Treatment of paediatric cerebral palsy with Dysport®

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Dysport® (Clostridium botulinum type A toxin-haemagglutin complex) has had its licence extended to include treatment of children aged 2 years and over with dynamic equinus foot deformity, caused by spasticity associated with cerebral palsy. Dysport® reduces muscle tone, thus improving function, relieving pain, and facilitating physiotherapy, application and tolerability of splints.

Cerebral palsy (CP) is defined as a permanent, but not unchanging disorder of movement and posture caused by a defect or other impairment to the brain preventing normal development (Bax, 1964). It results from damage to the immature brain in utero, during or shortly after birth and is a relatively common condition, affecting between 2.5 and 4 babies in every 1000 live births (Blair and Stanley, 1982).

For the majority of patients the predominant motor problem is spasticity, although dyskinesia (showing extrapyramidal signs such as variations in muscle tone, abnormal postures and involuntary movements) and ataxia (showing axial hypotonia, truncal oscillations and intention tremor) are not uncommon. In addition to these motor problems, patients may suffer from other manifestations of cerebral dysfunction, including learning disability, epilepsy, sensory deficits (hearing or visual loss) and emotional problems.

Most commonly CP is diagnosed towards the end of the first year as a result of abnormal motor development.

Patients with spasticity associated with CP can be classified anatomically in terms of limb involvement. Diplegics have legs affected more than arms, while hemiplegics have one side of the body affected, and quadriplegics have all four limbs equally affected. Within a limb one or more muscles can be affected to different degrees. It is the combination of muscles involved and the degree of severity that defines the functional problem demonstrated by the patient.

The most common type of CP is spastic diplegia, with spasticity predominantly affecting the calf muscles. The result is a dynamic equinus walking pattern where the patient is unable to achieve normal heel strike in the stance phase of the gait cycle and is unable to clear the ground in the swing phase. The result is that they walk up on their toes.

Children with spastic CP do not have any deformities at birth, their problems are secondary, partly the result of failure of muscle growth. CP lesions in the central nervous system result in loss of inhibitory reflexes that prevent muscles from contracting too much. Over time the consequence of muscle spasticity is that the affected muscles fail to lengthen in proportion to bone growth, and the contractures become progressively fixed.

Evidence that the failure of muscle growth is a result of increased tone came from studies that injected tetanus toxin (which makes muscles contract) into muscle and documented the subsequent failure of growth (Ranson and Dixon, 1928).

The goal of any treatment in spastic CP is to maximize function and to minimize the development of secondary problems, such as fixed contractures.

Currently, the mainstay of treatment for children with spasticity-associated CP is regular physiotherapy to stretch the affected muscles. Many patients also require orthoses or serial casting to assist with stretching. Mammalian studies have suggested that immobilization of muscles in a stretched position increases sarcomere number. However, changes reverted to baseline 4 weeks after cast removal (Tabary et al, 1972).

Orthopaedic surgery is often required to lengthen muscles that have developed fixed contractures and correct bone and joint deformities. Selective dorsal rhizotomy is used to reduce the

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muscle tone by interrupting the afferent pathway of the stretch reflex. As a child grows, it is not uncommon for them to require a number of surgical interventions. Systemic antispasticity drugs such as baclofen and diazepam are available but the associated systemic side-effects limit their use in paediatric populations.

RATIONALE FOR TREATMENT

Hyperactive muscle contractions in CP spasticity are characterized by an excessive response to the neurotransmitter acetylcholine (ACh) at neuromuscular junctions. Dysport® (Ipsen Ltd) — a botulinum toxin — has been developed to overcome this problem by blocking the synaptic release of ACh from cholinergic nerve terminals.

Botulinum neurotoxins are produced by different strains of the Gram-negative bacterium *Clostridium botulinum*, which synthesize seven serologically different types of toxin A to G. Dysport® is botulinum type A toxin–haemagglutinin complex, that has been isolated and purified.

Botulinum toxin is a protein comprising of one light chain (of around 50 000 molecular weight) and one heavy chain (of around 100 000 molecular weight) linked together by a disulphide bond. Haemagglutinin is a large protein, which stabilizes the toxin but has no therapeutic effect. The heavy chain is similar among all the different botulinum toxins, while the light chain — which represents the toxic part that blocks transmitter release — is responsible for differences in action between various strains.

