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Botulinum A Toxin Intravesical Injections in the Treatment of Refractory Overactive Bladder in Patients with Parkinson's Disease

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1. Introduction

In Parkinson's disease (PD) non-motor symptoms including urinary disorders have been recognized as important features of the disease (Emre, 2003; Hely et al., 2005; Mathias, 2002; Pfeiffer, 2003; Rojo et al., 2003; Senard et al., 1997; Winge et al., 2003; Lang & Obeso, 2004). In this chapter we will review the clinical features, the pathophysiology and the treatment of urinary disturbances in PD. We will also discuss recent data on the use of intradetrusorial botulinum A toxin injections (BoNT/A) (Giannantoni et al., 2009; Giannantoni et al., 2011).

2. Parkinson's disease and neurogenic bladder

2.1 Prevalence of urinary symptoms

Earlier studies suggested that the prevalence of urinary symptoms in patients with PD ranges from 38% to 71% (Andersen 1985; Berger et al., 1987; Hald & We, 1982; Hattori et al., 1992; Porter et al., 1971) however in a number of these studies the clinical distinction between PD and other parkinsonisms, including multiple-system atrophy (MSA) was not addressed. Furthermore, some studies were based on patients presenting to urology clinics with urinary symptoms. (Berger et al., 1987; Hattori et al., 1992; Pavlakis et al., 1983). More recent studies in PD using validated questionnaires showed that the prevalence of urinary symptoms varied between 27% (Araki & Kuno, 2000a) to 39% (Campos-Sousa et al., 2003) and using a non validated questionnaire was greater than 40% (Sakakibara et al., 2001). Additionally Araki and Kuno (2000a) found a correlation between urinary disturbances and neurological disability and between severity of urinary disturbances and stages of the disease (Sakakibara et al., 2001), suggesting a relationship between dopaminergic degeneration and voiding dysfunction (Sakakibara et al., 2001).

2.2 Clinical features of urinary symptoms

Nocturia is the most prevalent lower urinary tract symptom (LUTS) reported by PD patients (>60%) (Campos-Sousa et al., 2003). Patients complain also of urgency (33%–54%)

(Araki & Kuno, 2000a; Campos Sousa et al., 2003) and frequency (16%–36%) (Araki & Kuno, 2000a; Campos Sousa et al., 2003), and urge urinary incontinence, particularly if poor mobility complicates their bladder disorder (Araki & Kuno 2000a; Campos Sousa et al., 2003; Lemack et al., 2000). Men with PD often have a coexisting benign prostatic hyperplasia worsening detrusor overactivity. In female patients overactive (urgency, frequency, urge incontinence) and obstructive (hesitancy, poor flow, dribbling) symptoms may also coexist. Evidence of bladder dysfunction in genetically determined Parkinsonism is controversial. In one study at least three cases of PARK1 α-synuclein–positive individuals were incontinent (Spira et al., 2001), while in another none of 17 patients with autosomal-recessive–type juvenile PD had bladder dysfunction (Ishikawa & Tsuji, 1996).

2.3 Neurogenic causes of bladder symptoms and voiding dysfunction in PD

There are several neurogenic causes of bladder symptoms in PD. Some Authors have suggested that an impaired relaxation or bradykinesia of the urethral sphincter can result in voiding dysfunction (Christmas et al., 1988; Galloway 1983) due to bladder outflow obstruction and, therefore, to detrusor overactivity. Studies using cystometry, however, have shown that obstructive voiding patterns are not common in PD patients (Araki et al., 2000b; Dmochowski, 1999) indicating that other mechanisms play a significant role.

3. Normal nervous control of the micturition reflex

Urinary storing and micturition rely on the interplay of a number of neural structures in the brain, spinal cord and peripheral ganglia. The complex relationship between central and peripheral pathways makes lower urinary tract (LUT) susceptible to a variety of neurologic disorders.

