Clinical use of botulinum toxin

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Summary

Botulinum neurotoxin type A inhibits the release of acetylcholine from cholinergic motor and autonomic nerves. Intramuscular injection leads to muscle relaxation, and intradermal injection reduces sweat gland secretion. The recommended dose depends on which preparation of botulinum toxin type A is used and its dilution, the size of the muscle or gland being injected, and the method used to localise the injection site. Repeat doses are usually required as the effect of the toxin wears off after 3–4 months. Therapy including stretching, splinting and strengthening may prolong the effect of muscle relaxation. Realistic goal setting before treatment is vital.

Key words: muscle spasticity, neurotoxins.

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Introduction

Botulinum neurotoxin was first identified in 1897 and is a product of *Clostridium botulinum*, an anaerobic bacterium which causes botulism food poisoning. During the 1940s, botulinum toxin type A was purified and isolated in a crystalline form. In 1989 the US Food and Drug Administration (FDA) approved botulinum toxin type A for the treatment of strabismus, blepharospasm and hemifacial spasm. It has since been approved for cervical dystonia, hyperhidrosis and cosmetic use. There are now over 30 conditions in which botulinum toxin type A has been reported to be of benefit.

Mechanism of action

Botulinum neurotoxin type A blocks neuromuscular conduction by inhibiting the release of acetylcholine from motor or autonomic nerve terminals. Injected intramuscularly, it produces a localised chemical denervation of the muscle, resulting in localised muscle weakness or paralysis. When injected intradermally, the toxin produces chemical denervation of sweat glands and reduces local sweating. The denervation is reversible. Nerve endings recover over three or more months during which muscle tone increases and glandular secretion recommences.

Botulinum toxin products

There are two different preparations of the type A toxin commercially available in Australia; these are a purified neurotoxin complex (Botox) and a haemagglutinin complex (Dysport). They are dispensed in vials as a vacuum dried powder which is reconstituted with sterile normal saline. Once opened, vials should be stored in the refrigerator and used within 24 hours. The potencies of both preparations are expressed as units of activity, which relate to the median lethal dose in mice. The biological activity for each preparation is unique, so one unit of the neurotoxin complex is not equal to one unit of the haemagglutinin complex. As the potency and safety of these products differ, dose finding on a case by case basis may be necessary if both products are used in the same patient.

Another botulinum toxin type A product (Xeomin) is formulated without complexing proteins and has been approved for use in several European countries but not in Australia. It has recently been shown to be of benefit for focal dystonia and spasticity.

Botulinum toxin type B (Myobloc) is rarely used in Australia. It has been reported to be beneficial in adults with cervical dystonia who have developed resistance to botulinum toxin type A.[1]

Clinical indications

Considering whether to start a patient on botulinum toxin depends on balancing the risks of treatment against the potential improvements in active and passive function, level of pain, secondary effects of unwanted muscle overactivity and quality of life. In Australia, specialist medical practitioners such as ophthalmologists, neurologists, surgeons, rehabilitation specialists and paediatricians may access the government's Section 100 scheme. This provides reimbursement for the cost of botulinum toxin type A for the following conditions:

- blepharospasm
- spasmodic torticollis
- dynamic equinus foot deformity associated with cerebral palsy in children two years or over
- spasticity following stroke.

Botox is also approved for the treatment of strabismus in children and adults, focal spasticity of the limbs, primary hyperhidrosis of the axillae, and spasmodic dysphonia. Botox and Dysport are both approved for the treatment of glabellar forehead lines.

Blepharospasm

In blepharospasm and hemifacial spasm, botulinum toxin type A is administered by subcutaneous injection medially and laterally into the junction between the preseptal and orbital parts of the

upper and lower orbicularis occuli muscles of the eyes. Risks include corneal exposure due to reduced blinking and acute angle closure glaucoma due to the anticholinergic effect.[2]

Cervical dystonia (spasmodic torticollis) [3]

Patients with cervical dystonia have abnormal twisting or sustained postures of the head, neck and shoulders. Botulinum toxin type A is injected into the neck muscles to reduce pain and head rotation. Depending on the head position, a combination of the sternocleidomastoid, splenius, paravertebral, scalene and trapezius muscles may be injected. More than 50% of patients will have significant improvements in symptoms. Dysphagia is the most commonly reported adverse event, which in severe cases may lead to aspiration pneumonia.

