Journal of Experimental and Clinical Medicine
Deneysel ve Klinik Tıp Dergisi

Case Report

Constipation after Botulinum Toxin - an Injection in Lower and Upper Limb Muscles: A Transitory Systemic Autonomic Adverse Effect Report of Three Cases

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ARTICLE INFO

Article history:
Received 20 / 06 / 2009
Accepted 26 / 06 / 2009

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Keywords:
Botulinum Toxin Type A
Adverse Effects
Constipation
Patient
Treatment
Muscle

ABSTRACT

We report three patients who developed transient constipation after receiving therapeutic doses of Botulinum Toxin-A (BTX-A) for spasticity of the lower limbs (two cases) and the upper limb (one case). Constipation was observed within the first week after treatment. In all three cases, this symptom resolved completely almost simultaneously with disappearance of the therapeutic effects of BTX-A on mobility. None of the patients had previously received BTX-A injections. Two patients received a second treatment and both presented the same autonomic cholinergic remote symptoms. The third patient refused a second treatment due to the complication noted earlier. Familiarity with this autonomic systemic side effect of BTX-A is essential for those who treat patients already at risk for gastro-intestinal dysfunction. Because the adverse effects were treatable and transitory, we believe that constipation per se is not an absolute contra-indication, if from a therapeutic point of view view, BTX-A is indicated.

Introduction

In the past 20 years, Botulinum Toxin-A (BTX-A) has been used for a wide spectrum of therapeutic and cosmetic indications, whether or not approved by the Food and Drug Administration (FDA). One of such indications not approved by the FDA, but widely studied and reported in the medical literature, is spasticity due to cerebral palsy (CP) or due to acquired brain injury.

Botulinum toxin prevents presynaptic release of acetylcholine at the neuromuscular junction and as a result chemodenervation develops in the injected muscle. The toxin, in therapeutic doses, is considered to be effective and safe. Remote adverse effects are rare and include flu-like symptoms, anaphylactic reactions and excessive fatigue. Treatment of spasticity due to CP with BTX-A may be limited by the escape of the toxin from the muscle causing local and distant side effects. Not only spastic patients who are treated with intrathecal Ba-clofen therapy11, but also those who are treated with BTX-A can develop constipation as a side-effect, although the pathologic mechanism is probably entirely different.

We report three cases of patients suffering from severe spasticity, who repeatedly experienced a period of constipation as an important and disabling systemic autonomic cholinergic side effect after BTX-A treatment for spasticity.

Case 1

An eleven-year old boy, suffering from spasticity and epilepsy due to CP, was referred to the outpatient clinic because of impaired mobility and nursing problems. Clinical examination showed a severely mentally handicapped boy, who was able to assist while being transferred from bed to wheelchair and even to make some steps if supported. Furthermore, body hygiene and dressing were hindered by hip adductor spasm. The possibility of treating the patient with BTX-A was discussed with his parents, and the following treatment goals were defined: to facilitate nursing and to improve mobility.

We determined the muscles to be injected by clinical examination. Spastic hypertonia of a specific muscle leading to functional limitation was the criterion to inject. Therapy was initiated with informed consent of the parents. The child received BTX-A injections under general anaesthesia in the day-care department (JV). The target muscles were identified by muscular electrical stimulation. Dysport from Ipsen was used according to the recommended maximum dosage: 23 IU/kg bodyweight, limited to no more than 400 units per limb, within an overall maximum dose of 1200 IU per session, with a dilution of 500 units in 2 ml NaCl 0.9%. The child's bodyweight was 25 kg. The adductor longus, semitendinosus, semimembranosus and soleus muscles were injected with 50 IU Dysport each, and the gastrocnemius muscle with 100 IU (total dose 600 IU). The patient was seen at our outpatient clinic at 6 and 12 weeks after the intervention. We evaluated the effect and side effects by means of a standardised questionnaire. Caregivers had to fill out a list with all side-effects possible. The Visual Analogue Scale (VAS), an ordinal scale that ranges from 0-10 with 0 being the optimal situation and 10 the worst situation, was also used to evaluate the intervention.12 During follow-up, the mother observed an improvement in mobility (pre-treatment VAS: 5, post-treatment VAS: 1.3) and facilitation in nursing (pre-treatment VAS: 4, post-treatment VAS: 2.2). However, as a remarkable side effect she reported severe constipation, starting 4 days after the treatment, for which medication (macrogolum) was necessary.