3.1 The role of Central Nervous System (CNS) in the control of the micturition reflex

The normal micturition reflex in the adult is mediated by a spino-bulbo-spinal pathway, which passes through relay centers in the brain. Micturition occurs in response to afferent signals from the lower urinary tract, and the distension of the bladder wall is considered the primary stimulus (de Groat et al., 1999; de Groat & Yoshimura, 2001).

During bladder filling, once threshold tension is achieved, afferent impulses, conveyed mainly by the pelvic nerve, reach the CNS. Afferent neurons send information to the periaqueductal gray, and relay with the pontine tegmentum, where two different regions involved in micturition control have been described acting independently (Blok & Holstege, 1999a, Griffiths et al., 1990). One is a dorsomedially located M-region, corresponding to Barrington's nucleus or the pontine micturition center (PMC). A more laterally located L-region may serve as a pontine urine storage center, and likely suppress bladder contraction by regulating the activity of the striated musculature of the bladder outlet during urine storage. Centers rostral to the pons control the beginning of micturition. The forebrain, therefore, even though not essential for the basic micturition reflex plays a role in determining when and where micturition should take place (Blok & Holstege, 1999b). Recent positron emission tomography studies gave further information on the brain structures involved in urine storage and voiding (Athwal et al., 2001; Blok et al., 1997; Matsuura et al., 2002; Nour et al., 2000).

3.2 Neurotransmitters mainly involved in voiding dysfunction due to Parkinson's disease

The micturition reflexes use several transmitter systems that may be targets for drugs aimed at control of micturition. Among these, dopamine and GABA pathways are fully involved in the control of micturition reflex and depletion of dopamine and GABA has been observed in Parkinson's disease.

3.2.1 Dopamine

Central dopaminergic pathways can have both facilitatory and inhibitory effects on micturition by actions on D1-like (D1 or D5) and D2-like (D2, D3, or D4) dopaminergic receptors. Patients with PD often have neurogenic detrusor over activity and voiding dysfunction (Berger et al., 1987), possibly as a consequence of nigrostriatal dopamine depletion and failure to activate inhibitory D1-like receptors (Yoshimura et al., 1993). Micturition, however, can be activated via D2-like receptors involving brainstem and spinal cord circuits. Microinjection of dopamine into the pontine micturition center reduced bladder capacity and facilitated the micturition reflex in cats (de Groat et al., 1993). Apomorphine, which stimulates both D1- and D2-like receptors, induced bladder overactivity in anesthetized rats (Sillén et al., 1981). In female rats, the role of dopamine D1 and D2 receptors in the volume induced micturition reflex, was investigated cystometrically (Seki et al., 2001) and the results, which are in agreement with previously data (de Groat & Yoshimura, 2001), suggested that D1 receptors tonically inhibit and D2 receptors facilitate the micturition reflex. In conclusion central dopaminergic pathways exhibit different effects on micturition via multiple receptors at different sites in the central nervous system.

3.2.2 GABA

GABA pathways are also involved in voiding dysfunction due to Parkinson's disease. GABA (γ-amino butyric acid) has been identified as an inhibitory transmitter at both spinal and supraspinal synapses in the mammalian CNS. At least in some species, the supraspinal micturition reflex pathway is under a tonic GABAergic inhibitory control (de Groat et al., 1993, 1999). GABA functions appear to be triggered by binding of GABA to its ionotropic receptors, GABA-A and GABA-C, which are ligand-gated chloride channels, and its metabotropic receptor, GABA-B (Chebib & Johnston, 1999). Since blockade of GABA-A and GABA-B receptors in the spinal cord (Igawa et al., 1993; Pehrson et al., 2002) and brain (Maggi et al., 1987; Pehrson et al., 2002) stimulated rat micturition, an endogenous activation of GABA-A and GABA-B receptors may be responsible for continuous inhibition of the micturition reflex within the CNS. In the spinal cord, GABA-A receptors are more numerous than GABA-B receptors, except for the dorsal horn where GABA-B receptors predominate (Malcangio and Bowery, 1996; Coggeshall and Carlton, 1997). It is well known that stimulation of the PMC results in an immediate relaxation of the external striated sphincter and a contraction of the detrusor muscle of the bladder. Blok et al. (Block et al., 1997) demonstrated in cats a direct pathway from the PMC to the dorsal gray commissure of the sacral cord. It was suggested that the pathway produced relaxation of the external striated sphincter during micturition via GABA -mediated inhibitory modulation on the urethral sphincter motoneurons in the Onuf nucleus.