Focal hand dystonia (writer's cramp) [4]

Focal hand dystonia is a task-specific dystonia that may affect people who perform repetitive movements for sustained periods. The goal of treatment is to reduce the dystonic posture and improve function. The effect may not be as good when the goal is improvement of complex fine motor tasks, such as occurs with musicians. Electromyography or electrical stimulation is used to guide injections, and correct muscle selection is vital for a good outcome.

Hyperhidrosis [5]

Hyperhidrosis is a condition of excessive sweating of the axillae, palms and soles of the feet. Causes of secondary hyperhidrosis such as hyperthyroidism should be excluded before starting treatment. Botulinum toxin type A is injected intradermally and adverse events are rare.

Spasmodic dysphonia (focal laryngeal dystonia) [6]

Vocal cord spasm, typically adductor muscle spasm, may interfere with communication, and responds to botulinum toxin type A injections. Spasm of the abductor muscle also occurs but may be less responsive to botulinum toxin type A treatment. Laryngoscopy and electromyography are needed for diagnostic evaluation and injection. Injection of laryngeal muscles should be avoided in patients requiring a general anaesthetic for elective surgery.

Focal spasticity

Spasticity is one component of the upper motor neurone syndrome and is defined as a velocity dependent increase in muscle tone. Botulinum toxin type A is often used for managing hypertonicity in conjunction with other treatments such as splinting, stretching and strengthening antagonist muscles.

Children

Ideally, children receiving treatment should have access to a multidisciplinary clinic where other interventions for spasticity can be considered. The largest group of children receiving botulinum toxin type A for spasticity are those with cerebral palsy. Treatment has been shown to be effective in reducing equinus gait pattern in these children (injections to calf, hamstring and hip flexor muscles), improving upper limb function (injections to shoulder, elbow, wrist and finger flexor muscles), reducing pain (injections to hip adductors) and reducing the need for orthopaedic surgery.[7,8,9,10] Children with dystonia may also improve with botulinum toxin type A treatment, although muscle selection and dosing is clinically challenging.

Children with spasticity and minimal contracture, who have functional or care goals, may benefit from treatment as early as 12–18 months. In general, botulinum toxin type A is less effective, particularly in the lower limbs, beyond the first decade.

Adults

Spasticity in adults is seen most commonly after acquired brain injury, stroke, multiple sclerosis and spinal cord injury. Setting goals before treatment, along with the pattern of affected muscle groups and the tone abnormality, determines muscle selection. Early treatment with botulinum toxin type A after stroke has been shown to reduce disability and carer burden.[11,12]

Cosmetic use

Botulinum toxin type A is used for treating glabellar lines (corrugator or procerus muscles), crow's feet (lateral fibres of orbicularis oculi muscle), and forehead lines (frontalis muscle).

Other uses

Botulinum toxin type A has also been shown to be of clinical benefit for patients with Parkinson's disease by reducing jaw tremor and excess salivation.[13] It has been used to relieve sensory and motor symptoms associated with tics, Tourette's syndrome and restless legs syndrome, and for patients with migraine, drooling or neurogenic bladder.

Administration

Before injection the toxin is diluted, usually with 0.5–5 mL of saline per vial. The extent of dilution affects the spread of the toxin once injected and will vary depending on a number of factors including:

- the condition being treated
- the size of the muscle being injected
- the risk of spread beyond the muscle
- the effect of previous injection courses
- the methods used to determine the injection site.

There are several ways to localise the muscle or gland to be injected. Palpation and anatomical landmarks are no longer considered best practice for treatment of focal spasticity.

Electrical stimulation, electromyography, ultrasound or a combination of all three, are generally used for localisation of the muscle and neuromuscular receptors.

During the procedure, which may involve multiple injections, the patient needs to remain relatively still. Children should receive analgesia and sedation. In Australia, several centres perform injections when the child is under general anaesthesia, while others use conscious sedation (either inhaled nitrous oxide or intranasal fentanyl). Topical anaesthetic gel may be sufficient for adolescent and adult patients.

Research has suggested that specific uptake of botulinum toxin type A into the nerve terminal, with less systemic spread, may be improved by activating the muscles soon after the injections. This can be achieved by passively moving the injected limb, using electrical stimulation, or by having the patient exercise the limb.

