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Editorial: Toxins 2015

This special supplement to *Toxicon* is dedicated to the platform, podium, and poster abstracts submitted for the international conference "TOXINS 2015: Basic Science and Clinical Aspects of Botulinum and Other Neurotoxins," to be held in Lisbon, Portugal, January 14–17, 2015.

The rate of scientific and clinical investigation on botulinum and other neurotoxins has continued to accelerate rapidly, making it especially challenging for clinicians and medical professionals to keep pace with developments in the field. The TOXINS 2015 conference is the definitive forum for providing the latest information about the science and therapeutic use of neurotoxins.

Major topics included on the conference program and reflected in this publication include advances in knowledge of the mechanisms of action, structure, and pharmacology of the botulinum neurotoxins; updates on the use of the toxins for headache, genitourinary conditions, spasticity, cerebral palsy, and dystonias; investigational applications; and controversies and unresolved issues in the use of the botulinum neurotoxins.

Unfortunately, not all participants have been willing to allow publication of their abstracts due to unhappiness about Elsevier's behavior, and *Toxicon* is an Elsevier publication. A politically biased letter was published in *Lancet*; the editor now regrets the publication, but it has not been retracted and Elsevier has not issued any statement of their position on the matter.

I trust that you will find this supplement to be a useful aid in enhancing your research pursuits or medical practice involving the use of botulinum and other toxins.

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some data that standard physical therapy (Novak 2010) can improve treatment outcome, acting on sensorimotor relearning. However, the functional changes in brain activation and connectivity related to these treatments have not been fully elucidated (Delnooz 2013). We evaluated the duration of efficacy of combination treatment with botulinum neurotoxin (BoNT) and motor relearning techniques (MRT) in a case of cervical dystonia (CD), using a multiparameter approach.

Methods: A 56-year-old woman with CD (left torticollis) was evaluated before (T0) and after treatment (T1, after 40 days, and at follow-up [FU] after 3 months). The treatment consisted of BoNT injection and a combined biofeedback and spatial relearning (SaM Method) exercises. Outcome measures were Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Visual Analog Scale (VAS) for pain, neurophysiologic analysis with electromyography (EMG) mapping of cervical muscles and kinematic study of cervical region, and functional connectivity at rest (resting-state functional magnetic resonance imaging [fMRI]) among the nodes belonging to the default mode network (DMN).

Results: The following significant intervention related changes were observed: reduction of neck rotation at rest more evident at T1 (30°) than FU (16°); clinical scale score improvement (TWSTRS from T0=49/85 to T1=30.5/85 and 40/85 at FU; VAS from T0=8/10 to T1=2/10 to FU=1). The fMRI results showed asymmetric connectivity between the 2 hemispheres at T0, T1, and FU. We observed an increased functional connectivity at T1 among the posterior cingulate cortex (PCC), right lateral parietal and left lateral parietal lobes, which is preserved at FU, even if the correlation values begin to decrease, mainly between the 2 lateral parietal lobes.

Conclusions: Sensorimotor clinical and neurophysiologic parameters and fMRI results support the notion that a combined treatment has long-lasting effects in improving motor functioning in patients with CD by restoring motor control.

Keywords: Botulinum toxin; Cervical dystonia; Functional connectivity; Motor relearning techniques

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43. BOTULINUM TOXIN IN UROLOGY

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Onabotulinumtoxin A (onaBoNTA; Botox) received regulatory approval from the US Food and Drug Administration (FDA) for treatment of urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO) in 2011. A total of 691 patients with spinal cord injury or multiple sclerosis who had an inadequate response to or were intolerant of one or more anticholinergic medications were enrolled in the 2 pivotal phase 3 studies. These patients were randomized to receive 200 units (U) of onaBoNTA (n=227), 300 U of onaBoNTA (n=223), or placebo (n=241). In both studies, significant improvement in the primary efficacy variable of change from baseline in weekly frequency of UI episodes was achieved with 200 U of onaBoNTA compared with placebo. Improvement was seen after 2 weeks, and the average duration of response was approximately 10 months. Among patients who were not catheterized at baseline, catheterization for urinary retention (which is a temporary inability to fully empty the bladder, requiring clean intermittent catheterization) was initiated in 30.6% of patients following treatment with 200 U of onaBoNTA vs 6.7% of those on placebo.

In an exciting new development, positive data in a phase 2 study of abobotulinumtoxinA (Dysport) in patients with NDO has been reported in 2014.

OnaBoNTA also received FDA approval for treatment of idiopathic detrusor overactivity (IDO) in 2013. Phase 3 studies demonstrated the safety and efficacy of onaBoNTA in patients with overactive bladder (OAB) whose symptoms were not adequately managed with anticholinergic medications. OnaBoNTA reduced the daily frequency of urinary leakage episodes from baseline by approximately 50% or more by week 12 compared with placebo. The efficacy of onaBoNTA in reducing urinary leakage and other OAB symptoms lasted up to 6 months. The most common side effects reported with onaBoNTA treatment in clinical studies included urinary tract infection (18% vs 6% with placebo), dysuria (ie, painful or difficult urination; 9% vs 7% with placebo), and urinary retention (6% vs 0% with placebo). Urinary retention was more likely to develop in patients with diabetes mellitus treated with onaBoNTA.