4. The pathophysiology of voiding dysfunction in Parkinson's disease

The hypothesis most widely accepted is that in healthy individuals basal ganglia output has an overall inhibitory effect on the micturition reflex. In PD animal models depletion of dopaminergic neurones induces overactive bladder, (Yoshimura et al., 1993, 1998, 2003) and D1 receptor agonists produce inhibition of the micturition reflex in a dose-dependent manner while D2 receptor stimulation facilitates micturition. In PD degeneration of dopaminergic neurons in the substantia nigra leads to detrusor hyperactivity, through an inability to activate the D1-mediated tonic inhibition. A parallel mechanism may be that in PD, the inhibitory dopaminergic neurons originating in the substantia nigra may be more damaged than the excitatory dopaminergic neurons originating in the VTA, thereby inducing urgency and frequency.

Patients with PD and bladder symptoms have less uptake of [123I]-2ß-carbomethoxy-3 ß-(4-iodophenyl) tropane (ß-CIT) in the striatum than patients with PD but without bladder dysfunction, indicating a correlation between urinary dysfunction and degeneration of the nigrostriatal dopaminergic cells (Sakakibara et al., 2001). Winge and colleagues (Winge et al., 2005) recently demonstrated that the presence of bladder symptoms correlate with the decrease in the total number of dopaminergic neurones in the striatum and that the degeneration of the caudate correlates with severity of bladder symptoms. It is also possible that anti-parkinsonian medications may affect bladder function, but the results on the effects of levodopa or apomorphine are controversial. In one study, detrusor overactivity improved after administration of apomorphine and, to a lesser extent, after levodopa (Aranda & Cramer, 1993), but in patients showing on–off phenomena, detrusor overactivity improved with levodopa in some patients and worsened in others (Fitzmaurice et al., 1985). A recent study suggested that in advanced PD, levodopa exacerbates detrusor overactivity in the filling phase, but also improves bladder emptying through increased detrusor contractility (Uchiyama et al., 2003). The unpredictable effect of medication is not related to stage of disease, age, or whether the patient had symptoms of bladder dysfunction (Winge et al., 2002). In the study of Winge and colleagues (Winge et al., 2004), the authors suggested that the effects of medication are mediated through cortical mechanisms, as the ability to separate and integrate sensory input measured using urodynamics is influenced by medication.

5. Management of urinary symptoms in Parkinson's Disease

Questionnaires including "bother" scores identify LUTS in PD with higher specificity than questionnaires without "bother" scores (Winge et al., 2003). When addressing bladder problems in patients with Parkinsonism in daily clinical work, systematic interview is needed. Addressing nocturia, urgency, frequency feeling of incomplete emptying and (urge) incontinence often provides the needed information for initiating treatment. It is important to address how these symptoms affect the daily life of the patients, as symptoms of overactive bladder may be particularly unpleasant in a patient with an akinetic rigid syndrome with postural instability.

Neurogenic bladder symptoms are generally treated with anticholinergics (Andersson, 2000; Appell, 1997) including oxybutynin chloride, tolterodine tartrate, and trospium chloride and possibly also solifenacin. No placebo control double-blind or randomized studies, however, have been performed in PD. Anticholinergics can be used in PD patients with urgency and

frequency since they reduce the parasympathetic effect on the bladder. Patients generally tolerate anticholinergic drugs and benefit from their use. A study in patients without neurological diseases showed that the extended release tolterodine produces less side effects than oxybutinin (Sussman & Garely, 2002; Todorova et al., 2001). Anticholinergics usually provide only modest clinical improvement and in more than 60% of treated patients they induce adverse effects such as dry mouth and constipation (Di Stasi, 2001; Winge & Fowler, 2006). Another disadvantage is that anticholinergics may induce or worsen cognitive impairment (Kay & Ebinger, 2008; Winge & Fowler, 2006). There are no studies, however, addressing the issue of possible worsening of cognitive impairment using anticholinergics in patients with PD.

