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*Case report*

# Has botulinum toxin type A a place in the treatment of spasticity in spinal cord injury patients?

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**Objective**: To present and discuss treatment of severe spasms related to spinal cord injury with botulinum toxin type A.
**Design:** A 2-year follow-up study of an incomplete T12 paraplegic patient, who was reluctant to undergo intrathecal baclofen therapy, presenting severe painful spasms in his lower limbs treated with intramuscular injections of botulinum toxin type A.
**Setting**: Department of Physical Medicine and Rehabilitation, Hôpital de Gravelone, Sion, Switzerland.
**Subject**: Single patient case report.
**Main outcome measure**: Spasticity, spasms and pain measured with the modified Ashworth scale, spasm frequency score and visual analogue scale.
**Results**: Treatment of spasticity with selective intramuscular injections of botulinum toxin type A resulted in subjective and objective improvement.
**Conclusion**: Botulinum toxin type A has its place in the treatment of spasticity in spinal cord injury patients. This treatment is expensive and its effect is reversible. It can complement intrathecal baclofen in treating upper limb spasticity in tetraplegic patients. Tolerance does occur to the toxin. Although high doses of the product are well tolerated, the quantity should be tailored to the patient's need. The minimal amount necessary to reach clinical effects should be adhered to and booster doses at short period intervals should be avoided.

**Keywords:** spinal cord injury; spasticity; botulinum toxin type A; baclofen; infusion pumps

## Introduction

Spasticity is a major factor in the management of patients with a variety of chronic neurological disorders. Spasticity is caused mainly by interruption of the pyramidal pathways producing increased gamma motor neuron activity due to the release of descending inhibition. It is accompanied by increased muscle tone and enhanced stretch reflexes. The final pathway is excessive involuntary contraction of muscles. Problems stemming from spasticity include pain, restricted range of motion, clonus, overwhelming muscle antagonism, and intermittent spasms. Spasticity may also result in poor hygienic care and causes difficulty in fitting braces and urinary catheterization. Spasticity also negatively impacts on patient's quality of life: selfcare, sleeping patterns, cosmetic, self esteem, mood, pressure sore prevention, and sexual function. Physiotherapy plays a major role in the management of spasticity which is frequently accompanied by muscle weakness. Reducing spasticity may be helpful in alleviating pain, discomfort, and abnormal posture but may also reduce muscle strength. This can make standing or walking more difficult, as some patients may be relying on spasticity to perform these functions. Treatments currently available for spasticity include oral medications, surgical procedures, intrathecal infusion of baclofen (ITIB) and intramuscular injection of botulinum toxin type A (BTX) produced by Clostridium botulinum. Oral medications have a general effect and may fail to reduce spasticity significantly. Side-effects include sedation and generalized weakness. Antispastic agents and physiotherapy fail to provide satisfactory control in 25 to 35% of patients.[1] Nerve root sections, myotomy, and tenotomy carry surgical risks, and recurrence of spasticity is unpredictable.

A rational approach to the treatment of the extrapyramidal syndrome of dystonia and the pyramidal deficit would be to administer a drug that possesses a highly specific site of action, a sustained duration of activity and a high efficacy. Intramuscular botulinum

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toxin meets these criteria. Other potential advantages of BTX include the lack of sensory effects, ability to target specific muscle groups, absence of caustic chemicals such as phenol and the ability to weaken muscles in a graded fashion to achieve a maximal therapeutic outcome that is tailored to each patient and to each neurological problem. The most potent form of relief for spasticity is intrathecal infusion of baclofen. With ITIB, the muscle tone is lowered symmetricaly beneath the level of the catheter tip and it is not possible to target single muscle or muscle groups. Since its use in 1978 for therapeutic purposes in humans,[2] botulinum toxin type A has found a wide range of applications from blepharospasm to Parkinson's rigidity and tremor.[3–5]

## Case report

A 50 year-old obese man with severe psoriasis vulgaris and multiple food, pollen, and drug allergy had a T12 fracture with incomplete T12 paraplegia (ASIA impairment scale = C) in 1976 following a motorcar accident. Soon after the accident he developed spasticity in his lower limbs with frequent painful spasms predominantly at night and with cold humid weather. Diazepam had to be interrupted because of allergy. Muscle relaxants (baclofen and tizanidine) were tried unsuccessfully because of irregular therapeutic dosages due to the patient's fear of drug allergies, dry mouth and headaches.

During 1994 the spasms became more frequent and bothersome. They involved the calf and peroneal muscle groups as well as the dorsiflexors muscles of toes causing knee flexion, foot flexion-eversion and toes extension. These spasms affected more the left leg and were severe in the big toes. They caused a fracture of the proximal phalange of the right big toe and damaged his shoes which had to be changed frequently. As the patient was reluctant to have intrathecal baclofen delivery, he was treated with botulinum toxin type A.