The heavy chain directs the toxin to its target — a ganglioside and protein present only in cholinergic nerve terminals. The toxin molecule binds to the ganglioside and is endocytosed by receptor-mediated endocytosis into the cholinergic nerve terminal, from which it enters the cytoplasm. Here the light chains of toxin A and E selectively destroy the synaptosome-associated protein called SNAP-25, which participates in the process of neurotransmitter release. Inhibition of ACh causes a gradual decay of the end plate potential, until the muscle fails to contract.

The physiological effect of botulinum toxin is not irreversible, and the recovery of muscle contractility occurs gradually as new nerve terminals sprout and make contact with the postsynaptic membrane. Recent evidence suggests that in time the functionality of the original axon is restored and the new axon retracts (De Paiva et al, 1999). New growth and recovery both result in the need for repeated botulinum toxin administration for the long-term control of spasticity.

Dysport® was first licensed in the UK for use in blepharospasm and hemifacial spasm, and later for use in spasmodic torticollis.

PHARMACOLOGY

Rigorous pharmacokinetic studies of half life have proved difficult because of the minute doses of Dysport® involved, the large molecular weight of the compound, and the difficulty of labelling the molecule to produce botulinum toxin with a high specific activity.

CLINICAL STUDIES

One of the most significant studies in support of the clinical application of Dysport® in children was a randomized, double-blind placebo controlled study (Ubhi et al, 2000) of 40 patients with diplegia and hemiplegia. In the study video recording of the gait of 22 patients who were randomized to receive Dysport® and 18 who were randomized to receive placebo were reviewed 6 weeks after treatment by a blinded panel of physicians and physiotherapists.

The panel reported that initial foot contact was significantly better for Dysport® compared to placebo and that the improvement was still evident 12 weeks after treatment. In addition, participants treated with Dysport® showed significant improvements in the walking dimension of the gross motor function measure at 6 and 12 weeks. The Leeds Functional Mobility Questionnaire — which comprises 50 questions used to assess problems experienced by the patient in performing normal everyday functions — showed that children treated with Dysport® walked less frequently on their toes.

A retrospective study (Bakheit, 1999), which collected data from five European countries involving 1594 treatments in 758 patients, found beneficial effects for Dysport® treatment. The study, which assessed outcomes of treatment on a four-point scale of good, minimal, no response and worse, found that overall 82% of the responses were classified as good, with only 4% showing no response or a worsening of the condition.

The study also revealed that the best response was seen in the under 2 years age group, for which a good response was reported for 88% of treatments using doses of between 250 and 750 units. Adverse effects were only seen in 12% of patients, with the majority of adverse events caused by weakening of nearby muscle groups and injection site pain (Bakheit, 1999). This

reflects the finding of Ubhi et al in their randomized controlled trial.

Another significant study prospectively studied 39 ambulant patients with spastic cerebral palsy to assess improvement in the dynamic component of gastrocnemius muscle spasticity following Dysport®. The study demonstrated that Dysport® was able to increase the dynamic component and that long-term lengthening was still evident in some patients after 12 months. The authors concluded that by delaying muscle shortening, the injections might have a role in delaying the need for surgery (Eames et al, 1999).

Dysport® performs well when compared to serial casting. One study demonstrated a more prolonged effect and better tolerability for Dysport®. The study involved a group of 20 ambulant patients, aged between 2 and 9 years, presenting with dynamic equinus foot deformity who were randomized to receive either Dysport® or serial casting. Routinely, all the patients would have been offered serial casting. Clinical examination, videotape recording and three-dimensional gait analysis were performed at baseline and at 2 and 12 weeks post-treatment, with video recordings being reviewed by a blinded physician.

Researchers found that tone reduction in the Dysport® group allowed a prolonged improvement in passive dorsiflexion, which they speculated may allow greater opportunity for increases in muscle length. A sub-group of seven patients in the Dysport® group and five in the serial casting group were considered suitable for full gait laboratory analysis. As with the clinical examination and video assessment, both groups demonstrated improvements at week 2, without any significant between-group differences. However, by week 12 only patients in the Dysport® group maintained the improvement, whereas the cast group relapsed. Researchers concluded that Dysport® is at least as effective as serial casting for the conservative management of dynamic equinus; there are fewer side-effects and the effect is more prolonged (Corry et al, 1998).