6. Botulinum A toxin as second line treatment for refractory detrusor over activity and over active bladder symptoms

To date when urinary incontinence persists and patients become severely disabled a long-term indwelling catheter remains the only option for avoiding urinary incontinence. Botulinum A toxin has been successfully introduced for the treatment of intractable detrusor overactivity (Schurch et al., 2000) and it is now widely used for a number of neurological conditions characterized by muscle hyperactivity (Jankovic, 2004; Ward et al., 2006). Intravesical injections of BoNT/A provide satisfactory long-term results, and are now considered as second line-therapy in neurogenic patients who do not respond to standard anticholinergics. The use of botulinum neurotoxins in the lower urinary tract (LUT) was pioneered as early as 20 yr ago with injections into the urethral sphincter (Dykstra et al., 1988) reducing bladder-voiding pressures, urethral pressures, and post void residual (PVR) urine.

BoNT/A consists of a light chain attached to a heavy chain via a disulfide bond with an associated zinc atom. It is synthesised as a single-chain polypeptide with a molecular weight of 150 kDa, which is then cleft into its active dichain polypeptide form. The heavy chain (about 100 kDa) allows for binding to the neuron and internalisation of the toxin, whereas the light chain (about 50 kDa) actively cleaves SNAP25 (synaptosomal-associated protein with a molecular weight 25 kDa) on the protein complex that is responsible for docking and releasing vesicles containing neurotransmitters (Dolly, 2003).

In neurogenic detrusor overactivity as well as in patients with idiopathic detrusor overactivity, the post-treatment reduction in detrusor pressures during both phasic involuntary contractions and on voiding (Popat et al., 2005; Reitz et al., 2004; Schurch et al., 2005) suggests an effect of BoNT/A on the motor innervation of the detrusor, although the neurological deficit which additionally affects voiding efficiency in the NDO group may partly explain the high rate of posttreatment clean intermittent self-catheterisations (CISC). Patients, however, also report a rapid reduction in their sensations of urgency, which are associated with involuntary detrusor overactivity (Rapp et al., 2004; Schmid et al., 2006). Although the exact nature and cause of urgency remains to be elucidated, abnormal afferent activity is thought to be a significant cause of spinal NDO (Yoshimura, 1999), and much less is known about the role of afferents in IDO. In both neural and bladder tissue, BoNT/A affected the release of numerous sensory transmitters other than ACh, including adenosine triphosphate (ATP), substance P, calcitonin gene related peptide (CGRP), and glutamate. BoNT/A may also interfere with vesicle trafficking (Apostolidis et al., 2006), expression of sensory receptors (Apostolidis et al., 2005) and nerve growth factor (NGF) in the bladder

wall (Giannantoni et al., 2006). It is therefore likely that in addition to a direct effect on detrusor motor innervation, BoNT/A also modulates intrinsic bladder reflexes through a multimodal effect on sensory pathways.

In neurogenic patients it has been demonstrated that BoNT/A decrease symptoms of neurogenic detrusor overactivity. The majority of treated patients had spinal neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis. Despite heterogeneous designs, almost all single-injection published studies showed significant improvements in outcomes measures including frequency of incontinence episodes, maximum cystometric capacity and maximum detrusor pressure. In spinal NDO patients the mean percentage of those who became fully continent was 56.6% (range: 30–87%) whereas the rate of full return to continence was only 8% in patients with NDO due to cerebrovascular accident. After a rapid onset of effect (Kalsi et al., 2008), the mean duration of efficacy in single-injection studies was 8 months (range: 12–36 wk). Repeated treatments showed sustained clinical benefits in open-label studies using up to five injections of Botox or seven injections of Dysport (Del Popolo et al., 2008; Grosse et al., 2005; Karsenty et al., 2006, Reitz et al., 2007).

