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BOTULINUM TOXIN – MECHANISMS OF ACTION AND CLINICAL USE IN SPASTICITY

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Botulinum toxin is a potent neurotoxin produced by the bacterium Clostridium botulinum. There are seven serotypes, all of which block the release of acetylcholine from nerve endings, which gives the compound its theoretical base for reducing spasticity. Initial studies of the use of botulinum toxin in the management of spasticity were promising and now there are a number of well-designed, double-blind, placebo-controlled studies that confirm the place of botulinum toxin in our treatment armoury against focal spasticity. The studies have demonstrated both efficacy and safety. There is still more work to be done in terms of disability although early reports confirm functional improvements, particularly reduction of pain as well as improvements in nursing care, hygiene and carer burden. Further studies also need to be done to confirm the place of botulinum toxin in the overall context of other treatment possibilities in the management of spasticity.

Key words: spasticity, physiotherapy, oral anti-spastic medication, botulinum toxin

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BACKGROUND

The introduction of botulinum toxin into clinical practice over the last decade has made a dramatic difference to treatment possibilities for people with dystonia and spasticity and in more recent years for the management of a variety of other troublesome symptoms such as drooling and hyperhidrosis. It has also raised the possibility of treatment in a number of other long-term disabling conditions such as low back pain, neck pain following whiplash injury, chronic tension headache and migraine.

Botulinum toxin was first used by Alan Scott in California who initially experimented with botulinum toxin type A under EMG guidance to treat paralytic strabismus and blepharospasm. In 1989 the toxin was approved by the FDA and soon thereafter approved for use in many parts of Europe.

Botulinum toxin is a potent toxin produced by the bacterium Clostridium botulinum. There are seven immunologically distinct serotypes – named A, B, C, D, E, F and G. Type A toxin was the first to be produced commercially and is currently available through two manufacturers – Ipsen (Dysport) and Allergan (Botox). More recently, botulinum toxin type B has been launched in the States and across Europe (Elan Pharmaceuticals – Neurobloc). At the present time the other serotypes are not commercially available although development work is taking place on type C and type F toxins. Obviously the adverse effects of Clostridium botulinum have been known for many years and occasionally outbreaks of botulism still arise (1).

MECHANISMS OF ACTION

The botulinum toxins are the most potent neurotoxins known to man and have been investigated extensively over the last few decades, particularly in the context of the defence industry. Much early investigational work on the toxins was undertaken at the Centre for Applied Microbiological Research (CAMR) in Porton Down, UK. Indeed the basic toxin is still manufactured at this site. All the botulinum toxin serotypes have the end result of blocking the release of acetylcholine from nerve endings, thereby inducing muscle weakness (2). The side effects of the compound are also explained by the same mechanism, as the botulinum toxins also block the acetylcholine release from parts of the autonomic nervous system, inducing in particular dry mouth and reduced sweating. The differences between the serotypes depends on the particular part of the soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) complex affected. The SNARE complex is essential for acetylcholine release at the presynaptic nerve endings. The toxin structure consists of a heavy chain linked by a disulphide bond to a light chain containing an amino-acid sequence, which is indicative of the site of action. The botulinum toxin binds irreversibly to the presynaptic surface of cholinergic nerve terminals, which results in the inhibition of acetylcholine release. The toxins undergo endocytosis and then interact with the SNARE apparatus to disrupt acetylcholine release. The seven serotypes of botulinum toxin specifically interact with different components of the SNARE complex. Type A and E interact with synaptosomal-associated protein of M(r)=25kDa (SNAP 25), types B, D and F affect synaptobrevin-2 (VAMP) and type C acts on syntaxin. The inhibition of acetylcholine release is quite specific and long lasting. Collateral nerve sprouting eventually enables the nerves to refunction. In clinical terms, the injection lasts around three months, although longer effects are often reported in terms of the blockage of the autonomic nervous system. It seems likely, at

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least in animal models, that the botulinum injection also inhibits nocioceptive input by blocking substance P release. Thus in addition to being an anti-spastic agent the botulinum toxins are analgesic (3). It is known that retrograde axonal transport and intraspinal transfer of botulinum toxin also occur in animal models (4). This may provide an explanation for the occasional distant effects of injection.

Some individuals lose the beneficial response to botulinum toxin type A after repeated injection. The reason for this is not entirely understood but in many people this is due to the development of antibodies to the toxic and/or the non-toxic components of the botulinum complex (5). It is generally accepted that around 5–10% of the injected population will eventually develop such clinical resistance. Frequent injection intervals and larger doses of toxin probably predispose people to a higher likelihood of antibody development. The botulinum toxin serotypes are thought to be immunologically distinct and thus there is some rationale for alternative serotypes to be tried if clinical resistance develops (6).