44. THE EXPERIENCE WITH BOTULINUM TOXIN INJECTIONS IN 26 PATIENTS WITH WRITER'S CRAMP

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Introduction and Objectives: We evaluated the efficiency and safety of BTA injection in patients with writer's cramp (WC) using sonography.

Methods: Inclusion criteria were disease duration >1 year, ineffectiveness of other treatments, severe disorders of writing in patients for whom it is socially important. The average age of patients was 38.5±4.6 years; mean disease duration was 5.3±0.64 years. In order to choose the right muscles for injection of BTA, we performed sonography of forearm muscles during both the patients' rest and writing or hand-finger movements. We determined the accurate location of the muscles and their depth.

Results: We treated 26 patients with WC. We observed dystonic or complex WC in 15 (57.7%) patients and simple WC in 11 (42.3%). Sixteen patients (61.5%) had flexion of their wrists and fingers during writing; 3 (11.6 %) patients had extension of their wrists and fingers; 7 patients (26.9%) had both types. The average dose of botulinum toxin (Dysport) was 236 (range, 160, 280) units. Nineteen patients (73.1%) subjectively stated improvements after the injections. We registered decrease in symptoms on the Writer's Cramp Rating Scale from 10.5 (range, 8, 14) to 7.0 (6, 11) points ($P<0.01$). We saw reduction in indicators on the Symptom Severity Scale from 27.5±3.6 to 21.7±4.5 points ($P<0.01$). We observed hand muscle weakness in 5 (19.2%) patients. Most patients were satisfied with the result of the injection and, due to the decreasing clinical effect of BTA, agreed on the need to repeat injections.

Conclusions: Botulinum neurotoxin type A (BTA) is the method of choice for the treatment of focal dystonia. We need an individual approach to the development of injection schemes and calculations of doses. Treatment with BTA should be used in severe forms of WC in patients for whom WC has social significance.

45. AN INTERNATIONAL, PROSPECTIVE COHORT TO DOCUMENT THE EFFECTIVENESS OF 1 CYCLE OF BONT/A BASED ON ATTAINMENT OF INDIVIDUAL PERSON-CENTERED GOALS IN ADULT SUBJECTS SUFFERING FROM UPPER LIMB SPASTICITY FOLLOWING STROKE (ULIS II): SUBANALYSIS OF THE SOUTH ASIAN GROUP OF SPASTICITY PATIENTS

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Introduction and Objectives: A total of 456 patients were recruited globally for the ULIS II study. To compare the data from South Asia (SA) with the global (GLB) results, a subanalysis was performed.
Methods: A total of 51 patients from Hong Kong, Philippines, Thailand, Taiwan, Malaysia, and Singapore were included in this subanalysis. This subanalysis is a description of the differences between the 2 sets of data, as the original ULIS II trial was not statistically powered to perform such subanalysis.
Results: The mean age was 57.1 years (range, 47 to 68 years) in SA vs a mean age of 56.7 years (range, 18 to 88 years) in GLB. The male-to-female ratio was 2:1 in SA vs 3:1 in GLB. Forty-eight patients received Dysport, and 3 received Botox. The time from onset of stroke to treatment was 43.9 months in SA vs 61.4 months in GLB. Patients in SA had fewer significant general deficits vs GLB (fewer complaints of symptoms such as severe weakness, pain, and fatigue). The mean time since last injection was 14.7 months in SA vs 8 months in GLB. The mean dose of Dysport per patient used in SA was 675.2 U (median, 500 U) vs 748.3 U (median, 700 U) used in GLB. Fewer patients in SA set as their primary goal reducing involuntary movements (5.9% in SA vs 9.0% in GLB) or caring for the affected limb (11.8% in SA vs 28.9% in GLB). However, there was a trend for more patients in SA to set as their primary goal an active function goal of using the affected limb in some motor task (43.1% in SA vs 22.8% in GLB).
Conclusions: The variation in practices observed between SA and GLB could be due to differences in reimbursement for BoNT/A in SA. Between SA and GLB, differences exist in assessment, dosing, drug delivery and rehabilitation application. However, within the SA region, the same differences may hold true but not necessarily for the BoNT/A dose used.
Keywords: BoNT/A; Botox; Dysport; South Asia; Spasticity; Stroke

46. STUDYING F(AB')$_2$ ANTITOXINS DERIVED FROM EQUINE IgG AGAINST BOTULINUM NEUROTOXINS

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Botulinum antitoxins are F(ab')$_2$ antibody fragments derived from pepsin-digested equine IgG. An in vivo mouse potency assay is used to measure neutralizing titers by determining the quantity of antitoxin needed to neutralize a fixed quantity of toxin. For potency testing, survival is formally assessed 96 hours (h) after injecting equilibrated antibody-toxin mixtures. When animal observations were extended to several weeks, however, latent morbidity and mortality occurred in F(ab')$_2$ groups but not IgG-treated animals. A marked transition between nonprotective and protective doses of IgG occurred over a 25% to 50% increase in antibody, which is in contrast to F(ab')$_2$, where the neutralizing dose determined at 96 h must be increased 200% to 500% to fully protect by preventing the onset of latent illness.

