyes can produce ptosis, diplopia and an inability to close the eye fully.[70] Injections in the neck can produce weakness of neck movement, difficulty holding up the head against gravity, difficulty swallowing and weakness of the voice.

Dysphagia is a well known, rarely fatal, complication of botulinum toxin treatment for cervical dystonia, laryngeal dystonia and craniofacial dystonia.[73] Patients with pre-existing symptomatic dysphagia seem to be particularly at risk of (worsening) dysphagia,[74,75] but some patients have subclinical swallowing disorders as revealed by videofluroscopy prior to treatment.[76] Dysphagia as a remote adverse effect has been reported in a patient with amyotrophic lateral sclerosis receiving injections for leg spasticity.[77] The author has observed severe dysphagia after injection of 1000MU of Dysport® into the lower limbs in a patient with Parkinson's disease and swallowing difficulties.

Table IV. Adverse effects of botulinum toxin injections[70]

Paralytic
Excessive weakness of injected muscles
Weakness of uninjected muscles through regional spread
Weakness of remote muscles through presumed hematogenous spread ('botulism')[71]
Autonomic
Dry mouth
Reduced sweating
Reduced lacrimation (dry eyes)
Allergic
Skin rash
Immune mediated?
Flu-like illness
Brachial neuritis-like syndrome[72]
Traumatic
Bruising, bleeding
Pain

Although there are very few reports of dysphagia complicating botulinum toxin treatment of spasticity, special caution is advised when the patient has swallowing difficulties. Given the strong possibility of subclinical bulbar or pseudo-bulbar dysfunction in patients who are eligible for treatment of spasticity with botulinum toxin (those with stroke, multiple sclerosis, anoxic-ischaemic encephalopathy, amyotrophic lateral sclerosis or cerebral palsy) and the often large doses used, anyone injecting this drug should be aware of this potential complication and inform the patient accordingly.

Botulinum toxin for the treatment of spasticity is usually injected into the muscles of the limbs and limb girdles. When the limb is useless, excessive weakness cannot interfere with active function, although it might predispose the flaccid limb to joint and soft tissue damage. However, if there is residual voluntary movement, excessive weakness could interfere with limb function.

Despite its potential toxicity, therapeutic injections of botulinum toxin for spasticity seem to be quite well tolerated. In the RCTs of botulinum toxin-A, the adverse effects reported were mostly minor, the commonest being local pain at the injection site.[11,17-25] Others included rash, flu-like symptoms and fatigue.[17,19,21,24] No study reported any serious adverse event that could be attributed to the botulinum toxin injection. In studies where comparisons were made, the frequency of adverse events was not significantly increased in the treatment group compared with the placebo group.[17,19,25] Despite the potential for excessive weakness, this has not been reported to be a problem in clinical trials. This may be because most trials have focused on reducing spastic hypertonia in upper limbs that may have little residual voluntary movement to impair, or in lower limbs where very large doses of botulinum toxin would be required to cause overweakening. More reports of adverse functional consequences due to overweakening can be expected from trials that specifically attempt to improve voluntary movement and active function, especially in the hands.

There is very little information on the adverse reactions associated with botulinum toxin-B injected for the treatment of spasticity. Dry mouth seems to be prominent in cervical dystonia treated with botulinum toxin-B[78] and could be attributed to local spread. However, as mentioned earlier, dry mouth affected nearly all patients in the open and double-blind trials of botulinum toxin-B in patients with upper limb spasticity,[26,35] which can only be explained by haematogenous spread. Because of this potential for remote autonomic dysfunction, close attention has been paid to vital signs in the clinical studies but no significant changes have been recorded.

