Botulinum toxin and its orthopaedic applications

Emile Pierre van Ermengem, Professor of Bacteriology at the University of Ghent, first discovered the bacterium *Clostridium botulinum* in the late 19th century, naming it after the food poisoning sustained after ingestion of blood sausage described earlier that century by a German physician, Justinus Kerner (the Latin for sausage is *botulus*).\(^1\) Botulinum toxin (BTX) was used successfully as a research tool in the study of the physiology of the spinal cord in the 1970s, and subsequently BTX-A injections were first used therapeutically as a treatment for strabismus in the early 1980s.\(^2\) The first published report of the orthopaedic use of BTX-A to treat spasticity in children with cerebral palsy was published in 1993.\(^3\) In this review we describe the mechanism of action of BTX, discuss the methods of administration and consider some of the indications for its use in both paediatric and adult orthopaedic practice.

**Botulinum toxin and its mechanism of action**

*Clostridium botulinum* produces a complex mixture of proteins containing botulinum neurotoxin and several non-toxic proteins, such as haemagglutinin.\(^4\) There are seven different serotypes of the neurotoxin, named A to G. Although all inhibit release of acetylcholine from nerve terminals, they vary greatly in their intracellular protein targets, potency and duration of effect.\(^5\) BTX-A is the serotype which has been studied most widely in terms of therapeutic application. BTX-B and BTX-F have also been used in clinical practice, but are less potent than BTX-A and have a shorter duration of action.

The neurotoxin is synthesised as a relatively inactive single-chain polypeptide with a molecular mass of 150 kDa which is then cleaved and hence activated, by proteases, into a 100 kDa heavy chain and a 50 kDa light chain, that remain linked by a disulphide bond. These proteases may either be endogenous which are present in some clostridial strains, or exogenous such as trypsin which is used in the commercial manufacture of neurotoxin. The presence of high percentages of un-cleaved neurotoxin in preparations of botulinum toxin may be related to the formation of neutralising antibodies.\(^6\)

Botulinum neurotoxins bind via the heavy chain to specific external high-affinity receptors on the membranes of cholinergic neurones which are internalised by endocytosis. Here, the light chain binds with high specificity to proteins which are involved with release of a neurotransmitter into the synapse. The specific protein complex involved, a soluble (N-ethylmaleimide-sensitive fusion (NSF)) attachment protein receptor (SNARE) complex, mediates the fusion of neurotransmitter-containing vesicles with the synaptic membrane.\(^7\) The complex consists of synaptobrevin which is associated with synaptic vesicles, syntaxin and synaptosome-associated protein of molecular weight 25 kDa (SNAP-25). BTX-A destabilises the SNARE complex by cleaving SNAP-25.

By preventing release of acetylcholine at the neuromuscular junction, BTX reduces muscular activity in a dose-dependent manner. Within four weeks, restoration of the turnover of the SNARE protein complex allows exocytosis of acetylcholine to resume. Nerve conduction is also re-established, initially by new axonal sprouting and elongation of the end-plate and, eventually, by retraction of the new axonal sprouts.\(^9\) Clinically, this chemodenervation with muscle relaxation lasts for 12 to 16 weeks. A follow-up period of longitudinal muscle growth and functional carry-over may last for six months or more\(^11\) depending on the pathology involved.

Coers\(^12\) showed that extrafusal muscle fibres are innervated at the mid-point of the fibre and thus neuromuscular junctions in any given muscle lie within a defined end-plate zone, the topography of which varies with the morphology of the muscle itself. This was confirmed by
Saitou et al. A single innervation band is the pattern most commonly found in limb muscles, specifically those with a unipennate structure. A more complex configuration of the end-plate zone is found in multipennate muscles such as gastrocnemius or deltoid. Scattered innervation bands are found in sartorius and gracilis.

To maximise the clinical effectiveness of BTX-A, several conditions must be met. The toxin must be injected inside the fascial compartment of the muscle, in a dose sufficient to neutralise neuromuscular junction activity and in an appropriate volume so that diffusion to these junctions in the end-plate zone occurs while unwanted spread is minimised.

