CURRENT TOPIC

Position paper on the use of botulinum toxin in cerebral palsy

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There is growing interest in the therapeutic role of botulinum toxin A (BTA) in cerebral palsy.¹ The drug is currently unlicensed for this use, but a number of small trials have indicated that BTA may be used safely and effectively in the management of spasticity and dystonia in cerebral palsy.²⁻⁷ In 1995, a working party was established to examine the status of BTA treatment in this new context. This has resulted in the following position paper. The paper aims to summarise current evidence regarding indications, efficacy, and the known side effects of treatment.

Clostridium botulinum is an anaerobic bacterium that produces seven immunologically distinct strains of neurotoxin (A-G). This potent and potentially lethal toxin blocks the synaptic release of acetylcholine from cholinergic nerve terminals. The toxin exerts its main effect at the neuromuscular junction, resulting in irreversible loss of motor endplates. The muscle is paralysed until nerve sprouting establishes new junctions.⁸ BTA has been developed commercially, and in the UK is currently licensed for use in the treatment of blepharospasm, hemifacial spasm, and spasmodic torticollis. However, BTA is more widely used clinically: in adults, particularly in the management of focal dystonias and acquired spasticity.⁹ Since first reports in 1993,^{2,3} BTA has also been increasingly used in children with cerebral palsy.

The UK Botulinum Toxin and Cerebral Palsy Working Party was established in 1995. This multidisciplinary group meets annually to discuss developments in the clinical use of BTA and recent scientific advances. At every meeting scientific publications are reviewed and research questions are explored. The following position paper is fully referenced but does not include a comprehensive literature review (this can be found in a recent annotation by Forssberg and Tedroff¹⁰).

The initial meeting of the UK Botulinum Toxin and Cerebral Palsy Working Party was convened by Mac Keith Press and SCOPE, at which an organising panel invited acknowledged experts from various disciplines. Since then the group has been joined by others: those who have spoken at conferences or published in the field or have approached the group directly. The group aims to promote good clinical practice and to facilitate collaborative research. The

representatives of the working party and the terms of reference of the group are listed at the end of the report.

Criteria for patient selection

Patient selection should be done in a paediatric setting. A multidisciplinary team is required for patient selection, drug administration, and subsequent management. Team members should have experience in the management of cerebral palsy and, as a minimum, should include a doctor and physiotherapist, with an orthotist available. For effective management a certain level of expertise is required—for this we feel centres should be treating at least 10 children annually.

At the time of selection the specific aims of treatment need to be clearly identified for each patient so that outcome may be evaluated. Goals may include improved function, cosmesis, or ease of nursing care.

The main criterion for treatment is hypertonia, either persistent or dynamic (phasic) in the absence of significant fixed deformity. This is regardless of the anatomical site or overall distribution of the cerebral palsy. It is still not clear which type of hypertonia is most responsive to treatment nor is there an agreed definition of "persistent dynamic dysfunction". Finally, the strength of agonist and antagonist muscles is also likely to be a factor in outcome, with excessive muscle weakness a relative contraindication to treatment.

In the lower limb, indications for treatment include a dynamic equinus persistent throughout the gait cycle; a dynamic knee flexion angle greater than 20° during the gait cycle or interfering with gait; or significant scissoring and adduction at the hips. In the upper limb, indications for treatment include persistent thumb in palm or thumb adduction; wrist posture preventing effective hand use; or tight elbow flexion.

Dosage

There is no consensus in either paediatric or adult practice for a "correct" dose of BTA in spasticity. The dose is generally determined by the size of the muscle to be injected. The aim is to achieve a clinical response without excessive weakness or systemic side effects. When considering the response to BTA there appears

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to be individual variability in drug sensitivity; the subject's age and type of cerebral palsy may also influence the response (Eames N, ESMAC Meeting, Dublin 1996).

BTA is marketed as Dysport (Ipsen-Speywood, Maidenhead, Berks, UK) and as Botox (Allergan; High Wycombe, Bucks, UK). Doses for both products are usually expressed as LD₅₀ units. It must be stressed that units of the two preparations are not comparable. The products are produced by different assay processes and there is no agreed mathematical conversion between the two toxins. However, clinical data in adults¹¹ and the experience of the group suggests a ratio of Botox:Dysport of 1:2.5–5 units. For ease of discussion we refer to units of Dysport unless otherwise stated. A wide range of doses has been used effectively by different members of the group ranging from 0.25 units/kg/injection to 35 units/kg/injection. The Belfast group routinely uses around 25 units of Dysport/kg/session in lower limbs. Some maximum doses were recommended: Belfast recommends a maximum of 900 units of Dysport and 300 units of Botox in the older child (Cosgrove AP, personal communication), although other members of the group have used up to 1000 units of Dysport.

