117. Efficacy of repeated injections of Botulinum Toxin-A in patients with overactive bladder and idiopathic detrusor overactivity

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Introduction and objective: Botulinum Toxin-A (BTX-A) is emerging as an effective second-line treatment for idiopathic detrusor overactivity (IDO). However, little is known on its longer term effects. To further validate its use, we objectively assessed the efficacy of repeated intra-detrusor injections of BTX-A in patients with IDO.

Methods: 16 patients with proven IDO received repeated BTX-A injections (range 2–4, total number of injections 45). Outcome was assessed using urodynamics, voiding diaries and validated quality of life questionnaires (IIQ-7 and UDI-6) at presentation and then at 4, 12 and 24 weeks after each injection. Data were compared between the first and the last injections.

Results: The mean number of weeks between the 1st and 2nd, 2nd and 3rd, and 3rd and 4th injections was 57.0, 52.3 and 33.3, respectively. After both the first and the last injections there were significant improvements in urodynamic, IIQ-7, UDI-6 and OAB symptoms compared to baseline. No significant difference was found when comparing the data 12 weeks following the first and last injection for mean cystometric capacity ($p = 0.98$), reflex detrusor volume ($p = 0.55$), detrusor compliance ($p = 0.065$), maximum detrusor pressure ($p = 0.9$), frequency ($p = 0.38$), urgency ($p = 0.41$), urge urinary incontinence ($p = 0.1$), UDI6 ($p = 0.7$) and IIQ7 ($p = 0.7$).

Conclusion: BTX-A appears to have a sustained efficacy following repeated administration in patients with IDO.

All the authors are investigators for Allegan.

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118. The effects of repeated dosing of botulinum toxin type B (neurobloc®) in patients with cervical dystonia previously naïve to botulinum toxin: An open-label extension study (AN072-402 EU/CD)

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Objective: To evaluate the safety and efficacy of repeated doses of botulinum toxin type B (BoNT-B) in patients with cervical dystonia (CD) previously naïve to BoNT.

Methods: BoNT-naïve CD patients completing a double-blind, comparator (BoNT-A vs. BoNT-B) phase continued in this open-label (OL) extension study. All OL patients received 10,000 U BoNT-B. Investigators could then modify dose by 5000 U increments/decrements during the subsequent 5 sessions (range 5000–25,000 U). Efficacy was assessed via Patient Global Visual Analogue Scale (VAS), and safety by evaluating adverse events (AEs), clinical laboratory data and vital signs.

Results: 94 patients (45 and 49 had received BoNT-B and BoNT-A, respectively, during the previous double-blind study) were enrolled. 55 patients (58%) completed 6 OL treatment sessions (TS). Reasons for withdrawal included: AE ($n = 4$); transportation/lost to follow-up ($n = 11$); lack of efficacy ($n = 9$); subject/sponsor decision ($n = 11$); or other ($n = 4$). Mean BoNT-B dose at TS 6 was 15,170 U (range 5000–25,000 U). BoNT-B demonstrated statistically significant benefit at Week 4 in the Patient Global VAS following each TS injection. No drug-related serious AEs were reported. Four subjects experienced 9 AEs leading to withdrawal: only dry mouth in 1 subject and fatigue, anorexia, influenza-like illness, and nausea in another subject were considered study drug-related. Moderate or severe dysphagia and dry mouth occurred in 9.6% and 16.0% of patients, respectively. No clinically significant changes in laboratory values or vital signs occurred.

Conclusions: Repeated administration of BoNT-B provided persistent benefit and was well-tolerated in patients with CD previously naïve to BoNT treatment.

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Keywords: Botulinum toxin type B; Cervical dystonia; Clinical
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119. High doses of NT 201 (xeomin®) do not alter gastro-intestinal motility

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10 male Sprague Dawley rats per group received a single dose of either sterile physiological saline with 0.1% human serum albumin or NT 201 in doses 8, 16 or 32 LDU/kg by i.m. injection. An i.m. injection of 20 mg/kg morphine served as positive control. At 4 days after administration of NT 201 or vehicle paralysis was assessed, before the rats received a charcoal meal of 2.5 mL of 10% charcoal suspension in 5% arabic gum in sterile water. Morphine-treated rats got the charcoal meal 45 min after the injection. The NT 201 dose range and timing of the charcoal meal administration was based on a dose-range-finding study conducted prior to this study. At 20 min after administration of the charcoal meal, animals were sacrificed and the distance travelled by the charcoal in the GI tract was assessed. Intestinal transit was expressed as percentage of the total intestinal tract length. Paralysis of the injected hind limb was confirmed in all rats treated with NT 201 4 days after i.m. injection right before the charcoal meal. NT 201 administered i.m. at doses of 8, 16 and 32 mg/kg did not statistically significantly affect the intestinal transit. The positive control morphine induced a significant inhibition of charcoal meal propulsion.