7. Botulinum A toxin in the treatment of refractory detrusor overactivity and overactive bladder symptoms due to Parkinson's disease

Since 2000 we have been using BoNT/A as second line therapy for refractory overactive bladder symptoms and detrusor overactivity (DO) of both neurogenic and non-neurogenic origin. Here we review the results of our open label, prospective, non randomized study on the use of BoNT/A in patients with Parkinson's disease affected by intractable overactive bladder (OAB) symptoms and DO (Giannantoni et al., 2009, Giannatoni et al., 2011).

7.1 Patients and methods
Seventeen patients diagnosed with PD according to United Kingdom Brain Bank criteria and affected by overactive bladder symptoms and DO were enrolled in a prospective study. They were all refractory to standard anticholinergic therapy. Disease severity was assessed with the Unified Parkinson's Disease Rating Scale and Hoehn-Yahr stages 1 to 5. All patients had moderate-severe disability. Patients were studied while they were on their usual drug regimens for PD. Exclusion criteria were urogenital prolapsed in females, bladder outlet obstruction due to benign prostatic hyperplasia in men and recurrent urinary tract infections. No patients were on anticoagulant therapy or drugs interfering with neuromuscular transmission. The study was approved by the local ethics committee and patients provided informed consent. Patients unwilling or unable to perform intermittent catheterization, were excluded from the study. We used 150 ml as a cutoff residual volume for starting intermittent bladder catheterization.

7.2 Preliminary urological assessment
History, physical examination, serum laboratory tests, urinalysis, urine culture and urinary tract imaging by ultrasound were performed before commencing the study. The daily frequency of urinary symptoms was assessed with a voiding diary that patients completed for 30 days before the study. Patients were also asked to complete a standardized QoL questionnaire on urinary incontinence (I-QoL). Patients underwent urodynamics, including pressure flow studies and the recording of the electromyographic activity of pelvic floor muscle and external urethral sphincter, according to International Continence Society

Standards. During cystometry first volume and maximum pressure of uninhibited detrusor contractions (UDC) and maximum cystometric capacity were recorded. On pressure flow study detrusor pressure at maximum flow rate (pDetQmax), maximum flow rate (Qmax) and postvoid residual volume were monitored. All patients received a single treatment with BoNT/A (Botox, Allergan, Irvine-CA, USA) diluted in normal saline injected into the detrusor muscle. The trigone, the posterior and lateral walls of the bladder have been injected during cystoscopy, under short lasting general anaesthesia. Six out of the seventeen patients received 200 UI of BoNT/A, whereas eleven of the seventeen PD patients received 100 UI of BoNT/A. Primary outcome measures were: changes in day-time and night-time urinary frequency and frequency of daily urinary incontinence episodes and in I-QoL questionnaire; secondary outcomes were changes on the impact of urinary symptoms in daily life activities was evaluated with VAS scores and in urodynamic parameters. Clinical, urodynamic and I-QoL and VAS were performed before, one, three and six months after BoNT/A injection. Urinalysis and culture were performed also at the same time intervals.

7.3 Statistical analysis
Friedman's repeated measures ANOVA was used to evaluate changes in the clinical scores and urodynamic findings of PD patients. Wilcoxon's test was performed for the post-hoc analysis. Pearson's correlation coefficient was also applied and Holm's correction for multiple comparisons was used to disclose false significance. $P < 0.05$ was considered to indicate statistical significance.