The positive effects on mobility and nursing facilities lasted for more than 3 months and with lessening of these positive effects, the gastro-intestinal dysfunction wore off. After 4,5 months the clinical therapeutic effect was no longer detectable and at the same time macrogolum could be withdrawn.

One year after the first intervention there was a new request for repeated treatment because of increasing nursing and mobility problems. After a careful examination and discussing the systemic side effect of constipation observed the first time, a decision was made to repeat the initial treatment. Under the same conditions and with a bodyweight of 30 kg, the same muscles were injected with the same dose. The defined goals were reached but the same systemic gastro-intestinal side effect of constipation was observed. Again, as the positive effects on mobility and nursing diminished, the side effect faded away.

Case 2

This 19-year-old male was admitted to the rehabilitation department four months after a severe head trauma with diffuse axonal injury leading to impairments of his cognitive functions, speech and locomotion. At admission the patient presented a tetraplegia with generalized spasticity (Modified Ashworth Scale - MAS - 2 and 3) of upper and lower limbs, accompanied by a severe diminished range of motion of the knee and ankle joints bilaterally. Orthotic treatment was initiated. The patient was unable to stand and walk and was dependent for all transfers. During the rehabilitation program he eventually developed painful spasms in both legs. Oral spasmolytic medication (Baclofen and Tizanidine) at maximal therapeutic doses was insufficient. Treatment with BTX-A was then discussed and the patient and his parents gave informed consent. He had never been treated with BTX-A before.

One month after admission, the patient received his first BTX-A injection (Botox® from Allergan). The semitendinosus, the semimembranosus and the biceps femoris muscles of the left leg were treated with 100 units of Botox® each; 300 units in total (maximum recommended doses by the manufacturer: 600 units) in a dilution of 100 units in 5 ml NaCl 0.9%. Approximately 6 days after the injections a significant reduction of the muscle tone of the left leg was observed. The painful spasms disappeared. About 10 days after the treatment the patient reported severe constipation accompanied by abdominal pain. Treatment with laxatives (Bisacodyl and lactulose) was necessary. After two months, the intestinal function improved and at the same time the therapeutic effect of BTX-A was reduced, although the range of motion could be maintained with orthotic support.

Four months after the first treatment a second treatment with BTX-A was given, aiming to reduce the severe hypertonia of the calf muscles of the right leg. The following therapeutic scheme was used, with the same dilution as before: gastrocnemius muscle: 140 units and soleus muscle: 60 units. Within one week after BTX-A treatment the muscle tone of the right lower leg decreased substantially and a corrective orthosis

for the ankle joint could be fitted. Almost simultaneously with the reduction of the muscle tone in the leg the patient again complained about constipation. He also reported tiredness and difficulty with swallowing. Treatment with laxatives was started again. After one month the constipation wore off and the medication could be withdrawn. This time the reduction of muscle tone lasted for six weeks after BTX-A therapy. Electromyography of distant muscles of the upper limbs could not be performed due to the severe spasticity.

In view of the generalized character of the spasticity it was decided to treat this patient with intrathecal Baclofen (ITB). After a successful therapeutic trial one year ago a Synchromed® infusion system was implanted. At the time of this report the spasticity remains under control (MAS 1) and so far no systemic complaints have been reported.

Case 3

A 19-year-old woman sustained severe brain injury after a ten meters fall. The Glasgow Coma Score at admission to the Intensive Care Unit was 6. Magnetic resonance imaging of the brain showed diffuse contusional lesions and oedema. Furthermore, she presented a lesion of the third cranial nerve and multiple fractures of the pelvis, left clavicle, acromion and several ribs. A splenectomy had to be performed due to a spleen rupture. The hospital stay was complicated by a pulmonary embolism and a deep venous thrombosis. She also developed heterotopic ossification at the left hip and the right knee. Half a year later, the patient was referred to the rehabilitation centre for further treatment. At admission the patient presented a hypertonic tetraplegia, with limited range of motion of the left elbow and both knees. She was not able to stand without support and was unable to walk even with walking aids or manual assistance. She was otherwise incontinent for urine and completely dependent for all daily activities, including eating and personal hygiene.

