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REVIEW

Botulinum toxin for treatment of glandular hypersecretory disorders☆

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Summary The use of botulinum toxin to treat disorders of the salivary glands is increasing in popularity in recent years. Recent reports of the use of botulinum toxin in glandular hypersecretion suggest overall favourable results with minimal side-effects. However, few randomised clinical trials means that data are limited with respect to candidate suitability, treatment dosages, frequency and duration of treatment. We report a selection of such cases from our own department managed with botulinum toxin and review the current data on use of the toxin to treat salivary gland disorders such as Frey's syndrome, excessive salivation (sialorrhoea), focal and general hyperhidrosis, excessive lacrimation and chronic rhinitis.

Botulinum toxin is a neurotoxin that inhibits presynaptic acetylcholine release by nerve endings thereby interfering with nerve impulses. Acting at the neuromuscular junction it leads to loss of myogenic tone, whereas in glandular tissue it inhibits cholinergic sympathetic nerve function. In 1895, Emile Van Ermengem first isolated the bacterium *Clostridium botulinum* from which the toxin is derived but it was not until 1949 that investigators determined the ability of the toxin to block neuromuscular transmission.[1] Strains of the *Clostridium botulinum* bacterium produce seven antigenically distinct neurotoxins, serotypes A–G. Each neurotoxin consists of two polypeptide chains linked by a disulfide bond.

The first therapeutic use of the agent was by Scott in 1973 to treat strabismus. FDA approval for botulinum toxin A came in 1989 and covered its use in specific neurological disorders: blepharospasm, strabismus, and hemifacial spasm in patients over 12 years old. In 2002 it was licensed for use in the reduction of moderate to severe wrinkles although it had been used for many years prior to this. Botulinum toxin is being increasingly used in the treatment of several disorders characterised by inappropriate or excessive muscle contraction, including stroke, cerebral palsy, multiple sclerosis, hemifacial spasm, torticollis, dystonia, anal fissures and benign prostatic hyperplasia. It

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has also become an important agent in the management of a number of opthalmological disorders including paralytic strabismus, esotropia or exotropia.[2]

The ability of botulinum toxins to inhibit parasympathetic and sympathetic cholinergic transmission prompted further investigations into their use in related conditions. A number of autonomic disorders resulting in glandular hypersecretion, such as excessive axillary and palmar hyperhidrosis, sialorrhoea and gustatory sweating, respond well to botulinum toxin injections. The response in some cases seems to be much longer lasting than when used as a muscle paralysing agent.[3] Such positive reports have fuelled interest in the broader application of botulinum toxin to include management of chronic rhinitis, hyperlacrimation and rare cases of focal hyperhidrosis.[3–5] We review the use of botulinum toxin in disorders of glandular hypersecretion and report the cases of six patients treated in our department. We include a case of the successful treatment of a patient with chronic parotitis, an application of botulinum toxin that is rarely reported.

Hyperhidrosis

Hyperhidrosis is defined as excessive and unphysiological sweating caused by overactivity of the eccrine sweat glands of the skin. It has been reported to affect 2.8% of the population with a typical childhood onset. It may be generalised or focal, commonly affecting the axillae, palms and soles. The majority of patients with hyperhidrosis have morphologically normal sweat glands but which respond abnormally to stimulation of the hypothalamic sweat centres. Hyperhidrosis significantly impacts on patients lives, socially and psychologically. The condition may be primary (idiopathic) or secondary to a number of medical conditions or pharmacological agents and attempts should be made to identify reversible conditions prior to treatment. Several different agents have been used with variable success in the management of hyperhidrosis. Systemic medications, including beta blockers and anticholinergic agents, have limited efficacy and substantial side-effects, including orthostatic hypotension, dry mouth and blurred vision.[6] Recently, botulinum toxin has been used with good results. Heckmann studied 145 patients with axillary hyperhidrosis unresponsive to traditional topical therapies. Botulinum toxin injections resulted in significant reduction in mean sweat production which persisted to 24 weeks after the injection.[7] In subsequent investigations low (100 iu) and high (200 iu) dosage regimens have proven to have similar efficacy.[8] One study demonstrated both objective and subjective improvements in sweating with improved quality of life scores.[9] A significant reduction in axillary sweating when the toxin was applied in a topical formulation has also been observed.[10] Further studies have indicated comparable efficacy and safety using two of the most popular commercial agents.[11] It appears from these reports that botulinum toxin is an efficacious treatment for axillary and palmar hyperhidrosis. Most studies determine it to be a safe treatment. However occasional adverse side-effects have been reported, most commonly pain associated with palmar injections, which may limit its use.[9,12]