7.4 Clinical results
Before treatment all seventeen patients complained of increased daytime (9.29±0.3 episodes/day) and night-time urinary frequency (4.11±0.6 episodes/night) and daily episodes of urinary incontinence (5.05±0.2 episodes/day). They also had urgency and low I-QoL scores (22.8±2) and VAS scores (3.3±0.1). After BoNT/A treatment daytime and night-time urinary frequency and the number of daily episodes of urinary incontinence were significantly reduced (daytime urinary frequency: $p < 0.0001$; night-time urinary frequency: $p = 0.002$; daily urinary incontinence episodes: $p = 0.001$) (Fig.1) at one, three and six months follow up. Six out seventeen patients achieved a complete urinary continence at one and 3-mos follow up. After BoNT/A treatment there was also a significant improvement in the I-QoL and VAS scores after BoNT/A (I-QoL: $p < 0.0001$; VAS: $p < 0.0002$) at one, three and six months. Finally, we did not find any significant difference between the improvement observed in daytime and night-time urinary frequency, in the number of episodes of daily urinary incontinence and in the I-QoL and VAS scores in PD patients who received 100 UI with that obtained in patients treated with 200 UI of BoNT/A ($p > 0.05$). Clinical results are showed in Fig.1.

7.5 Urodynamic results
Baseline: all the patients showed detrusor overactivity; mean values of UDC-first volume UDC-p max and maximum cystometric capacity were 219±20ml, 30±2cmH20 and 265±16ml, respectively. On pressure-flow studies, mean values of pDetQmax and Qmax were 22.3±2 cmH$_2$O and 18.3±1.5ml/sec, respectively. All patients completely emptied their bladders.
After BoNT/A treatment, we observed a significant decrease in the first volume and the maximum pressure of uninhibited detrusor contractions and a significant increase in

maximum cystometric capacity at one, three and six months after treatment. Changes in these parameters were similar in both groups of PD patients (Fig.2). With regards to post-void residual volume, it was similar in PD patients receiving 100 and 200 UI of BoNT/A at one month, whereas it returned to baseline values only in PD patients receiving 100 UI at three and six months after BoNT/A injection. Overall, three patients needed to perform intermittent catheterization twice daily for 3 months due to a high increase in post void residual volume after BoNT/A injection.
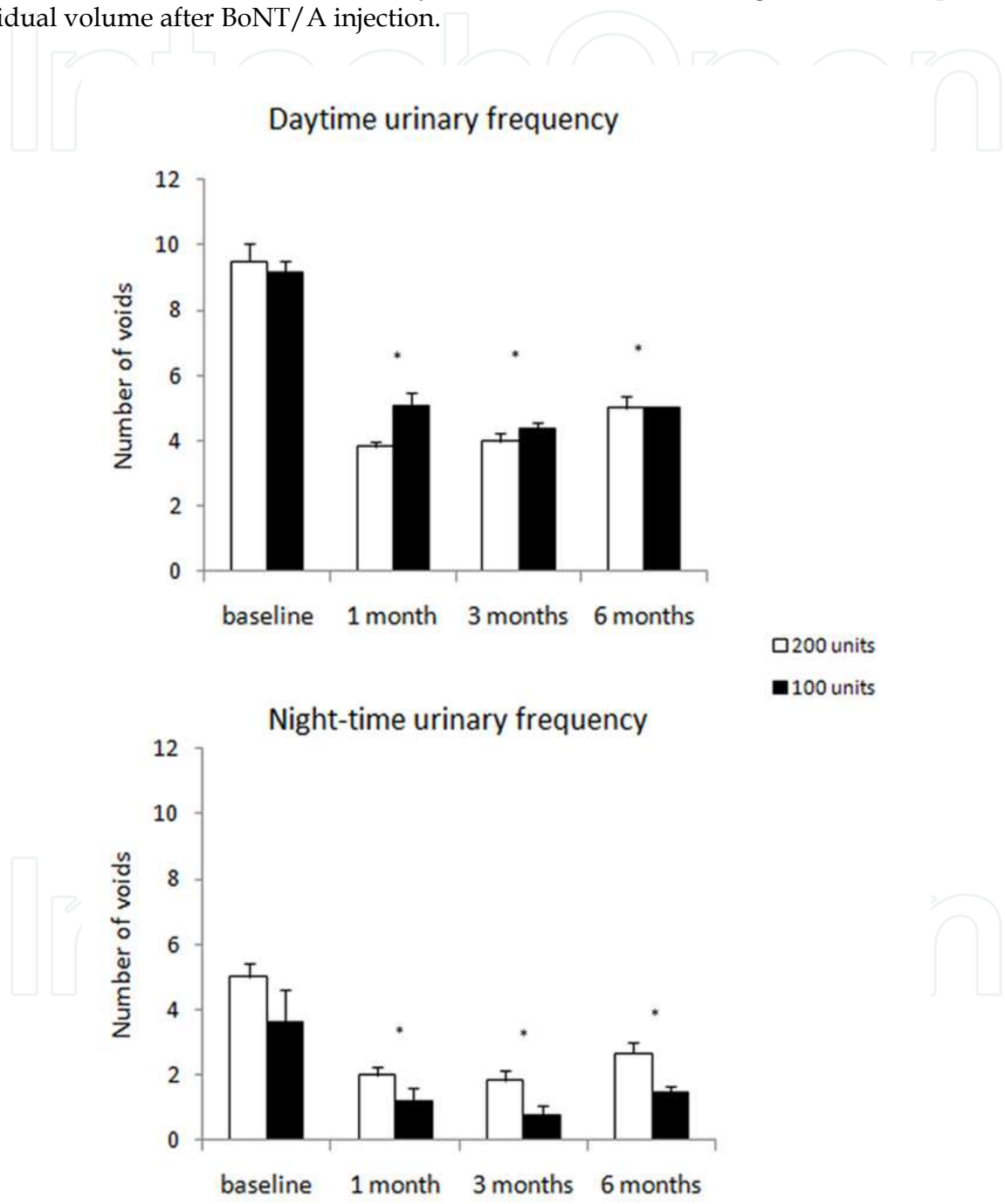
Fig. 1. Daytime urinary frequency (upper panel) and night-time urinary frequency (lower panel) in patients with Parkinson's disease at baseline, one, three and six months after BoNT/A injection. Open bars represent mean data ±SE in patients injected with 200 units, closed bars data in patients injected with 100 units. Asterisks indicate statistical significance