Between October 1994 and September 1996 the patient had eight treatments with Botox® (Allergan Inc.-USA). EMG guidance is not required for injection into most muscles. However, it can facilitate the injection of deeper muscles and help to identify challenging hyperactive muscles. Motor points of selected muscles were first identified using Perotto's anatomic guide for the electromyographer.[6] A disposable Teflon coated hypodermic needle with a bared tip supplied by Allergan, connected to a muscle stimulator using single twich mode, was used for muscle identification and toxin injection. The dose of toxin injected in each muscle was divided between two and four sites depending on muscle size with higher doses for larger muscles. This was our first paraplegic patient to be treated with BTX. In the first settings we injected only both gastrocnemius muscles. Later on, different muscles were injected according to the localization of spasticity and the patient's complaints. The quantity of the toxin delivered in each muscle depended on the effect obtained from the previous setting and the muscles treated were not necessarily always the same (Table 1).

Clinical evaluation included spasticity using the Modified Ashworth Scale (MAS),[7] spasms using the

**Table 1** Dates of treatment, muscles injected and doses. Patients evaluation: 2 = good effect, 1 = moderate effect, 0 = no effect

| | *Date of injection* | *Total U* | *Muscles injected* | *Units* | *Evaluation* |
|---|---|---|---|---|---|
| 1 | 10.10.1994 | 100 | 2 heads of left gastrocnemius (GN) | 2 × 50 | 2 |
| 2 | 12.12.1994 | 100 | 2 heads of left GN | 2 × 50 | 1 |
| 3 | 13.05.1995 | 200 | 4 heads of GN* | 4 × 50 | 2 |
| 4 | 19.06.1995 | 200 | left tibialis ant | 50 | 2 |
| | | | left peroneus tertius | 50 | |
| | | | left extensor digitorum longus | 50 | |
| | | | left extensor hallucis longus | 50 | |
| 5 | 10.07.1995 | 200 | 4 heads of GN* | 4 × 35 | 2 |
| | | | 2 soleus* | 2 × 30 | |
| 6 | 28.11.1995 | 300 | 4 heads of GN* | 4 × 30 | 1 |
| | | | 2 soleus* | 2 × 40 | |
| | | | 2 extensor hallucis longus* | 2 × 50 | |
| 7 | 03.05.1996 | 380 | 4 heads of GN* | 4 × 40 | 2 |
| | | | 2 soleus* | 2 × 30 | |
| | | | 2 peroneus tertius* | 2 × 30 | |
| | | | 2 peroneus longus* | 2 × 30 | |
| | | | 2 extensor hallucis longus* | 2 × 20 | |
| 8 | 20.09.1996 | 400 | 4 heads of GN* | 4 × 50 | 0 |
| | | | 2 soleus* | 2 × 50 | |
| | | | 2 extensor digitorum longus* | 2 × 25 | |
| | | | 2 extensor hallucis longus* | 2 × 25 | |

* = both sides

Spasm Frequency Score (SFS),[8] and pain using the Visual Analogue Scale (VAS) where 0 represents no pain and 10 represents pain as bad as it could be.[9] Medicine intake was recorded. Before Botox injections MAS was estimated at 2 to 3, SFS at 4 (ten or more spasms in the last 24 h) and VAS at 8. He took 150 mg tramadol and 10–12 mg of flunitrazepam daily (2–4 mg at bedtime) without any benefit. The effect of botulinum toxin appeared after 24–72 h and the patient was evaluated clinically 10–14 days later. The patient felt and slept better. He reduced his flunitrazepam consumption to 2–4 mg at bedtime. He decreased his daily wine consumption. Tramadol intake remained unchanged. He was less spastic (MAS = 1+ to 24), had fewer spasms (SFS =2: between one to five spasms a day) and less pain (VAS = 1). The patient also noticed that some of his daily living activities such as the transfers, putting on his trousers and shoes and managing toileting needs were less difficult. Moreover, he was able to sit for longer periods to achieve home tasks and did not have to buy new shoes during the observation period. There were neither systemic nor distant effects of local injections.[10–12]

## Discussion

Sleep disturbance is often a major source of discomfort and a major problem affecting the quality of life of patients suffering from severe lower extremity spasticity associated with spinal cord damage. Flexor spasms were reported by Little *et al*[13] to occur most frequently at night in 50% of the patients and during the morning in 15%. They interfered with sleep in 82% of the patients with incomplete lesions and 50% with complete lesions.