When low, nonprotective quantities of IgG were combined with F(ab')$_2$, the severity of latent illness was diminished, suggesting that IgG may cooperate with F(ab')$_2$ antitoxin to protect animals. In animals exhibiting latent symptoms one week after injection of equilibrated F(ab')$_2$-toxin mixtures, rapid recovery was facilitated by subsequent IgG injection, suggesting that active neurotoxin, probably in the form of F(ab')$_2$-toxin complex, remains in the circulation 7 days after injection. Challenge-rescue experiments showed that antibody administered post-toxin challenge, regardless of IgG or F(ab')$_2$, was effective at doses 30 to 40 times higher than needed to neutralize in vitro. Surprisingly, rescue with F(ab')$_2$ facilitated a more rapid recovery than IgG.

We attribute the favorable rescue outcome to quicker penetration of F(ab')$_2$ into tissues compared with larger IgG molecules. The onset of latent illness caused by injection of pre-equilibrated F(ab')$_2$-toxin complexes may be due to the absence of the Fc domain in F(ab')$_2$ antitoxins. This suggests that the observed advantages of IgG during neutralization reactions are due to Fc-mediated clearance of IgG-toxin or IgG-toxin-F(ab')$_2$ complexes. In contrast, rescue with adequate quantities of F(ab')$_2$ does not lead to latent disease but requires nearly 10-fold higher molar quantities of F(ab')$_2$ than IgG. We conclude that rapid F(ab')$_2$ neutralization during treatment may offer an advantage over IgG, but small quantities of IgG within F(ab')$_2$ antitoxins can offer a dose-sparing benefit.

47. BOTULINUM TOXIN INJECTION TO THE UPPER LIMB INDIRECTLY IMPROVES GAIT IN PATIENTS WITH POSTSTROKE SPASTICITY

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Introduction and Objectives: Injection of botulinum neurotoxin (BoNT/A) is an effective treatment for patients with poststroke upper limb (UL) spasticity. Arm swing during gait has some physiologic functions, and hence the reduced motility and swing of a spastic arm may further compromise the already impaired gait in patients with poststroke spastic hemiparesis. Our objective was to evaluate whether isolated injections of BoNT/A to the UL can improve gait disturbance in patients with poststroke spastic hemiparesis.
Methods: Consecutive patients with poststroke UL spasticity newly or routinely treated by BoNT/A were recruited for the study. Evaluation was performed twice: a few hours prior to BoNT/A injections and 4 to 6 weeks following the treatment. It included the following clinical assessments: 1) Ashworth Spasticity Scale (ASS) for the injected muscles; 2) Timed Up and Go (TUG) test; 3) Functional Ambulation Classification (FAC) scale; and 4) Functional Independence Measure (FIM) scale. Gait analysis conducted at the Center of Advanced Technologies in Rehabilitation included overground gait speed (GS) and spatiotemporal parameters obtained by using the Zebris FDM-T treadmill (Medical GmbH, Germany).
Results: Eight patients (7 males; mean age±SD, 62.3±14.8years) were recruited. All patients were ambulatory. The mean dose±SD of BoNT/A (Dysport; abobotulinumtoxinA) was 1148±382 IU. A significant clinical improvement in UL spasticity was evident, as the ASS score diminished from 19.9±3.5 preinjection to 11.7±4.8 postinjection (P<0.001). Following the injection, gait speed increased from 0.40±0.24 m/s to 0.57±0.24 m/s (~+40%; P=0.05). Foot rotation (outward inclination) decreased from 11.5±5.7° to 9.6±4.3° (P=0.046). Gait line length in the paretic leg only tended to increase in response to BoNT/A injections (from 197±66 to 224±73 mm; P=0.075), indicating more dynamic control during stance. The scores of other neurologic scales, the TUG, and other gait parameters (eg, step length) did not change significantly.
Conclusions: Isolated injection of BoNT/A to the UL improves gait in patients with poststroke spastic hemiparesis. An explanation for this observation may be the partial restoration of arm swinging during walking. Future studies in larger cohorts are mandatory to consolidate our findings.
Keywords: Botulinum toxin; Gait; Spasticity; Upper limb

48. CAMPTOCORMIA

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Camptocormia is defined as an abnormal flexion of the thoracolumbar spine during standing and walking that abates or disappears in the recumbent position. It is a recognized feature of Parkinson's disease (PD) and other pathological conditions involving the basal ganglia. Its pathophysiology is probably multifactorial, but a dystonic component of the