As for a relationship between dose and adverse effects, one dose-ranging study of Dysport® (500, 1000 and 1500 units) in upper limb spasticity did not show any significant differences in adverse events between the groups.[23] However, another dose-ranging study of Dysport® (500, 1000 and 1500 units) for hip adductor spasticity showed twice as many adverse events in the higher dose treatment group than in the two lower dose groups.[21] In a dose-ranging study of Botox® (75, 150 and 300 units) in upper limb spasticity, there were no significant differences in adverse events between the three groups.[17]

Similar safety profiles were seen in the open-label studies for botulinum toxin-A and botulinum toxin-B. Here, the most commonly reported adverse effects were weakness of the injected muscles and local pain from the injections. There was one case of local infection.[39] Many studies reported no adverse events. An examination of isolated case reports revealed two cases of a generalised botulism-like syndrome.[79]

4.2 Adverse Events in the Treatment of Paediatric Spasticity

Although this paper is on adult spasticity, it is instructive to examine the safety profile of botulinum toxin in the treatment of paediatric spasticity. In a large multicentre retrospective review, Bakheit[80] analysed 1594 treatments in 758 patients, most of whom had cerebral palsy: all received injections of Dysport® into their lower limbs. The incidence of adverse events was low at 7%, and most of the adverse events were minor. Focal muscle weakness occurred following only 1% of treatments (n = 16). Six patients developed generalised muscle weakness, but the doses given were not stated. Other minor adverse effects were fever, fatigue, skin rash, somnolence and injection site pain. Because of the nature of the paediatric population, there was a wide range of botulinum toxin doses given. As expected, there was a correlation between adverse events and total dose (highest with Dysport® doses >1000MU) but curiously not when the dose was expressed as units per bodyweight. A good subjective benefit occurred with 82% of treatments, and 94% of patients at least partially achieved their treatment goals.

4.3 Adverse Events in the Treatment of Other Neurological Conditions

Although very few adverse effects have been reported in the treatment of adult spasticity with botulinum toxin, it is helpful to be aware of those arising in treatment of other neurological conditions. Some regional adverse effects have been mentioned already, but there are some noteworthy reports of systemic effects. Injections of botulinum toxin have been reported to unmask or exacerbate disorders of neuromuscular transmission, such as myasthenia[81,82] and Lambert-Eaton Myasthenic syndrome,[83] sometimes after years of uncomplicated botulinum toxin treatment for conditions such as blepharospasm and Meige's syndrome. Successful treatment of cervical dystonia in a myasthenic patient has also been reported.[84]

Adverse effects arising in areas that are remote from the injected sites have been attributed to haematogenous spread.[85] Remote effects on neuromuscular transmission have been studied with single-fibre EMG several times (for example, see Lange et al.[85]), but the changes have been generally limited to increased jitter, which is not associated with weakness.

Autonomic complications are a feature of systemic botulism and symptoms such as dry mouth are common in botulinum toxin treatment of cervical dystonia.[86,87] Furthermore, blockade of muscarinic and sympathetic cholinergic synapses is a therapeutic mechanism in hypersalivation and hyperhidrosis. The most serious autonomic complication of botulism is cardiac conduction disturbance, and so sub-

clinical cardiac effects have been investigated with therapeutic treatments. In an unblinded study of cervical dystonia treatment with Dysport® (250–1000MU), no changes were found in heart-rate variability or cardiovascular reflexes 14 days after injection.[88] In contrast, a similar study found long-lasting impairment of heart-rate variability only after the second injection.[89] These abnormalities have been, for the most part, subclinical,[88,89] although one patient experienced postural hypotension.[90] It should be noted that botulinum toxin-B seems particularly prone to causing autonomic adverse effects.[91]

Among the listed precautions or contraindications for botulinum toxin is treatment with certain antibacterials, mainly the aminoglycosides that are known to interfere with neuromuscular transmission. Aminoglycosides have been shown to increase the neuromuscular blockade of botulinum toxin-A in frogs[92] and have been implicated in one death due to infantile botulism,[93] but so far there have been no reports of this drug interaction when botulinum toxin is used therapeutically in humans.