PREPARATION AND INJECTION TECHNIQUES

Botulinum toxin type A is commercially available as lyophilised freeze-dried preparations that require refrigeration. It is prepared by dilution with normal saline. It is important for the reader to be aware that the two commercial type A preparations come in different units. The Allergan preparation (Botox) is available in ampoules of 100 units whereas the Ipsen (Dysport) preparation is available in ampoules of 500 units. The conversion ratio is approximately 3.5 Dysport units:1 Botox unit, but information on the conversion ratio varies considerably. The newer botulinum type B (NeuroBloc – MyoBloc in the USA) is a liquid preparation that does not require lyophilisation. This solution is available in three vial sizes containing 2,500/5,000/10,000 units. The relative dose equivalents between the type A and type B toxins in clinical terms are not yet fully defined but as a guide around 10,000 NeuroBloc units is broadly equivalent to around 500 Dysport units.

Once either type A or type B solution has been prepared the injection technique is identical. Both toxins are given by intramuscular injection into the muscles that require relaxation. Some centres use EMG guided injection techniques whereas others simply use clinical identification of the muscles. Although most authorities accept that EMG guidance is required for smaller muscles (e.g. muscles for writer's cramp) most would also agree that the larger and more easily identified muscles (e.g. adductors, quadriceps, biceps, etc.) do not require EMG guidance for satisfactory clinical injection. The doses will vary between 100 Dysport units for smaller muscles up to 1,000 Dysport units for larger muscles. Most authorities would make an appropriate dosage reduction to allow for the smaller muscle bulk in children. There is a wide range of effective dosage, which will need adjustment according to clinical response and side effects at each clinic visit. Protocols for injections do exist and should be used by the inexperienced. Clinical experience will eventually reduce the need for adherence to rigid protocols (7, 8).

The toxin effects usually develop over a course of 4–5 days and the clinical effect will last around three months (but probably a little longer in autonomic blockage such as for drooling and excessive sweating). Injection will need repeating at this point. Botulinum toxin has now been used in clinical practice for over 10 years and there are no known long-term adverse affects from repeat injection, except for the risk of atrophy and the development of antibody formation, and thus reduced clinical efficacy, in a small proportion of people (see above).

CLINICAL USAGE

The initial clinical use of botulinum toxin was for the management of paralytic strabismus. However, botulinum quickly became established in the early 1990s as first line choice for the treatment of focal dystonia. There is now a very considerable evidence base confirming the efficacy of botulinum for the whole spectrum of dystonic conditions (9). The first formal report of the use of botulinum toxin for spasticity occurred in 1989 (10). Several open label studies went on to support these findings. The open label literature is indeed extensive and during the period of 1996–2000 there were over 50 publications on the subject. The great majority of the initial open label literature was positive and confirmed both clinical efficacy and safety in a variety of spastic conditions. In the mid 1990s the literature developed and there are now 20 or more good quality randomised placebo-controlled trials that produce firm evidence for antispastic efficacy (11). The majority of studies have been conducted for individuals with adductor spasticity/calf spasticity and spasticity in the upper limb. Regrettably many of the studies have used a heterogeneous population including those with stroke, traumatic brain injury and multiple sclerosis. Using mixed populations makes it difficult to compare studies. However, despite these difficulties the use of botulinum toxin for the management of spasticity is now well recognised (12). Most studies report benefit in terms of spasticity, but a number of studies also report improvement in terms of pain and hygiene (13). Virtually all the studies confirm the lack of clinically significant side effects (see below). The early placebo-controlled studies largely used impairment-based outcome measures but more recently studies have begun to use more disability related outcome measures. Pierson et al. (14) used a retrospective analysis of 39 cases of spasticity secondary to a variety of pathologies and documented not only improvements in spasticity and range of motion but also orthotic tolerance, pain relief and subjective functional improvements. In 2000, Bhakta et al. (15) published a study on 40 patients with stroke who had spasticity in a functionally useless arm. Individuals were randomised to receive either intramuscular botulinum type A or placebo in a total dose of 1,000 Dysport units of toxin divided between the elbow, wrist and finger flexors. Spasticity, muscle power, joint

movement and pain were assessed, and disability and carer burden were measured using new scales. Disability was reduced at week six in the botulinum group compared to placebo. Reduction in carer burden was seen at week six and continued for at least 12 weeks. Forearm flexor spasticity was reduced up to 12 weeks after treatment. There were no seriously related adverse effects in the botulinum group although grip strength was reduced. A final example comparing botulinum to placebo in people with arm spasticity following stroke was published recently in Stroke (16). The study used three dosages of Dysport (500, 1,000 and 1,500) compared to placebo injected into five muscles of the affected arm in a total of 83 post-stroke patients. All doses of Dysport toxin showed a significant reduction from baseline in muscle tone compared to placebo. The study was not able to demonstrate a statistically significant improvement in terms of functional ability. Thus, whilst it is clear that botulinum definitely reduces spasticity in terms of impairment the functional impact of such reduction has yet to be fully clarified. It is likely that botulinum toxin alone has a limited functional impact and that it is the overall holistic and multidisciplinary management of the individual with spasticity that is required for maximum functional benefit. Thus, there are a number of good quality-randomised, placebo-controlled studies that confirm the efficacy of botulinum at least in terms of impairment both in the upper and lower limb as well as in the context of various disorders, including multiple sclerosis, traumatic brain injury, stroke and spinal cord injury (17).