The MAS was 2 for the right arm, and 1 for the left arm and both legs. However, the spasticity of the left arm increased during the following months to a MAS 3, but patient's mother refused pharmacological treatment either with systemic spasmolytic medication or local neuromuscular blocks. Intensive physical therapy and orthotic management for the elbow and knee contractures resulted in a slight improvement of the range of motion of the right arm and the knees. Nevertheless, the muscle tone of the left arm increased further, causing painful spasms of the arm. Eventually, one year after trauma, patient's mother gave her consent for treatment of the left arm with BTX-A injections. Dysport® (Ipsen) was used in a volume of 2.5 ml per vial of 500 units. The left biceps muscle was injected in two sites with 150 units of Dysport® each and the brachioradial muscle with 200 units; 500 units in total.

The patient was evaluated two weeks after the injections. A remarkable reduction of the spasticity of the left arm flexors was seen (MAS 1). She was able to dissociate flexor and extensor movements selectively. However, the mother reported that three days after BTX-A treatment her daughter was hindered by severe constipation and was feeling more tired than usual. She also noticed that the speech articulation and the swallow function had become more difficult. At first, the constipation responded positively to treatment with Bisacodyl. However, the patient decided on her own to withdraw the medication and the constipation appeared again. After resuming the Bisacodyl one week later, the constipation wore off. These symptoms persisted during three months. The therapeutic effect on the left arm lasted for five months after the initial BTX-A treatment. Because of the aforementioned complication, the patient and her mother refused a second injection. At the last control, two years after trauma, the range of motion of the left arm was maintained with orthotic support and the elbow flexors showed a MAS of 2. She reported no gastrointestinal nor swallowing complaints.

Discussion

Although the therapeutic goals were reached in all three patients, they repeatedly showed severe constipation as an autonomic side effect after treatment sessions with BTX-A. As the colon is not in close proximity to the injection sites, this symptom is likely related to a systemic effect of BTX-A. We have performed this treatment in more than 50 children and more than 200 adults. After each intervention, a list with

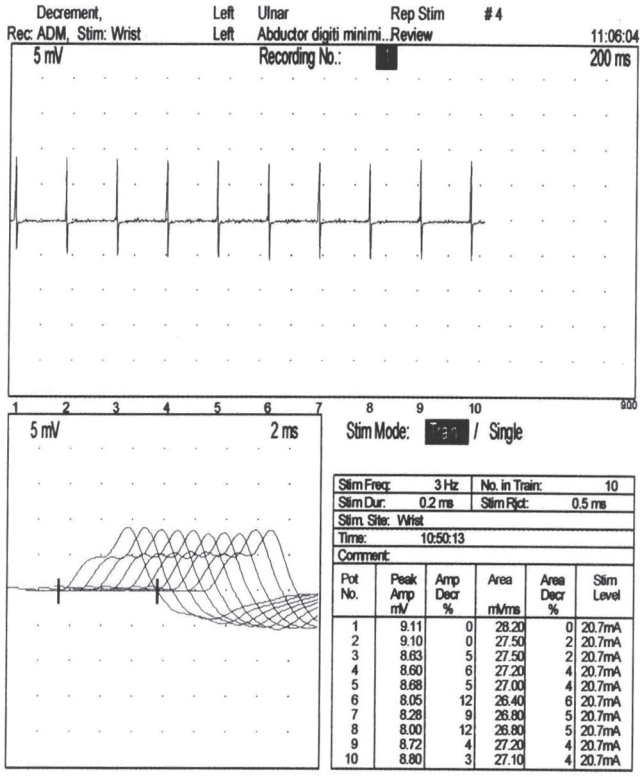

Fig. 1- In the first patient described a slow repetitive stimulation of a motor nerve (RNS) was performed in order to investigate the presumed systemic reaction on BTX-A. EMG recordings were made from the hypothenar while stimulating the ulnar nerve at the wrist. The amplitude of the initial response was normal, but after prolonged 3 Hz stimulation a slight decrementing response occurred. An average of 11% decrement in amplitude was visible from sixth to eighth compound muscle action potentials. This indicates that fewer muscle fibers responded to nerve stimulation during a train of stimuli, due to generalized blockage of acetylcholine release in nerve terminals. The patient did not show generalized weakness.