Pregnancy is also a listed contraindication, but there have been no reports of adverse events resulting from therapeutic botulinum toxin during pregnancy and one case report of four successful pregnancies.[94]

In conclusion, adverse events from injections of botulinum toxin-A appear to be minor, self-limiting and predictable from the mechanism of action. Most studies report good tolerability of the injections. The most worrying adverse effect of botulinum toxin injections is local weakness of the injected muscles or those nearby. Although this might result in functional deterioration, the weakness is self limiting. Anyone injecting botulinum toxin should be aware of the potential for remote weakness, particularly of the bulbar muscles, in patients who have swallowing disorders or who might have subclinical bulbar dysfunction.

4.4 Secondary Resistance: Immunogenicity

Although not strictly an adverse reaction, the development of secondary clinical resistance, probably mediated by neutralising antibodies, is of concern in long-term treatment with botulinum toxin. This is of particular concern as a risk factor for resistance is a large dose at each injection session,[95] which is a common occurrence with spasticity. Early reports of resistance occurred most often in patients with cervical dystonia where high doses were used, for example approximately 200MU of Botox®, and the incidence has been reported as being as high as 10%.[96]

Changes in the administration of the toxin since 1997, as well as in the protein content of Botox®, may have led to the reduction in the development of resistance to Botox® in the treatment of cervical dystonia.[97,98] A search of PubMed from 1966 to 27 November 2005 using the keywords 'bolulinum', 'toxin', 'spasticity' and 'resistance' revealed no reports of resistance in the treatment of spasticity, except for one in a patient with spastic bladder.[99] Nonetheless, some cases may have gone unreported so complacency should be avoided and persons injecting botulinum toxin should continue to use the lowest dose possible and to avoid booster injections.

5. Comparison with an Alternative Treatment: Phenol

Until therapeutic botulinum toxin became available, the pharmacological treatments for spasticity included oral agents (chiefly baclofen, diazepam, tizanidine and dantrolene), intrathecal pumps delivering baclofen and intramuscular or perineural injections of phenol. The principal neurosurgical procedure was dorsal rhizotomy.

The choice of antispasticity treatment is often dictated by the size of the area to be treated. Large regions of spasticity, such as quadriplegia, paraplegia, hemiplegia or monoplegia, are usually treated with several oral antispasticity agents. Intrathecal baclofen is another option for such patients, but is usually employed for spastic paraplegia from spinal cord injury. Injections of botulinum toxin are usually reserved for treating focal areas of spasticity and the main alternative treatment is phenol.

Before botulinum toxin became available, phenol was the mainstay of medical treatment for focal spasticity. The use of phenol was, and still is, apparently confined to rehabilitation specialists, rather than neurologists. Phenol injections are given perineurally around the nerve trunk innervating a

muscle or group of muscles[100] or intramuscularly,[101,102] into the motor point of the target muscle. Phenol is given in concentrations of 5–7%, which, at this strength, destroy the myelin sheath and axon.[103] Recovery occurs when the axons regenerate.

Phenol is not selective for sensory or motor axons and so with perineural injections there may be sensory symptoms, mainly paresthesiae, which are usually temporary (several weeks) but may become permanent and painful (chronic neuropathic pain).[104] Because of this, phenol is not usually used on nerves with very high sensory fibre content, such as the median nerve. Intramuscular injections largely not associated with the sensory complications, but can be painful. Phenol denatures protein and there have been reports of damage to adjacent tissues such as blood vessels and the ureter.[105]