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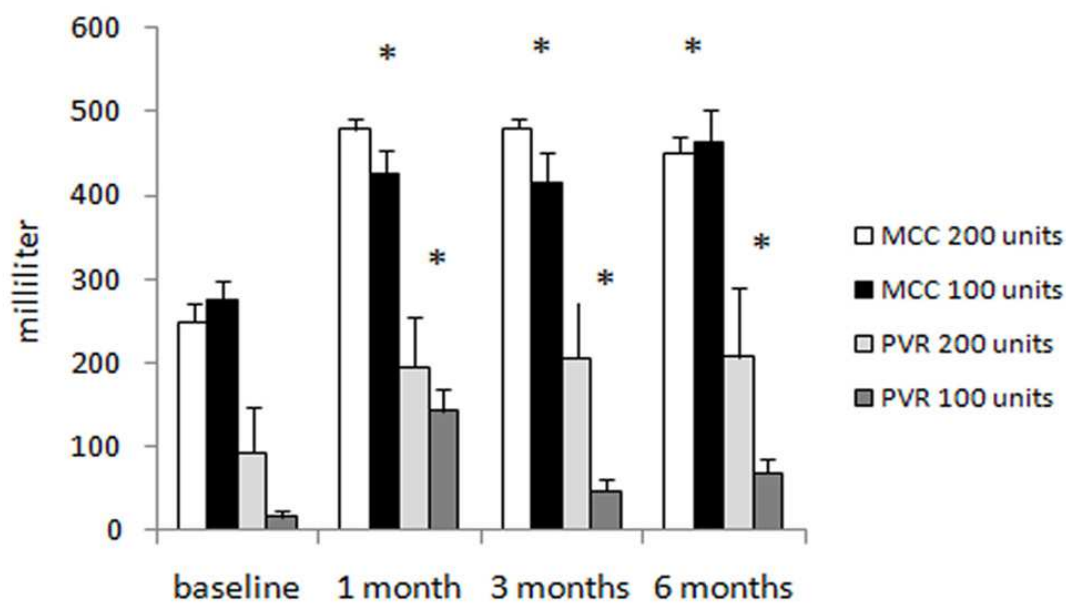
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Fig. 2. Maximum cystometric capacity and post-void residual volume in patients with Parkinson's disease at baseline, one, three and six months after BoNT/A injection. Each bar represents mean data ±SE in patients injected with 200 units and 100 units. Asterisks indicate statistical significance.