Techniques for administration

BTX-A is available as two commercial preparations, Botox (100 International Units (IU) per vial; Allergan Inc, Irvine, California) and Dysport (500 IU per vial; Ipsen Ltd, Slough, United Kingdom). One unit is equivalent to the amount of toxin which is lethal to 50% of Swiss-Webster mice after intraperitoneal injection, but the companies use different biological mouse assays which means that the published data on the relative potencies of the two products vary considerably. Thus, a fixed-dose ratio cannot be used when comparing trials of clinical efficacy or adverse events of the toxins. The most effective dose per muscle is unknown, although recommendations have been given. It is likely that the dose required for effective muscle weakening varies with the density of neuromuscular junctions in any given muscles and perhaps with the pathology being treated as well as its chronicity. There is a total-body dose which must not be exceeded if toxicity is to be avoided. The recommendations for a safe total-body dose are 12 units/kg for Botox and 30 units/kg for Dysport, but experienced clinicians have stated that they regularly exceed those doses under certain circumstances.

Children receive a lower dose than adults although in an animal model, Ma et al noted that while the neuromuscular junctions are smaller in juveniles their density within muscle is higher than that in the adult. If this is representative of age-dependent differences, then relatively higher doses in children may be appropriate, similar to the pattern of use with anaesthetic neuromuscular blocking agents.

In over 50% of studies in the current literature, BTX injections have been administered under local or general anaesthesia, or with conscious sedation depending on the age of the patient, the number of sites to be injected and the underlying pathology. Discomfort often relates to the volume injected.

Localisation of the individual target muscle is often done by palpation and based on clinical experience and anatomical knowledge. This may be accurate for certain indications for neuromuscular blockade, for example, in the cosmetic industry, but recently, placement of the needle and injection of toxin based on such simplistic means have had some criticism in orthopaedic practice. In large muscle...
groups in the lower limbs, manual placement of the needle may be accurate between 46% and 78% of the time,\textsuperscript{19,20} but in smaller muscle groups, the accuracy decreases to between 18% and 37%.\textsuperscript{13,20,21} The use of electrical stimulation, e.g. a Stimuplex needle (B Braun Medical Ltd, Sheffield, United Kingdom) aids precise localisation, particularly for the small muscles within the flexor compartment of the forearm or deep muscles in the lower limb such as tibialis posterior or flexor hallucis longus. Chin et al\textsuperscript{20} have recommended the use of electrical stimulation or other guided techniques for the accurate placement of the needle in all muscles except gastrocsoleus, although whether this leads to better functional outcomes is still unknown. Other guiding techniques which are less commonly used include ultrasound,\textsuperscript{22,23} fluoroscopy, and CT.\textsuperscript{24} Once the method for localisation of the muscle has been established there is then uncertainty as to where the injection should be sited within the muscle, whether a single or multiple injection is most effective and whether it should be of high or low volume.\textsuperscript{14,25} Since the toxin exerts its effect at the neuromuscular junctions and as, in many muscles, these lie in well-defined zones, there is a view which supports targeting the injection at the end-plate zone.\textsuperscript{25} There is, however, little clinical evidence to support this belief. Needle electromyographic stimulation can be used to search for the characteristic visual or audible ‘noise’ of the motor end-plate, but this technique demands a relaxed patient and muscle and is not applicable in certain muscles, e.g. tibialis posterior, in which the end-plate zones do not fall in characteristic bands.

Motor points, defined as the area in a muscle where a minimal-intensity, short-duration electrical stimulus causes contraction, are used to localise phenol nerve blocks. Anatomically, the motor point corresponds to the area in the muscle where small motor nerves terminate, and effectively correlates with a point distal to the entrance of the nerve into the muscle. For many muscles, localisation of the motor point is probably as logical, appropriate and easier than that of the end-plate zone. More accurate identification of the point of entry of motor nerves into the muscle in each muscle group may be helpful in increasing the accuracy and hence the clinical effectiveness of BTX injections.\textsuperscript{26,27}

It is possible that the exact technique used should depend on the type of muscle which is being injected and, perhaps, the pathology which is being treated.