In this study the NOAEL of single i.m. injection of NT 201 for effects on gastro-intestinal motility in rats is at least 6 times higher than the max. recommended clinical dose.

Keyword: Xeomin
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120. Clinical application of *Clostridium botulinum* type A neurotoxin purified by a simple procedure for patients with urinary incontinence caused by refractory detrusor overactivity

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Type A neurotoxin of *Clostridium botulinum* was purified by a simple procedure using a lactose gel column. This procedure was previously reported for type B neurotoxin. Hemagglutinin-positive toxins (19S and 16S) were bound to the column under acid conditions, and the neurotoxin alone was dissociated from these hemagglutinin-positive toxins by changing the pH of the column to an alkaline condition. The toxicity of this purified toxin preparation was retained for at least 1 year at ?30 °C by supplementing it with either 0.1% albumin or 0.05% albumin plus 1% trehalose. This preparation was used to treat 18 patients with urinary incontinence caused by refractory idiopathic and neurogenic detrusor overactivity; 16 of the patients showed excellent improvement. Improvements started within 1 week after injection in most cases and lasted 3–12 months.

Keywords: Neurotoxin; Purification; Therapy; Urinary incontinence; Detrusor overactivity
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121. Gastrointestinal tract

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The use of botulinum toxin for treatment of spastic disorders of the GI tract has gained widespread acceptance over the last 15 years, especially in the treatment of chronic anal fissures and achalasia. More recently, its use has also been explored in obesity, with some studies reporting impressive short-term outcomes. In other disorders, BoNT administration may be most useful in "ruling in" a disorder. As in SOD and pelvic floor dyssenergia, a positive response to BoNT may indicate the correct diagnosis and potential treatment strategies. A non-response may direct further investigations to other diagnoses. From a scientific perspective, much needs to be learnt about both the mechanism of action and the long-term effects of BoNT in the unique environment of the enteric nervous system. There are several important differences between this system and that of the skeletal neuromuscular junction, and this provides both a challenge and an opportunity for further research. This will further our understanding of the toxin itself as well as point to new therapeutic targets.
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122. Differentiated botulinum toxin treatment of sialorrhea in 15 patients suffering from Parkinson's disease, MSA, PSP, and brain injury in early childhood

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The question is as follows: Is it possible to apply specific approaches with BoNT for the various diseases that can cause sialorrhea?

We examined 15 patients who were seriously affected by sialorrhea. Three diagnostic groups were involved: Parkinson's disease (PD) ($n = 8$), brain injury in early childhood (BI) ($n = 5$) and two patients with MSA and PSP, respectively. Our first step was BoNT treatment of parotid glands (PG); if this did not show adequate results, submandibular glands (SM) and sublingual (SL) glands were injected as well. All of the PD patients experienced reduced salivation after only one injection into their PG. None of these cases showed the required subjective benefits; the actual reduction was still inadequate. Subsequent injection of only the SM resulted in clearly reduced salivation in all of the 8 patients. In the group of patients with BI, treating only the PG, or the SM, respectively, did not produce adequate results. Injecting both salivary glands finally resulted in beneficial effects for the patients. Additional injections into the SL did not lead to any further improvement. Successful BoNT treatment of sialorrhea in patients with PD (predominantly production at rest) can be accomplished with injections into only the SM. Patients with BI will need injections into the PG and the SM.

Keywords: Sialorrhea; Botulinum toxin
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123. The lowest effective dose of botulinum toxin in detrusor sphincter dyssynergia

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Detrusor sphincter dyssynergia is a spastic condition due to lack of coordination between the bladder and the external sphincter. It results in excessive bladder pressures and inability to empty the bladder completely. Botulinum toxin type A has been injected either transurethrally via cystoscope or transperineally under electromyographic control. The dose and dilution volume vary from author to author. This was a prospective, randomized, double-blind, dose-ranging clinical trial to define the lowest effective dose of botulinum toxin type A and