7.6 Correlations between clinical and urodynamic variables

Changes in the I-QoL significantly correlated with daytime urinary frequency (r=-0.69, p=0.002) in all the PD patients.

7.7 Discussion

In our PD patients, BoNT/A intradetrusorial injection induced a significant reduction in daytime and night-time urinary frequency and in the frequency of urinary incontinence, an increase in the quality of life scores and a significant amelioration in urodynamic parameters. The follow-up assessment extends our previous findings at three months (Giannantoni et al., 2009) by showing that the BoNT/A-induced clinical and urodynamic improvement lasts at least six months (Giannantoni et al., 2011). We also noted that clinical and urodynamic amelioration was similar when comparing patients treated with 100 UI of BoNT/A with those treated with 200 UI. Worth of noting, incomplete voiding symptoms were unrelated to the BoNT/A dosage used. Also patients with multiple sclerosis treated with 100 Units and patients with idiopathic overactive bladder treated with 200 and 300 units of BoNT/A showed an increase in post-void residual volume (Flynn et al., 2009; Mehnert et al., 2010; Sahai et al., 2009). Our results on post-void residual volume are in contrast with those reported by Kulaksizoglu and Parman (Kulaksizoglu & Parman, 2010) who treated parkinsonian patients with Dysport 500 Units. In their series none of the patients studied needed intermittent catheterization. Despite of the presence of post-void residual volume in our PD patients, we did not observe a significant reduction in other parameters accounting for detrusor muscle strength (PdetQmax, Qmax). It is well known

that BoNT/A induces striated muscle denervation and weakness lasting about 3-4 months (Hamjian et al., 1994; Schiavo et al., 1994). In striated muscle it has been observed that the neurotoxin not only modulates extra-fusal component but also influences the altered muscle spindle afferent input (Abbruzzese et al., 2006; Currà & Berardelli, 2009; Rosales & Dressler, 2010; Trompetto et al., 2008). In detrusor smooth muscle the effects of BoNT/A injection last longer than in striated muscle. In vitro and in vivo experimental studies suggest that the long-lasting effect of the BoNT/A injection in the detrusor muscle could be attributed to the lack of axonal sprouting, as observed in detrusor biopsies after toxin injection (Haferkamp et al., 2004). Studies on biopsies from patients with neurogenic overactive bladder who receive an intradetrusor BoNT/A injection (Apostolidis et al., 2006; Giannantoni et al., 2006), however, have shown decreased levels of sensory receptors P2X3, TRPV1 and NGF, thereby suggesting that BoNT/A may act by reducing the afferent nervous transmission.

7.8 Conclusions

PD patients with OAB symptoms and detrusor overactivity refractory to standard treatments can be successfully treated with intravesical injections of BoNT/A. Low doses (100 U BoNT/A) induces similar clinical and urodynamic efficacy as higher doses of the neurotoxin. The reported increase in post void residual volume is present only in some patients and lasts for a limited time. Low doses of BoNT/A can be used as second-line treatment for OAB symptoms and DO also in patients with PD.

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Towards New Therapies for Parkinson's Disease

Edited by Prof. David Finkelstein

Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of ?-synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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