Safety

Adverse events tend to occur 1–2 weeks after injection and are usually transient. Localised pain, tenderness or bruising may be associated with the injection. Rare events include skin rash, pruritus and allergic reaction. Children sometimes experience transient incontinence, local weakness or in rare cases more generalised weakness. Local weakness represents the expected pharmacological action of botulinum toxin type A, but may be in excess to what is desired clinically. Overdose may present with symptoms of botulism, including ptosis, diplopia, deterioration in swallowing and speech, generalised weakness and respiratory failure.

There have been reports of deaths in children and adults following treatment with botulinum toxin type A. Some of the patients had major risk factors including significant swallowing problems, seizures and cardiovascular disease. Caution is recommended in children and adults who are significantly debilitated or have risk factors such as severe dysphagia.

Botulinum toxin type A is contraindicated in patients with known hypersensitivity and in patients with myasthenia gravis, Eaton-Lambert syndrome or who are pregnant (pregnancy category B3). It is also contraindicated if there is infection at the proposed site of injection. Botulinum toxin type A may interact with medications that affect neuromuscular transmission including aminoglycosides or curare-like compounds. The potential for interaction with these drugs may be up to 3–6 months after administration of botulinum toxin. Toxin preparations contain albumin, which carries a theoretical risk for transmission of viral or prion diseases.

Lack of response

Explanations may include inadequate dose, inappropriate muscle selection or injection site, underlying muscle changes (such as contracture), or neutralising antibodies to the toxin. As botulinum toxin type A is derived from foreign proteins, there is potential for the body to mount an immune response which may reduce the therapeutic benefit of treatment. To avoid this, botulinum toxin type A injections should be given at least three months apart.

Conclusion

Botulinum toxin is used for an increasingly wide range of clinical problems, principally related to muscle or sweat gland overactivity. The effect is temporary, lasting 3–6 months. Adjunctive therapies such as stretching or strengthening of antagonist muscles may allow for more sustained functional improvements after the biological effect of the botulinum toxin has ceased. Adverse effects are uncommon and usually temporary, although more serious effects including generalised weakness and dysphagia have been reported.

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Further reading

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Both Allergan and Ipsen have supported research conducted in Dr Scheinberg's department and in which he was a researcher.

Self-test questions

The following statements are either true or false (answers on page 55)

5. The two botulinum toxin type A formulations available in Australia are bioequivalent.
6. Drooping eyelids may indicate an overdose of botulinum toxin.

Book review

Therapeutic Guidelines: Psychotropic. Version 6.

Melbourne: Therapeutic Guidelines Limited; 2008. 325 pages. Price $39, students $30, plus postage. Also available in electronic format as eTG complete.

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Many general practitioners have a full set of Therapeutic Guidelines on their shelf or computer. With a veritable rainbow of useful guides (there are now 14 in the series), the challenge for a generalist is to ensure the pearls of wisdom they contain are used regularly and efficiently. So when a new edition of a guideline arrives, my approach is to scan through the contents and the tables in the appendix, before checking out the chapters on conditions I encounter frequently in my practice.

On reviewing the latest edition of Psychotropic Guidelines, it took me a while to determine which sections had undergone the 'major revision' promised on the Therapeutic Guidelines website. There has been a reorganisation of chapters, with the useful 'Getting to know your psychotropic drugs' still prominent in the guide. The large table in previous editions listing potential drug interactions has been omitted, so one has to look up individual medications for this information. Presumably many interactions listed in the old table were not clinically significant, although it's worth heeding the warning on page 1 that not all interactions are listed and that one should refer to the Australian Medicines Handbook or http://medicine.iupui.edu/flockhart for more information.

The most useful tables in the new edition are the 'switching' table (for checking antidepressant-free intervals when changing antidepressants, pages 112–3) and the table that differentiates features of selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome, adverse effects of SSRIs, symptoms of depression, and serotonin toxicity (pages 4–5). Distinguishing between these conditions can be quite tricky in general practice, where patients often stop their medications without telling their doctor.

A drawback of the Psychotropic Guidelines is that it gives diagnostic advice in some sections, but these comments cannot replace a full mental health assessment in all patients before prescribing. Similarly, while there is advice about medication adherence and duration of therapy, there is limited advice on frequency of follow-up, and no reference to monitoring tools. These are not major omissions for a guide that is predominantly about prescribing medications, but prescribers should not rely on the Therapeutic Guidelines for assessment and management (as opposed to simply prescribing) advice.