Methods of administration

Informed parental consent should be obtained in all cases and the drugs unlicensed status needs to be emphasised. Treatment should then be given in a paediatric setting with anaesthetic cover available. With increasing experience, general anaesthetic is less frequently required for injection, however all groups use some form of topical local anaesthetic (EMLA cream or lignocaine). In addition, many groups also use systemic sedation. Injections may be given with or without electromyography (EMG) guidance. In the adult population there is evidence that EMG guidance allows more accurate identification of the motor endplate where lower doses of BTA may be effective.^{12 13}

Effects of treatment

OUTCOME MEASURES

Where possible, the effects of treatment should be evaluated by objective, standardised tests. Ideally, these should include neurological and biomechanical measures. Function may be objectively measured using videos,^{2–4 6 7} formal gait analysis,⁵ and EMG. Joint ranges may be assessed clinically and with goniometry.^{2 5 6} To evaluate spasticity, the Ashworth scale^{6 7} and more recently resonance frequency have been used (Graham HK, meeting proceedings of BTA in spasticity, Evian, France, 1995). The gross motor function measures and physician rated scales are also widely used.^{3 4 7}

Standardised questionnaires such as the pediatric evaluation of disability inventory (PEDI)¹⁴ and the functional independence measure for children (WeeFIM)¹⁵ may be used to gauge the wider functional effects of treatment. The subjective impressions of the patient and carers about posture, function, pain, and cosmesis should also be evaluated.^{3–5}

LONG TERM EFFECTS

The onset of weakness is usually detectable from two to three days after injection and is maximal at about three weeks. Generally, the weakness wears off by three months, although functional improvement may persist for considerably longer than this. Clinical reassessment is therefore indicated around these times. In adults, long term repeated BTA injections have been given without adverse effects.^{16 17} To date there is limited experience of repeated injections in children, except in the Belfast group who have found the treatment safe and effective (Cosgrove AP, personal communication). It is possible that BTA induces more subtle central effects,¹⁸ however the long term effects of BTA injections, either beneficial or adverse, remain uncertain. One might postulate that in the young child such treatment may result in improved motor learning.

ADVERSE EFFECTS

Adverse effects are reported infrequently. No member of the working party had seen systemic botulism as a result of BTA injections. The most common complaints were of excessive weakness in the injected muscle or unwanted weakness in adjacent muscles. Over-correction of posture sometimes led to temporary functional deformity. There were anecdotal reports of increased liability to upper respiratory infection immediately after injection and of increased dysphagia in some patients who had pre-existing bulbar involvement. Some children have reported generalised mild fatigue.

The incidence of antibodies and resistance to BTA is not established in the paediatric population. Because side effects may appear over a period of two weeks after the initial injection, repeat administration should be less frequent than this and is generally not recommended within eight weeks of initial treatment. Furthermore, in adults it has been suggested that short injection intervals may encourage antibody formation.¹⁹

Conclusions

To date, BTA has shown promising short term results when used in treating spasticity and dystonia associated with cerebral palsy. However, there are a number of unanswered questions: appropriate dosages and safety aspects still require clarification. Further work is needed to clarify the best responders to BTA injections, both in terms of muscle groups and the specific subsets within the motor disorders of cerebral palsy. In the long term it remains unproved whether the current strategy of using BTA in this way is clinically and economically effective. We feel that these issues can only be clarified by definitive controlled studies. With increasing media exposure, however, there is a risk that BTA may become the "vogue" in management of cerebral palsy and such studies may soon be precluded.^{20 21}

The working party represents the following disciplines: paediatrics, paediatric and adult neurology, orthopaedics, adult rehabilitation, pharmacology, physiotherapy, and orthotics.

The participants were: Mr R Baker, Dr A Bakheit, Dr B Bhakta, Dr L Carr, Mr AP Cosgrove, Mr C Drake, Mr N Eames, Dr P Gringras, Dr J Heckmatt, Ms L Katatchburian, Mr GJ Maclean, Dr R McWilliam, Dr G McArthy, Dr AP Moore, Dr R Morton, Dr C Murray-Leslie, Professor B Neville (Chairman), Mrs F Polack, Ms K Richardson, Dr S Roussounis, Mr D Scrutton, Dr V Shrubbs, Dr M Smith, Ms E Wills, Professor A Wallace, and Professor C Ward.

The group plans to liaise with professional bodies and users of BTA by establishing a register of recognised groups using BTA in the research and management of cerebral palsy. The group further aims to promote and coordinate research, particularly collaborative studies. It is therefore compiling registers of research in progress, which are held at the Neurosciences Unit, Institute of Child Health, The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP, UK with details of research projects and their coordinators.

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