all possible side-effects had to be filled out by the patient or by the caregiver. All these data were entered into a database. Although in 10 patients side effects occurred, only in these three patients constipation was reported during evaluation. The action of BTX-A appears to be limited to cholinergic terminals where BTX-A inhibits release of acetylcholine and co-transmitters in both somatic and cholinergic autonomic terminals.8,9 In the first patient described a slow repetitive stimulation of a motor nerve (RNS) was performed in order to investigate the presumed systemic reaction on BTX-A

Electromyographic recordings were made from the hypothenar while stimulating the ulnar nerve at the wrist. The amplitude of the initial response was normal, but after prolonged 3 Hz stimulation a slight decrementing response occurred. An average of 11% decrement in amplitude was visible from sixth to eighth compound muscle action potentials. This indicates that fewer muscle fibers responded to nerve stimulation during a train of stimuli, due to generalized blockage of acetylcholine release in nerve terminals. The patient did not show generalized weakness.

The efficacy of BTX-A in children with adductor spasticity was demonstrated in a randomized controlled trial by Mall et al. using the Goal Attainment Scale.4 The safety profile of BTX-A (Dysport®) in patients with muscle hypertonia was retrospectively studied by Bakheit et al. and they reported adverse events in only 7% of treatment.13 Incidence of adverse effects was related to the total dose rather than the dose calculated on basis of body weight. The highest incidence of adverse events was observed in patients who received more than 1000 IU of BTX-A per treatment session. Constipation as a remote autonomic side effect was not reported in this publication.

Autonomic function as a measure of side effects using Dysport® in a range of doses (18-44IU/kg) was studied by Robertshaw et al.14 Their hypothesis was that BTX-A might reduce parasympathetic activity and, therefore, cardiac variability. They conclude that BTX-A is safe using the standard dosage. Only 1 out of 30 children had distant side effects, which lasted for 6 weeks. Constipation was not mentioned as a side effect.Autonomic side effects occur far more often after Botulinum Toxin-B (BTX-B)15 In a group of 30 patients (24 cervical dystonia; 6 hyperhidrosis) constipation was observed as a remote side effect in 3 patients.In a double blind randomized trial, autonomic function after BTX-A or B was studied in patients with cervical dystonia.16 More Patients treated with BTX-B showed constipation as compared to those treated with BTX-A (3/9 vs 0/11).In a retrospective study, constipation as a side effect of BTX-A (Botox®) treatment on upper limb impairment and function was observed in 1 of 18 patients (aged 2-17 years).17 Furthermore, severe dysphagia has been reported as a remote side effect of BTX-B treatment of the lower limbs and lumbar paraspinal muscles in a 29-year-old women.18Our patients showed constipation as an adverse remote effect in response to all interventions and did so repeatedly. To our knowledge this has not been reported before after treatment with BTX-A. An explanation for this individual sensitivity is difficult. Probably it is in line with the observed interpersonal variability in autonomic ratio (AR) as described by Robertshaw et al. studying the effect of BTX-A on ECG parameters.14 This study reported that the child suffering from distal side effects for 6 weeks, had the lowest AR. Dysfunction observed in the gastro-intestinal tract is not uncommon in neurologically handicapped patients. The enteric nervous system contains more neurons than the spinal cord.19 Therefore, it is not surprising that generalized insults to the central nervous system (i.e. asphyxia or ischemia) may result in significant neural dysfunction in the gastro-intestinal tract as is shown for the spinal cord.20 On the other hand, feeding and intake problems may result from various (motor) problems other than the increased muscle tone observed in these patients. However, from a clinical point of view there is a strong indication that the gastro-intestinal problems in these 3 patients appeared in connection with the BTX-A treatment.

Conclusion

We conclude that severe constipation may be an autonomic systemic side effect of BTX-A treatment due to blockade of autonomic neurons via systemic spread. Knowledge of this possible side effect is important for those who treat patients already at risk for gastro-intestinal dysfunction. A carefully taken clinical history during the treatment period makes prevention and management possible. Because the adverse effects were treatable and transitory, we believe that constipation per se is not an absolute contra-indication if, from a therapeutic view, BTX-A treatment is indicated.

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