### Side-effects

Side-effects are uncommon if the protocols of dosing and technique are followed closely,\textsuperscript{16} but may be classified as localised to the site of injection, and focal but distant from the site of injection. Generalised pain at the site of the injection is mild and is rarely a clinical problem. Weakness in adjacent muscles caused by diffusion of BTX across muscle boundaries is the most common adverse event occurring focally. The effects are temporary and are dose- and site-related, but may be clinically significant. The diffusion characteristics of BTX-A in human muscle have not been described scientifically but animal work and clinical practice suggest that diffusion occurs preferentially along the muscle within its muscle compartment and that fascial planes limit diffusion of toxin by about 23\%.\textsuperscript{28,29} Generalised side-effects are rare and include mild generalised weakness, urinary incontinence, constipation and dysphagia in vulnerable patients, particularly children. Many of the indications for intervention are in children or adults who, although they have tight spastic muscles, are weak and alteration in their overall muscle balance can lead to some unpredicted effects on motor function. The most serious side-effect is aspiration pneumonia in patients with cerebral palsy who have total-body involvement and pre-existing pseudobulbar palsy. This can occur even with the systemic spread of small amounts of BTX and can further impair pharyngeal function.\textsuperscript{30} Therefore, a history of pseudobulbar palsy, gastro-oesophageal reflux, and frequent chest infections are relative contraindications to the use of BTX. In adults, the use of BTX is not recommended in pregnant or lactating women. Other contraindications include a history of disease affecting the neuromuscular junction, such as myasthenia gravis, and the use of aminoglycoside antibiotics and non-depolaris-

### Table I. The indications for the use of botulinum toxin

<table>
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<tr>
<th>Aim</th>
<th>Example</th>
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<tr>
<td>Alter motor function by improving the balance between agonist and antagonist forces</td>
<td>Improve equinus gait in cerebral palsy</td>
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<td></td>
<td>Improve arm function following a cerebrovascular accident</td>
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<td></td>
<td>Bladder control in spinal injury</td>
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<td>Prevention of deformity</td>
<td>Acetabular dysplasia in cerebral palsy</td>
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<td>Glenoid dysplasia in obstetric brachial plexus palsy</td>
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<td></td>
<td>Equinus contracture post-head injury</td>
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<td>Decrease ‘spasticity’-related pain</td>
<td>Post-operatively multiple sclerosis</td>
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<td></td>
<td>Myofascial pain syndromes</td>
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<tr>
<td></td>
<td>Cerebral palsy</td>
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<tr>
<td>Improve quality of life</td>
<td>Of the patient</td>
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<td></td>
<td>Of the carer</td>
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<tr>
<td>Enhance self-esteem</td>
<td>Prevention of involuntary movements</td>
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<td></td>
<td>Management of athetoid cerebral palsy</td>
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<td>Dystonia</td>
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<td>Pre-surgical diagnostic tool</td>
<td>Predicting the effect of release of tendo Achillis</td>
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<td></td>
<td>Improvement of hand function in cerebral palsy</td>
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<tr>
<td>Protection of soft-tissue repair</td>
<td>Flexor tendon repairs in children</td>
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</table>
ing muscle relaxants, since these medications potentiate the action of BTX.

Despite concerns regarding the development of toxin-neutralising antibodies after repeated injections of BTX, there is no current evidence that this results in subsequent non-response.  

**Indications for use**

In musculoskeletal practice, the use of BTX has gained popularity as a treatment for spastic or dystonic muscle, most commonly due to damage to the central nervous system. Its most frequent use is in children with cerebral palsy, but many other potential uses have been identified. The indications for the use of BTX are listed in Table I. It is important to remember that the licensed indications for the orthopaedic use of both preparations of botulinum toxin are few. Most usage occurs ‘off-licence’ and the success or otherwise of much of the treatment is dependent on the adjunctive use of physiotherapy and/or splinting. Similarly, for those indications in which repeated treatments are necessary, little is known about the long-term effects of regular muscle denervation, particularly in conditions such as cerebral palsy in which weakness may be as important a feature as spasticity.