Frey's syndrome

Frey's syndrome is an uncommon disorder that arises from injury to or surgery near the parotid gland, damaging the secretory parasympathetic fibres of the facial nerve. It is believed that after injury these fibres regenerate and miscommunication occurs between them and the severed postganglionic sympathetic fibres that supply the cutaneous sweat glands and blood vessels. This aberrant connection results in subjective gustatory sweating and facial flushing which appear with mastication. Duphenix has been credited with originally describing gustatory sweating in 1757. However it was Lucja Frey, a Polish neurologist, who defined the underlying pathophysiological mechanism when she observed the phenomenon in a soldier with a gunshot injury to his parotid gland.[13] Frey's syndrome as a complication post parotidectomy has been reported to be between 4% for benign disorders and 20% in surgery for malignant disease. It is believed that objective gustatory sweating as proven by Minor's starch-iodine test occurs in a much larger percentage of patients but only a small number consider it troublesome.[14] Over the years a range of treatments have been tested including topical anticholinergics such as scopolamine or hyperhidrotics. A variety of surgical procedures have also been described: resection of the auriculotemporal nerve, excision of the affected area of skin, interpositional dermal grafts and radiotherapy.[15–18] Intradermal injection of botulinum toxin is now considered the treatment of choice for this condition. A good number of clinical studies have reported significant responses to first and subsequent treatments.[19–22] All studies reported that treatment was well tolerated with no side-effects. One prospective study demonstrated increased effectiveness with a higher concentration of botulinum toxin A over a lower concentration (20 MU/ml versus 10 MU/ml).[21] Taylor et al. demonstrated no significant differences in treatment outcome in relation to gender, operative procedure or postoperative radiation.[22] One investigator reported it to have no effect on facial flushing while another reported flushing to regress post treatment.[21,23]

Sialorrhoea

Sialorrhoea, or excessive salivary secretion, can be a significant problem for patients with a range of neurological disorders such as cerebral palsy, multiple sclerosis or post-cerebrovascular event. Incompetent control of oral, facial or neck musculature leads to pooling and spilling of salivary secretions and may cause maceration of the skin, infection and increased risk of aspiration. Drooling is a stigmatising problem which impedes social integration, negatively impacts self esteem and increases the burden on the caregiver. The majority of salivary secretions are contributed by the parotid and submandibular glands which provide 80–90% in equal proportions. Similar to the eccrine gland, salivary secretion is under sympathetic and parasympathetic innervation. Treatment of excessive salivation often begins with conservative measurements (i.e. postural changes, biofeedback exercises) with progression to medications. The usefulness of anticholinergic drugs, as with hyperhidrosis, is often limited by adverse side effects or toxicity. On occasions

when hypersialorrhoea is intractable, the more drastic treatment of radiation or surgery to the salivary glands is undertaken. The use of intraglandular injection of botulinum toxin in this setting has been reported by a number of investigators. The majority cite significant reductions in drooling.[24–26] O'Flaherty et al. also demonstrated a considerable improvement in quality of life assessment scores in a study involving children with cerebral palsy.[24] Studies evaluating botulinum toxins in management of drooling associated with Parkinsonism have also reported significant improvements with no worsening of dysphagia in treated patients.[25] Similar results were shown in a study including patients with motor neuron disease.[26] Overall results are positive with very few reported side-effects in any study.

Epiphora

Epiphora, or watery eyes, is caused by either overproduction of tears or inadequate drainage of the lacrimal system. Gustatory epiphora, also known as crocodile tears, is a syndrome associated with excessive tear production occurring on eating or smelling food. This typically follows Bell's palsy or a cerebrovascular event, involving the proximal facial nerve or its nucleus. Treatment ultimately depends on identification and targeting of the underlying cause. A small number of case studies have reported beneficial effects of intraglandular injection of botulinum toxin (confirmed by Shirmer test differences).[4,27,28] Reported side effects included mild ptosis and diplopia which resolved spontaneously. Once again, the long-term efficacy, side-effects and ideal dosage regimens have yet to be determined. However botulinum toxin has been suggested as a promising treatment for those with resistant cases of excessive tearing or irreparable damage to the lacrimal drainage system.