BOTULINUM TOXIN AS AN ADJUNCTIVE TREATMENT IN THE MANAGEMENT OF SPASTICITY

There have been a few studies indicating that botulinum toxin should be seen as part of an overall treatment strategy for an individual with spasticity and not usually as a treatment in its own right. Regrettably there is very limited work on this subject at the present time. A study by Reiter et al. (18) compared a lower dose of botulinum toxin compared with ankle taping against a more standard dose of toxin into the calf muscles. Both groups showed a reduction in spasticity as well as an increase in gait velocity and step length. The only difference between the groups was less gain in passive dorsi flexion in the combination group. They concluded that both regimes were equally effective in reducing foot inversion. A randomised, placebo-controlled study assessed combination treatment with short-term electrical stimulation (19). Four treatment groups were used in 24 people with stroke. Injections of either placebo or toxin (1,000 units of Dysport) into six upper limb flexor muscles were combined with additional electrical stimulation in two of the groups. The stimulation was given three times for half an hour for three days and assessments of tone, limb position and difficulties with three upper limb motor tasks were carried out before injection and 2, 6 and 12 weeks after. Most improvements were seen in the combination group. A statistically significant improvement in palm cleaning occurred and differences in tone and placing the arm through a sleeve were noted. It was concluded that short-term electrical stimulation enhances the effectiveness of botulinum type A in the treatment of chronic upper limb flexor spasticity after stroke. There is clearly a need for more research on this subject. However, it is more than likely that whilst botulinum toxin has an important role to play for the management of spasticity it is only one role of many that will need to be applied to the individual patient to produce maximum overall benefit.

BOTULINUM TOXIN IN CHILDREN

Most of the published studies have focused on adults with spasticity. There is separate literature that has also confirmed the efficacy of botulinum toxin for the management of spasticity in children with cerebral palsy. Pioneering work was carried out by the team based in Belfast in the early and mid 1990s (20-22). There is now compelling evidence that botulinum has a distinct role to play in cerebral palsied children. Botulinum appears to be efficacious in delaying surgery until the child is older, when definitive surgical procedures can be undertaken for spasticity problems such as equina varus deformity. Botulinum can also be useful in this age group for diagnostic purposes, post-operative analgesia and to facilitate the fitting of a variety of orthotic appliances (23).

SIDE EFFECTS

The overwhelming majority of studies confirm the clinical safety of botulinum toxin. A few rare systemic affects can occur after injection, including a generalised rash and flu-like symptoms in a small number of people. In a recent overview by Bakheit et al. (24) data was analysed in 758 people who received a total of 1,594 treatments of botulinum toxin type A. Of all treatments, 7% resulted in some adverse events, with the incidences being related to the total dose rather than the dose calculated on the basis of body weight. The highest incidence of adverse events was observed in people who received more than 1,000 (Dysport) units of botulinum type A. The only real clinical problem results from presumed spread of the toxin from the immediate injection site. Such spread can cause weakening of muscles in neighbouring sites. Sometimes this can be a desirable clinical effect but obviously occasionally adverse reactions result. Swallowing disorders, for example, occur in about 5% of cases following injection of botulinum in the neck muscles for cervical dystonia. The weakening of muscles can of course be undesirable in those who are barely ambulant and occasionally people can be rendered non-ambulant by the injudicious use of botulinum toxin. In theoretical terms caution needs to be exercised in people with neuromuscular junction disorders, such as myasthenia gravis or those on drugs, such as Gentamicin, that can affect the neuromuscular transmission. However, in practical terms such associations are rare

and there are virtually no contra-indications to botulinum therapy. In the long-term antibody resistance may develop. This probably occurs in some 5% of individuals and is usually due to the development of antibodies against both toxic and non-toxic components of the botulinum complex. It is likely that using the lowest dose compatible with clinical effect reduces the longer term risks of botulinum toxin, whilst spacing out the injection intervals as much as practically possible also seems to be desirable, although such evidence is far from convincing.

BOTULINUM TYPE A VERSUS BOTULINUM TYPE B

As stated above botulinum type B (Neurobloc or Myobloc) toxin is now available. Recent studies have emerged indicating similar efficacy to type A toxin in the context of dystonia (25) but so far there is very limited efficacy of botulinum type B in spasticity. The side effect profile is similar, although it is possible that there are more autonomic side effects associated with B toxin, including dry mouth. Duration of action is not yet determined with any accuracy. The other serotypes of botulinum toxin are not yet available commercially.

CONCLUSION

It is now clear that botulinum toxin has an important role to play in the overall management of spasticity in both adults and children. There is no doubt that botulinum is antispastic and analgesic and can improve impairment parameters. There is an increasing evidence base that botulinum toxin can produce functional improvements and thus reduce disability. However, it is likely that botulinum is only one part of our armoury in the overall management of spasticity. It should not detract from the use of physiotherapy, splinting, casting, appropriate seating, oral medication, intrathecal baclofen and other measures that all have a role to play. The exact place of botulinum toxin therapy is yet to be determined and indeed there are many clinical questions that remain unanswered, such as the exact role of the toxin with other treatments and the place of botulinum toxin type B. However, these unanswered questions should not detract from the very significant advances that botulinum toxin has enabled us to make in the management of disabling spasticity.

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