**Cerebral palsy**

In cerebral palsy in which there is a generalised abnormality of muscle tone, BTX is used as focal treatment for a dynamic muscle imbalance which is interfering with function, producing deformity, or causing pain, in the absence of significant fixed deformity. The aim of injections of BTX is to achieve muscle weakening in spastic muscles in the belief that they will encourage muscle strength and hence muscle growth while allowing the weak antagonists to be strengthened, thereby preventing the development of bony deformity secondary to abnormal muscle pull and contracted tendons and joints. As younger children tend to have more spasticity and less fixed-deformity than older children, they respond better to injections of BTX-A. Before injection, clinical examination must be directed specifically towards differentiating spasticity from fixed contracture, although minimal degrees of contracture may improve with BTX-A injections. It is hoped, but not proven, that in young children the instigation of all elements of non-operative management such as physiotherapy, casting, orthotics and spasticity management including the use of regular BTX injections may delay or decrease the need for surgical intervention reserving single-event multi-level surgery for fixed musculotendinous contractures and bony deformity in the older child.

In the lower limb, several randomised, double-blind, placebo-controlled trials have proved the short-term efficacy and safety of BTX-A in the management of spasticity, with improvements in deformity and gait. In the spastic hemiplegic or diplegic child, a dynamic equinus gait or the equinus component of more complex gait patterns can be helped by injection of gastrocsoleus. If this fails to correct an equinovarus deformity fully, tibialis posterior can be injected or, if more appropriate, tibialis anterior.

Similarly, overactivity of the hamstrings can be improved by injection of BTX-A and the response to injection may also help to predict the results of hamstring lengthening or adductor tenotomy. Injection of the hip flexors is more technically demanding and may require ultrasound guidance for the accurate localisation of the muscle, and hence the toxin. Overall, it is disappointing when reports fail to define which muscles within the adductor or hamstring group have been injected and which technique has been used.

The complex gait patterns shown by children with cerebral palsy often require treatment at multiple levels in a manner similar to the development of the single-event multilevel surgery strategy. Each muscle must then receive a dose adequate for a clinical response and yet care must be taken not to exceed the recommended total-body dosage. Alternative neuromuscular blocking agents, such as 50% concentrated alcohol solution, can be used for any remaining muscle injections. In clinical terms, the effect of such a multilevel approach may be equivalent to a medical rhizotomy.

In children with total-body involvement, treatment of adductor spasticity can lead to improvements in positioning, perineal hygiene, and orthotic tolerance. In patients with progressive subluxation of the hip, symptoms of pain and stiffness can be improved by the injection of the involved adductors and iliopsoas, when combined with bracing of the hip in abduction. A reduction in, or stabilisation of the hip migration percentage may occur, especially in a child under the age of two years whose initial subluxation shows a migration percentage > 30%. The concomitant use of a plaster cast with BTX injections is quite common, although its use as a method of applying stretch at the time of the injection is illogical since the reduction in stretch reflex and spasticity has not yet had time to develop. One recent publication has shown that the equinus associated with considerable soft-tissue contractures is worsened when BTX-A is added to a serial casting regime. If BTX-A injection alone is used in patients with fixed contractures, severe spasticity or mixed hypertonia, who cannot tolerate serial casting well, it is unlikely that significant improvement in movement will occur.