Rhinorrhoea

Nasal hypersecretion generally occurs in association with allergic or infective rhinitis or may be primary (vasomotor rhinitis). Allergic rhinitis commonly responds to avoidance of the offending irritant, with/without decongestants and antihistamines. Infective rhinitis is typically viral but may trigger a superimposed bacterial infection. Treatment is generally symptomatic with addition of appropriate antibiotics in cases of secondary bacterial infection. Vasomotor rhinitis is a chronic condition characterised by intermittent vascular engorgement of the nasal mucous membrane leading to watery rhinorrhoea and sneezing. Aetiology is uncertain, and no allergy can be identified. Treatment traditionally involves trial and error and is not always satisfactory. Both animal and human studies[29–31] have reported a demonstrable benefit to botulinum toxin injections into the lower and middle nasal turbinates. The less invasive local application of toxin-soaked sponges has also proven successful.[32,33]

Sialadenitis

Inflammation of a salivary gland may be acute or chronic and most commonly involves the parotid. Causes range from simple infection to autoimmune disorders. Acute sialadenitis is usually secondary to infection, the most common organisms being *Staphylococcus aureus* or *E. coli*. The chronic form of the condition is associated with pathologies linked to decreased salivary flow (calculi, salivary stasis), with superimposed infection. Management approaches range from conservative measures (maintenance of hydration, oral hygiene, antibiotics), to more invasive surgical methods (injection of methyl violet — a sclerosing agent, ductoplasty, ductal ligation, tympanic neurectomy). Rarely, due to its associated morbidity, parotidectomy is undertaken. There are very few reports of botulinum toxin use in these disorders. Ellies et al. reported the successful reduction of salivary flow in patients with chronic sialadenitis with minimal side effects. The average duration of effect was 3 months.[34]

Case 1

An 80-year-old male had a wide excision of a malignant melanoma excised from his left preauricular area to include a superficial portion of the left parotid. The defect was reconstructed with a split-skin graft. His wounds healed well but he developed gustatory sweating in the region of the graft. Intradermal injection of 200 U (1 ml) of Dysport® (botulinum toxin A) was administered to the affected area using a sterile 25 gauge needle (0.1 ml/cm^2). The patient reported an excellent response to the first treatment within 1 week and subsequent treatments were repeated at 6-monthly intervals.

Case 2

A similar case involved a 71-year-old male who had wide local excision and superficial parotidectomy for a melanoma involving his left ear with local nodal metastasis. Two years after his surgery he began to experience gustatory sweating on his left cheek. The area was injected intradermally with Dysport® (200 U) to which he responded well and two further treatments were administered at 4-monthly intervals.

Case 3

A 16-year-old male experienced extensive sweating localised to an area over his left shoulder. This had been present since childhood and was exacerbated by exercise. He was initially treated with topical aluminium chloride hydrohexate therapy with limited effect and subsequently with botulinum toxin injections. Botox® (100 U; 4 ml) of (botulinum toxin type A) was injected intradermally to an area measuring 20 cm^2 (0.2 ml/cm^2) using a 25 gauge needle. He had a very impressive response to the initial injections within 3 days and required just one further treatment. Minor's iodine-starch test was performed prior to injection to delineate the affected area (Figure 1).

Case 4

A male infant with severe hypoxic ischaemic encephalopathy suffered profound generalised hypotonia, seizures and

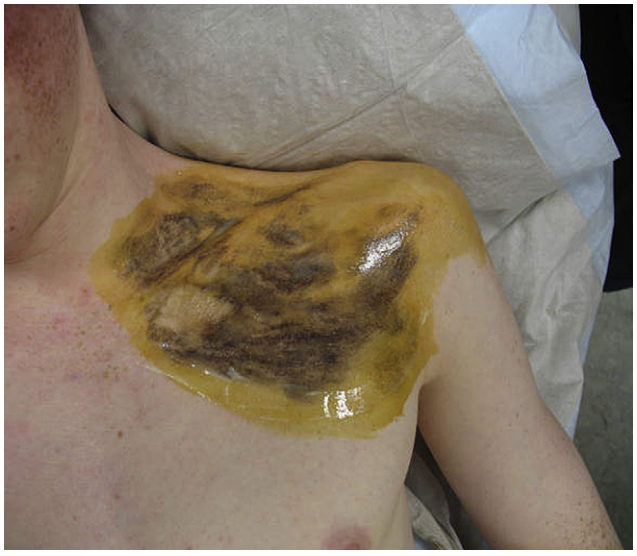

Figure 1 Minor's starch-iodine test in a 15-year-old male with excessive hyperhidrosis of his left shoulder area.

