

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Botulinum toxin type A

Botulinum toxin is the most potent naturally occurring neurotoxin known, with a median lethal dose of about 1 ng/kg. It is estimated that a few hundred grams could theoretically kill every human on earth. The toxin causes flaccid paralysis of skeletal muscle by blocking pre-synaptic release of acetylcholine from nerve terminals. After binding with high affinity to receptors on nerve endings, the toxin penetrates the cell membrane by receptor-mediated endocytosis and then crosses the endosome membrane by pH dependant translocation. When it reaches the cytosol, the toxin acts as a zinc dependant endoprotease to cleave polypeptides that are essential to exocytosis. In the absence of these peptides, nerve impulses can no longer trigger the release of acetylcholine. When injected intramuscularly at therapeutic doses botulinum toxin Type A produces a localised, partial and reversible chemical denervation of the muscle and localised muscle paralysis.

Two formulations of botulinum toxin are available in Australia for therapeutic use: Botox® and Dysport®. They are both Type A Botulinum but are derived from different strains, and have different molecular weights and are manufactured differently. Due to the lack of an international unit, the two formulations of botulinum toxin are not therapeutically equivalent.

Botulinum toxin use in the cosmetic industry is well known, and its application to reduce fine lines and wrinkles has a temporary effect on the aging face. It has also a number of medical applications and is available as a subsidised section 100 item on the Australian Pharmaceutical Benefits Scheme. Botox® is approved for use for the treatment of blepharospasm associated with dystonias and hemifacial spasm in patients over 12 years, and to treat paediatric cerebral palsy patients over two years of age with dynamic foot deformity, and also to treat patients with spasmodic torticollis. Dysport® is also approved for treatment of moderate to severe spasticity of the upper limb in adults post stroke. Botulinum toxin is also used intradermally to treat primary hyperhidrosis of the axillae.

Side effects of botulinum toxin include generalised weakness, fatigue, pain and swelling at injection site. Some more serious adverse effects include anaphylaxis, dysphagia, pneumonia and aspiration pneumonia. There have been some deaths reported after treatment with botulinum toxin.

Other applications for use of botulinum toxin are currently under investigation. Phase III clinical trials are currently underway in Australia investigating the efficacy of botulinum toxin (Botox®) for the treatment of urinary incontinence caused by neurogenic detrusor overactivity in patients who have not been adequately controlled with oral anti-cholinergic therapy. These trials are specifically aimed at spinal cord injury patients and patients who have multiple sclerosis. A series of injections are given throughout the lateral and posterior walls of the bladder via cystoscopy. Patients are assigned 1 of 2 doses of Botox® (200 units or 300 units) or placebo. Results from clinical trials conducted overseas have shown improvements in key uro-dynamic parameters in treatment groups compared to placebo.

The evidence for use of botulinum toxin type A in managing overactive bladder symptoms is becoming more established and further work is required to define outcomes in reference to duration of benefit and therapeutic effect.

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