There are few randomised trials in the current literature which have examined the efficacy of BTX-A in the upper limb, but Corry et al and Fehlings et al found improvements in spasticity and the range of movement in joints in the upper limb with BTX-A, although the numbers of patients were small. The results of BTX-A injection on spasticity of the upper limb are less consistent and may be related to inaccuracy of the placement of the needle in the smaller muscles of the forearm and hand, and weakening of neighbouring muscles by diffusion of toxin. A recent Cochrane collaborative review concluded that there was insufficient current evidence to support the efficacy of BTX-
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A as an adjunct in the treatment of the upper limb in children with cerebral palsy and called for further research. Other indications for BTX-A in cerebral palsy include post-operative or post-treatment control of pain. The medium- and long-term effects of the use of BTX in cerebral palsy are as yet unknown. Concerns include atrophy of muscle fibres and potentiation of muscle weakness, particularly in children with pre-existing weakness masked by spasticity.

Other conditions of the central nervous system

Multiple sclerosis. Nearly all patients with multiple sclerosis develop spasticity at some stage and the use of BTX has been recommended for relief from pain, improvement in the range of movement, specifically related to perineal hygiene, and for management of dys-synergia of the bladder musculature.

Stroke. The management of the hemiplegic limb secondary to a stroke is similar, in some respects, to that of a child with cerebral palsy and improvements in the pain associated with spasticity, the range of movement in the joints and function of the upper limb have been noted after BTX injections.

Head injury. In both adults and children, BTX injections have been used to try and alter the natural history of the condition. In a randomised, clinical trial examining the prevention of equinus deformity in the acute phase after a head injury, the use of BTX injections did not add to the benefit seen with early, active intervention with physiotherapy and splinting. However, once an equinus posture had developed, BTX injections improved gait and the range of movement.

Spinal injury. In this group of patients, BTX injections are used most frequently to aid the control of bladder function. Injections have also been used for relief from pain and the avoidance of joint contracture and muscle shortening.

Other paediatric orthopaedic conditions

Congenital talipes equinovarus. The rationale for the use of BTX in congenital talipes equinovarus assumes that a reduction of tone in the most contracted muscles may facilitate their lengthening by manipulative stretching. Initial reports using injections into tibialis posterior, the gastrosoleus complex and other muscles in both infant feet and post-surgical relapses were encouraging. More recently, Alvarez et al treated the gastrosoleus muscle complex of 51 patients with 73 idiopathic club feet with BTX-A as an alternative to tenotomy of tendo Achillis after a course of manipulation and Ponseti casting. One foot ‘failed’, requiring a tenotomy, and 12% of the feet relapsed as a result of non-compliance with bracing. It was suggested that the use of BTX-A produced satisfactory results with less skin scarring and deep tissue fibrosis than a percutaneous tenotomy of tendo Achillis. By contrast, a recent prospective, randomised, double-blind study of 20 newborn infants with congenital talipes equinovarus found no significant difference between BTX-A and placebo in conjunction with serial manipulation and casting with respect to the speed of correction, the need for percutaneous tenotomy and the risk of relapse. Further studies are therefore required to resolve this conflicting evidence.

Idiopathic toe walking. BTX-A injection into gastrocsoleus, in conjunction with immediate casting in 10˚ of dorsiflexion for one week, has been used effectively in the treatment of idiopathic toe walking. In this study, toe walking had resolved in all ten treated patients at three months after injection. Eight of the ten patients maintained normal walking for up to 18 months. In a more recent study, five children who were idiopathic toe-walkers and had been treated with gastrosoleus BTX-A injections, achieved a normal gait pattern both clinically and on electromyography, with the improvement persisting when reviewed after 12 months.

Congenital muscular torticollis. This common form of torticollis in children presents as an idiopathic tightness of the sternocleidomastoid muscle without a palpable sternomastoid tumour. When conservative treatment is ineffective, surgery is considered but BTX-A may be an additional option. Joyce and de Chalain reviewed retrospectively 15 children with idiopathic tightness who had been treated with BTX-A injection and subsequent additional physiotherapy after a poor response to conventional physiotherapy and stretching exercises. Good improvement in the range of movement of the neck and in position of the head, thus avoiding the need for surgical release was achieved in 14 children. In another retrospective series, Oleszek et al reviewed 72 children with idiopathic sternomastoid tightness treated with BTX-A injections into the sternomastoid and/or the upper trapezius muscles, observing improvement in cervical rotation or head tilt in 20. Two had transient side-effects, specifically mild dysphagia and weakness of the neck.