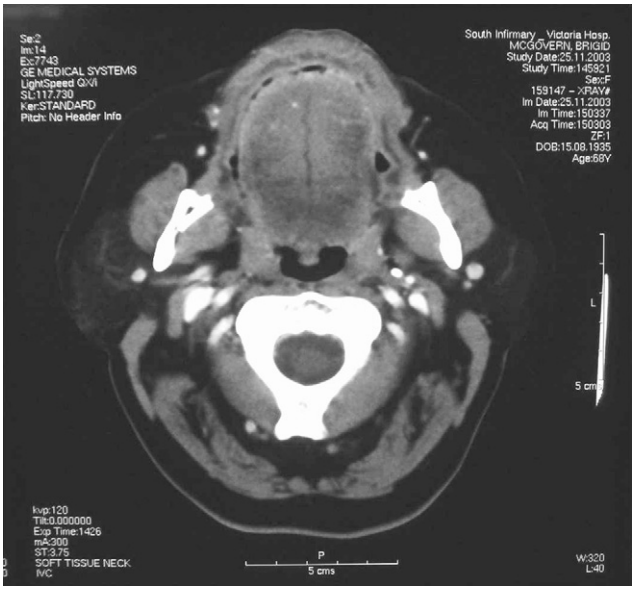

Figure 2 CT of parotid glands demonstrated prominent ductal system consistent with sialectasis.

persistant drooling. At 12 months he developed difficulty maintaining his airway secondary to excessive oral secretions manifesting in intermittent cyanotic episodes which were extremely distressing for both himself and his parents. He was treated with a hyoscine patch. His seizure activity worsened and increases in phenobarbitone led to a further increase in oral secretions. Intraglandular injection of 400 U Dysport® using a 23 gauge needle was attempted at this stage and this reduced secretions slightly over subsequent weeks. He had further reduction of secretions with glycopyrolate therapy.

Case 5

A 49-year-old male post total laryngectomy presented with excessive oral secretions and recurrent leaking of a speaking valve. His symptoms were due to a tight pharyngo-oesophageal segment. Under fluoroscopic guidance 200 U Dysport® was injected directly into the tight segment using a 22 gauge spinal needle. A good result was obtained with immediate improvements in voice quality and management of secretions.

Case 6

A 70-year-old female presented with intermittent right cheek swelling, pain and tenderness occurring intermittently over a 3 year period. Computerised tomography (CT) of sinuses demonstrated increased density of the right parotid gland with slight prominence of the ductal system which contained small calculi (Figure 2). A diagnosis of sialectasis was made and a course of antibiotics was prescribed. The condition persisted over the next 2 years despite numerous courses of antibiotics and anti-inflammatories and the option of surgery was considered at one point. A trial of botulinum toxin injections was then undertaken. Dysport® (200 U) was injected into the right parotid gland using a sterile 23 gauge needle. A favourable response was noted within 1 week of the injections with resolution of pain and symptoms for 3 months. A further course of treatment was administered which completely relieved her symptoms.

In the above cases 500 U vials of Dysport® were reconstituted using 2.5 ml normal saline with minimal vial agitation. 100 U vials of Botox® were reconstituted with 4 ml normal saline. It is important to note that doses for Dysport® and Botox® are not interchangeable. Studies have shown that Dysport® dose equivalents to Botox® range from a 3:1 to 4:1 ratio.

Discussion

The indications for the use of botulinum toxin are ever increasing to include a great variety of glandular secretory conditions. Despite the sparsity of randomised trials, the consensus is that it is generally a very effective treatment with minimal side-effects. However, studies are still necessary to determine optimum dosing and treatment schedules and to analyse long-term outcomes. Side-effects reported mainly relate to pain on injection. In the treatment of disorders of muscle contraction injection must be repeated at 3—4 monthly intervals often indefinitely. Because of this up to 10% of patients eventually develop antibodies to the toxin; this occurs more frequently in those who receive larger doses at more frequent intervals. This resistance is believed to result from the production of antibodies to the toxin over time. From the current reports this does not appear to be a problem in glandular disorders. It may be that its efficacy and ability to completely resolve many cases within three to four treatments preclude its use for periods long enough for antibodies to develop. However this could only be demonstrated by controlled trials.

The above cases illustrate some of the current uses of botulinum toxin. Its use in Frey's syndrome, hyperhidrosis

and sialorrhoea are well documented.[7,8,19,20,24] However we report one of the very few documented cases demonstrating its application in parotitis.[35] Recently anti-inflammatory properties of botulinum have been suggested through inhibition of the neuropeptide substance p. A role for substance p has been proposed in a variety of chronic inflammatory disorders and pain. This effect may well underly its successful use in chronic inflammatory glandular processes such as sialadenitis and hidradenitis suppurativa. Furthermore, botulinum toxin may revolutionise the management of pathologically related conditions such as dacrocystitis (infection of the lacimal sac) for which it has not yet been tried. Controlled studies for botulinum toxin in many of these conditions may, however, ultimately prove to be unobtainable because of the limited incidence of these disorders. However, the successful use in individual cases and small series encourages ongoing investigation of botulinum toxin therapy in these difficult conditions.

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