SAFETY

Adverse events related to the use of Dysport® can be classified as localized to the site of injection, focal but distant from the site of injection, and generalized or systemic.

Local weakness of skeletal muscles caused by local diffusion of Dysport® from the site of injection is the most common adverse event, and sometimes increased frequency of falling, urinary incontinence and injection site pain have been noted. Furthermore somnolence, asthenia, fatigue, influenza-like symptoms and vomiting have sometimes been reported. Four cases of neuralgic amyotrophy associated with botulinum toxin treatment have been reported. Two reports concerned patients with spasmodic torticollis (Glanzman et al, 1990; Sampaio et al, 1993), and two were reported in patients with writer's cramp (Sheean et al, 1995).

The majority of adverse events are typically first reported within 2 weeks of Dysport® injection, closely mirroring the onset of therapeutic effect. Most are mild and transient in nature, lasting less than 2 weeks. It is rare for treatment to be discontinued as a result of an adverse event.

Since teratological and other reproductive studies have not been performed with Dysport®, its use is not recommended in pregnant or lactating women. Contraindications for treatment include any patients with a disease of neuromuscular junctions, like myasthenia gravis, and people taking aminoglycoside antibiotics, since both situations potentiate the effect of Dysport®.

CLINICAL PRACTICE

In treating patients with dynamic foot equinus, Dysport® is principally targeted to the gastrocnemius muscle, although injections of the soleus and tibalis posterior may also be considered. Recent evidence suggests that the gastrocnemius is more often responsible for equinus in diplegics, while the soleus is more often responsible in hemiplegics. Where doubt exists, electromyography can be used to identify the most active muscles.

Patients who are anxious about receiving intra-muscular injections may benefit from sedation and/or local anaesthesia. The typical number, dose and location of the injection sites for each muscle vary between centres. One common aspect of Dysport® therapy is that it is regarded as an adjunctive therapy, so that patients continue to receive their usual anti-spasticity treatments.

A starting dose of 30 units/kg of body weight is recommended. If only one calf is affected a dose of 15 units/kg should be used. The optimal dose will vary between patients, and so subsequent treatment should be determined after evaluating the outcome of the starting dose. The increased incidence of adverse events at doses above 1000 units suggests that this dose should not be exceeded. When there is evidence that the initial dose results in

excessive weakness of the target muscles it should be reduced.

Concerns have been raised that repeated injections of antigenic toxin proteins could stimulate the immune system with the development of toxin-neutralizing antibodies, and a consequent reduction in clinical response. Despite such theoretical risks only one report of secondary non-responsiveness in children has been found in the literature. This patient developed secondary treatment failure and tested positive for the presence of neutralizing antibodies to Dysport® after six successful treatments over 36 months involving a cumulative dose of 2600 units (Heinen et al, 1997).

Clinicians can reduce the risk of antibody formation by using the smallest effective dose and/or extending the interval between treatments.

Clinical improvement should be seen within the first 2–3 days following injection, with peak benefit occurring after about 2 weeks and usually lasting for 16 weeks. A frequent observation is that functional benefit is often maintained even when the pharmacological effects of Dysport® have disappeared, possibly reflecting the fact that reducing muscle tone may allow more effective physiotherapy.

CONCLUSION

Used in a carefully controlled manner, Dysport® provides a valuable addition to treatments available for managing patients with dynamic foot equinus associated with CP. It reduces spasticity, significantly improves function and decreases pain and improves ease of care. The advantage is that by specifically targeting spastic muscles Dysport® can be used to relax affected muscles without a systemic effect. Dysport® facilitates the conservative management of children before surgery and there are suggestions that it could delay or even prevent surgery (Cosgrove and Graham, 1995). HM

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KEY POINTS

- Dysport® is an effective treatment for patients with dynamic foot equinus associated with cerebral palsy in children.
- Dysport® relaxes affected spastic muscles.
- Clinical improvement is usually seen within the first few days following injection and may last more than 12 weeks.
- By reducing spasticity, Dysport® significantly increases function and mobility.