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Short Communication

Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity

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Introduction

Botulinum neurotoxin A (BTX) has been used in a growing number of indications for the treatment of muscle spasticity including detrusor sphincter dyssynergia in patients with neurogenic bladder dysfunction.[1,2] Recent articles describe its use for the treatment of neurogenic detrusor overactivity as after a spinal cord lesion.[3–4]

The advantage of this treatment is the local administration, on the site of muscle hyperactivity, without the generalised effects of muscle relaxants that are orally administered and therefore can lead to systemic side effects.

However, in our experience we had two cases of severe generalised muscle weakness after injection of BTX in the detrusor muscle. These cases are reported here.

Case 1:
A 57-year-old woman, paraplegic Thoracic 9, ASIA-Frankel A for 11 years complained of severe bladder hyperreflexia and regular attacks of autonomic dysreflexia. She had been treated with oxybutinine, tolterodine and an indwelling transurethral and afterwards suprapubic catheter without great success. She was treated twice with an injection of BTX in the detrusor muscle. During the first session 500 units were injected (Dysport®) but no amelioration of bladder capacity or reduction of dysreflexia was observed. In a second session 3 months later, a dose of 1000 units of BTX (Dysport®) were injected. Again no increase of bladder capacity or decrease in dysreflexia was noted. However the patient developed general muscle weakness for around 3 months, which caused her severe difficulties for transfers out of the wheelchair.

Case 2:
A 24-year-old man, tetraplegic C8-T1, ASIA-Frankel A, for 9 years, complained of urinary incontinence despite the intake of different anticholinergic drugs and intermittent self-catheterisation six times a day. Urodynamic tests showed severe bladder overactivity, detrusor sphincter dyssynergia and high pressures in the bladder at low filling. He received 300 units BTX (Botox®) in 30 injections divided over the bladder wall outside the trigone. Within 2 weeks he experienced a general weakness of the arm muscles and a loss of general condition which substantially influenced his transfers and his participation in sports activities. He lost his qualification for the Paralympics. This muscular weakness lasted for 3 months when he slowly regained his original strength. The bladder spasticity had been almost completely abolished after the injection but reappeared within 2 months.

Discussion

The clinical treatment of neurogenic bladder overactivity by endoscopic injection of botulinum toxin in the detrusor muscle of patients with a spinal cord lesion was first described by Schurch *et al*.[3]

The Clostridium botulinum that produces the toxin secretes several serotypes which all have a heavy and a light chain linked together by a bisulphide bridge. With the heavy chain the toxin binds to the muscle cell

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surface and helps the light chain to migrate through the cellular membrane. Inside the muscle cell, the light chain acts as a zinc-dependent endopeptidase that splits several proteins needed for the fusion of neurotransmitter vesicles with the cell surface, thereby blocking the neuromuscular end-plate. This process takes about 1 week to complete. The toxin thus interferes with nerve transmission by blocking the liberation of acetylcholine.[5] Functional recovery after BTX is due to the formation of new neural sprouts.[6] This normally takes at least 2–3 months in striated muscles but probably takes much longer in smooth muscles as much longer clinical effects have been described when injections of BTX are given in a smooth muscle such as the detrusor. Up to now only the serotype A is commercially available. There exist two varieties: Botox®, produced in the United States (Allergan Inc, Irvine, California, USA) and Dysport®, produced in Great Britain (Porton Down, UK). It is generally assumed that the activity of 1 unit of Botox equals 3–5 units of Dysport.[7]

The known side effects of botulinum toxin: nausea, vomiting, dry mouth, dysphagia, weakness of the respiratory muscles and paresis have not been described in patients treated locally for detrusor sphincter dyssynergia.[8] However weakness or pathological EMG changes in muscles distal to the injection site have been reported in different applications.[9–10] Caution is needed in patients with impaired neurotransmission such as with myasthenia gravis, or taking aminoglucosides or other drugs that may interfere with neurotransmission.[11] Our patients described here did not have such drug intake nor did they have such predisposing conditions.

The effects of purified BTX type A on cholinergic, adrenergic and non-adrenergic, atropine-resistant autonomic neuromuscular transmission have been documented.[12] Apart from the effects on striated muscles, a relaxing effect of the bladder with increasing residual urine was described after injection of 12.5 ng Dysport® in the adductor muscles.[13] Transient paralysis of the bladder was described recently due to wound botulism.[14]

It is clear that with more generalised exposure to BTX, autonomic and somatic side effects may occur. The two patients described here, who suffered general muscle weakness after treatment for bladder overactivity with injection of BTX in the detrusor muscles, each received a different type of BTX. The reason why these side effects occurred are not clear. One was treated with a dose within the accepted range while the added dosage given to the first patient on two occasions was normal but the cumulative dosage might be rather high. It is noteworthy that in both patients the result on the detrusor activity was limited and/or short. Was the bladder wall, especially between trabeculation bars, too thin so that diffusion perivesically occurred together with a limitation of the local effect? Though the cause is uncertain, it seems obvious that in these two patients the expected tight binding of the toxin locally, which would prevent passage in the circulatory system, and resultant systemic side effects did not work.[15]

There is a definite need for close observation of general effects, and for studies on the optimal dose and the optimal injection technique in this type of treatment. Meanwhile, patients should be warned that temporary general muscle weakness may occur.

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