Unlike botulinum toxin, the paralytic effect of phenol is not easily predictable in either magnitude or duration and the effect can last several years.[104] The chief advantages of phenol over botulinum toxin are that it is inexpensive, works quickly and is not prone to induce neutralising antibodies. The fact that it affects sensory nerves, unlike botulinum toxin, provides another mechanism for phenol to reduce spasticity; this could result in spasticity reduction with less weakness than with botulinum toxin. There is a maximal safe dose *per se*ssion of approximately 1g (20mL of 5% solution), but otherwise there is no limit.[104] This means that many muscles can be injected, including large proximal muscles. Botulinum toxin, on the other hand, is usually restricted to a maximal dose of about 600 units of Botox® or 2000 units of Dysport® per session,[106] which limits the number of muscles that can be injected at a time and usually means that only one or two large, powerful proximal muscles can be treated. Furthermore, it is usual to adhere to a minimum 3-month interval between botulinum toxin injection sessions to avoid secondary resistance due to antibody formation. This restriction not only means that patients are effectively limited to 600 units or so every 3 months, but also that an underdose cannot be addressed for 3 months. With phenol, there is no such restriction and 'top-up' injections could be given to rectify an initial underdose.

Most of the literature regarding phenol treatment of focal spasticity concerns open-label studies.[104] There has been only one double-blind trial that compared phenol with botulinum toxin in spasticity.[107] Therefore, it is difficult to objectively compare the two treatments for safety and efficacy. In this study, phenol (5%, 3mL) was injected perineurally into the tibial nerve and botulinum toxin (Botox®, 400MU) was injected into the calf muscles to treat spastic plantarflexion in stroke patients. There was no difference in efficacy at 3 months. The only serious complications occurred in the phenol group, for example common peroneal nerve palsy, so the authors concluded that botulinum toxin was safer. There has been no study comparing botulinum toxin with intramuscular phenol.

In summary, the most important differences in adverse reactions between botulinum toxin and phenol are that phenol is prone to causing unpleasant or painful sensory symptoms and that it may, rarely, damage tissues, whereas botulinum toxin has neither of these problems. There are very little data to allow a proper benefit comparison between these treatments, let alone a benefit-risk comparison. Further clinical trials are needed for this analysis. Interested readers are directed to an excellent review of the use of phenol for spasticity by Gracies et al.[104] Phenol is much less costly than botulinum toxin, which is a factor that would weigh heavily in a cost-benefit analysis.

6. Conclusion: Benefit-Risk Evaluation

Injections of botulinum toxin-A and botulinum toxin-B appear to be effective in reducing adult spasticity of the upper and lower limbs resulting from a variety of causes (mainly stroke and multiple sclerosis). Spastic tone can be reduced in elbow, wrist and finger flexors in the upper limbs, and in hip adductors and ankle plantarflexors in the lower limbs, at least for the short term (about 3 months), after a single injection session; longer studies of repeated injections are awaited.

Clearly, botulinum toxin-A can reduce spastic muscle tone if a sufficient dose is given. This will probably also be proven true for botulinum toxin-B, as there is no physiological reason for it to not do the same, but the only RCT performed so far has failed to show this. The clinical benefit arising from the reduction of spastic tone is more difficult to judge. There are data to indicate that caregiver burden is

reduced in patients with severe paralysis of the upper limb after stroke and that certain disabilities related to passive function of the upper limbs can improve. However, there is not yet any convincing evidence from RCTs that voluntary movement of the upper or lower limbs can be improved by reducing spastic motor overactivity. This is not to say that it is not, because experience in carefully selected patients has shown that voluntary movement and active function can improve, and the results of some of the open-label trials support this. The reasons for the lack of a positive outcome in RCTS, with regard to active function, are largely based in trial design and have been discussed previously.[108]

Injections of botulinum toxin for spasticity seem to be very well tolerated. Adverse effects are minimal, temporary and mainly local (trauma of the injection), except for the nearly universal dry mouth associated with upper limb injections of botulinum toxin-B. There is also the possibility of excessive weakness of muscles, which may interfere with function, but even this seems uncommon.

As a final statement, one can say that spastic tone can be safely reduced in the short term by botulinum toxin injections and that this reduces pain and passive function disability and makes life easier for caregivers. It remains to be proven whether voluntary movement and active function can be improved. If this can be done, the benefit-risk balance will tip even more heavily towards benefit, with the only caveat being the potential for impairment of residual function by overweakening.

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