Acquired muscular torticollis. In adults, acquired muscular torticollis is often secondary to dystonia or one of the myofascial pain syndromes. Both can be treated reliably, if temporarily, with injections of BTX.

Neonatal injury to the brachial plexus. Unwanted muscular co-contraction or inappropriate activation of antagonist muscles can hamper co-ordinated movement, such as hand-to-mouth movements, in children with severe neonatal brachial plexopathy. BTX-A injections have been used successfully to inhibit such co-contractions in biceps and triceps, and activation of antagonist muscles such as the adductors and internal rotators of the shoulder in the rehabilitation of such patients. Recently, BTX-A injections into the internal rotators of the shoulder, namely pectoralis major and/or latissimus dorsi, have been shown to be a useful adjunct to the primary and secondary surgical treatment of brachial plexus birth injuries, with significantly higher grades of shoulder function in the 74 patients treated with BTX-A in comparison with the 74 without BTX-A at a minimum follow-up of two years. It is hoped that the
early treatment of certain infants with obstetric brachial plexus palsy with BTX injections may result in stronger, normal muscles and may prevent the development of glenoid dysplasia, secondary to an unbalanced muscle pull on immature bones.

**Other indications**

**Pain syndrome.** The study by Barwood et al\(^31\) which found a significant reduction in post-operative pain in children with cerebral palsy secondary to a reduction in muscle spasm, has implications for the management of pain secondary to muscle spasm in other circumstances. After the use of BTX injections, the relief from pain is usually due to its direct effect on the pain fibres. There is also some evidence to support the use of BTX in certain patients with whip-lash-associated disorders and low back pain.

**Lateral epicondylitis.** Morre, Keizer and van Os\(^74\) first reported the use of BTX-A in the management of lateral epicondylitis in 14 patients with chronic symptoms resistant to non-operative treatment. The common extensor origin was injected and relief from pain in more than 50% on a self-assessment scale was achieved for three to four months in nine patients, with pain disappearing completely in four. This prompted a randomised, controlled trial by the same group, comparing injection of BTX-A and surgical release with 20 patients in each group.\(^75\) Similar results were found between surgery and injection with respect to subjective (e.g. visual analogue scores of pain) and objective (e.g. grip-strength testing) outcomes for up to two years after treatment, suggesting that BTX-A was equally as effective as surgery, but less invasive.

Two more recent investigations have cast doubt on the validity of these results. Hayton et al\(^76\) in a double-blind, randomised, controlled trial involving 20 patients in each group comparing BTX-A injections with injections of normal saline at the site of maximum tenderness, found no significant difference with regard to grip strength, pain, or quality of life at three months. In a larger, double-blind, randomised, controlled trial Wong et al\(^77\) compared BTX-A and placebo injections and found lower pain scores in the BTX-A group at three months, but no change in objective measures such as grip strength. Significantly, four patients experienced weakness of finger extension at four weeks in the BTX-A group, whereas no cases of paresis were observed in the placebo group.

At present, there is insufficient long-term evidence to support the use of BTX-A in the management of lateral epicondylitis.

**Tendon repair.** A recent report described the use of BTX injections to ‘protect’ flexor tendon repairs in zone II and to aid post-operative rehabilitation in a group of seven young children.\(^78\) The authors believe that BTX injections could serve as an alternative or adjunct to current regimes of rehabilitation in children or other patients in whom compliance with conventional management may be difficult.

**Conclusions**

Botulinum toxin is undoubtedly a powerful neurotoxin which, potentially, has many uses within the field of musculoskeletal medicine, but much remains to be learnt with respect to the most appropriate method of delivery of the toxin to the neuromuscular junction. Similarly, although its chemodenervation effects are well recognised, the most appropriate indications for its use still require further study.

**References**