lntrathecal baclofen administration is a complex procedure and requires careful patient selection and close monitoring. Overdosage may result from too rapid increase in dosage, filling and programming error, and pump malfunction.[14–16] Withdrawal symptoms result more commonly from an empty reservoir or pump dysfunction, erroneous pump filling and programming, and may result from catheter problems such as a kink, break, leak, blockage and disconnection or dislodgement from the subarachnoid space.[1,17–30] The catheter is by far the most vulnerable part of the system with complications affecting as many as 40% of patients.[31] Patients missing scheduled appointments for refills may present withdrawal symptoms as well.[26,27] Increased spasticity with a functioning system may be related to drug tolerance. Often, the daily doses must be increased over time.[23,24,29] lntrathecal administration of baclofen can offer many advantages for patients who experience intolerable side effects at effective doses of oral medications. Delivering the medication directly to the target site means that cerebrospinal fluid levels can be much higher than with oral administration which crosses the blood-brain barrier poorly. In addition to long-term reduction of spasticity, ITIB also reduces pain, improves bladder function, decreases intolerable side effects, and improves the quality of life. When ITIB is considered, patients and family need to be informed of potential complications including unusual side effects and signs of possible infection. Patients need to be responsible. The pump needs to be filled every 6–12 weeks and changed every 5 years. Patients need to keep their appointment for refill to avoid empty pump with withdrawal symptoms (spasticity, agitation, fever, tachycardia). This therapy is cost effective with proper patient selection.

On the basis of studies with adult primates, the lethal dose of BTX by injection in humans has been estimated as approximately 1 ng (30–40 units)/kg of body weight, or 2500–3000 U for an adult of average weight.[32] Doses higher than 400 U per treatment should be avoided.[33] The clinical effects begin to appear within the first few days (24–72 h) after the injection, peak in approximately 4–6 weeks, and are sustained for 3–4 months. Some authors reported that the effect lasted longer, up to 15 months.[34–36] In patients with spinal cord injury, BTX has been used in detrusor-sphincter dyssynergia with good results.[37–41] As far as spasticity in those patients is concerned, we found only five reports in the literature mentioning the positive effect of botulinum toxin in six patients without further details. Indications for such therapy included severe lumbar paraspinal muscle spasms with backache[42-case 5], spasm of the adductor muscles of the thigh[42-case 9, 43-case 6], unspecified lower limb spasticity,[44] spastic foot drop[45-case 10] and painful myoclonus of the left quadriceps muscles.[46] When proximal adductor muscles of the thigh are injected, one must keep in mind the possibility of distant effect of botox on the bladder with increased post-voiding residuum as reported by Schnider *et al*.[47]

Antibodies to botulinum toxin are found in some patients after several injections and may be responsible for the tolerance to BTX. When a patient fails to respond to BTX therapy, both the patient and the treatment paradigm should be carefully examined to determine the reason for lack of response[48] (Table 2).

Several centers have reported the frequencies of BTX antibodies to vary from 3–11%, up to

**Table 2** Factors to be considered for primary and secondary non-responders

1. The dose may be too low.
2. Injection technique requiring some modification, i.e. EMG guidance.
3. Muscle weakness and/or atrophy.
4. Changes in pattern of muscle involvement during treatment
5. Inappropriate reconstitution or storage of toxin.
6. Neutralizing antibodies as confirmed by assay.

57%.[49–51] These patients received more frequent 'booster' injections 2–3 weeks after initial injections, and higher doses per treatment. Patients who develop immunoresistance to serotype A toxin may benefit from other serotypes of botulinum toxin, such as type B and F. Botulinum toxin type F was shown effective in the treatment of torticollis in patients who are immune to type A.[50,52]

Our patient weighing 116 kg tolerated very well Botox® and showed no side or distant effects. However, under treatment, during the period of May to July 1995 spasticity and spasms were important. There were no changes in the neurologic examination suggesting syringomyelia and there was no urinary tract infection or any other factor which could explain this phenomenon. The pattern of spasticity had also changed. These events as well as the patient mood and psychological status encouraged us to inject BTX at shorter intervals. There was 5 weeks interval between the 3rd and 4th injection and 3 weeks between the 4th and 5th. The patient responded well to treatment but for the last injection which remained without clinical effects. Unfortunately assays for BTX antibodies were not available and we do not know whether our patient did develop antibodies.

## Conclusions

Each of intrathecal infusion of baclofen and botulinum toxin type A has its place in the treatment of spasticity in spinal cord injury patients. The effect of each is reversible. Both treatments are expensive. Contrary to BTX, ITIB demands full understanding and collaboration of the patient. BTX can complement ITIB for example in treating upper limb spasticity in tetraplegic patients. Tolerance does occur to both botulinum toxin and intrathecal baclofen. Although high doses of BTX are well tolerated, doses should be tailored to patient's need. The minimal amount necessary to reach clinical effects should be adhered to and booster doses at short period intervals should be avoided.

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