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ORIGINAL ARTICLE

Initial experience with the treatment of neurogenic detrusor overactivity with a new β-3 agonist (mirabegron) in patients with spinal cord injury

J Wöllner and J Pannek

Study design: It is a retrospective chart analysis.
Objectives: In patients with neurogenic lower urinary tract dysfunction (NLUTD) due to spinal cord injury (SCI), neurogenic detrusor overactivity (NDO) can cause both deterioration of the upper urinary tract and urinary incontinence. Antimuscarinic treatment is frequently discontinued due to side effects or lack of efficacy, whereas injection of onabotulinumtoxin into the detrusor is a minimally invasive procedure with risks of urinary retention, infection and haematuria. Mirabegron, a new β-3 agonist, is a potential new agent for treatment of NDO. Aim of the study was to evaluate the efficacy of mirabegron in SCI patients with NLUTD.
Setting: Swiss Paraplegic Center, Nottwil, Switzerland.
Methods: A retrospective chart analysis of SCI patient treated with mirabegron.
Results: Fifteen patients with NDO were treated with mirabegron for a period of at least 6 weeks. Significant reduction of the frequency of bladder evacuation per 24 h (8.1 vs 6.4, $P=0.003$), and of incontinence episodes per 24 h (2.9 vs 1.3, $P=0.027$) was observed. Furthermore, we observed improvements in bladder capacity (from 365 to 419 ml), compliance (from 28 to 45 ml cm^{-1} H_20) and detrusor pressure during storage phase (45.8 vs 30 cm H_20). At follow-up, 9/15 patients were satisfied with the therapy, 4/15 reported side effects (3× aggravation of urinary incontinence, 1× constipation).
Conclusions: Mirabegron may evolve as an alternative in the treatment of NDO. We observed improvements in urodynamic and clinical parameters. Due to the limited number of patients and the retrospective nature of the study, prospective, placebo-controlled studies are necessary.
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INTRODUCTION

The normal function of the lower urinary tract, storage and evacuation of urine is disturbed after spinal cord injury (SCI), and a life-long control and therapy is required.[1,2] Neurogenic detrusor overactivity (NDO) is characterized by reduced bladder capacity, elevated detrusor pressure during the storage phase and/or reduced compliance.[3] Besides urinary incontinence and impaired quality of life, NDO can lead to irreversible deterioration of the upper urinary tract with subsequent renal failure.[3] Therefore, an adequate treatment of the elevated detrusor pressure is necessary to achieve continence, to improve the bladder capacity, and to protect the upper urinary tract.[4] Commonly, antimuscarinic treatment is the first line NDO therapy.[4] Nevertheless, treatment with antimuscarinic drugs is frequently discontinued due to side effects (dry mouth and constipation) or a lack of efficacy.[5] In particular in patients with SCI, who suffer from a neurogenic bowel dysfunction, the concomitant antmiuscarinic treatment will worsen the constipation. Therefore there is a need for therapy alternatives. Botulinumtoxin is often used as a second line therapy.[6] The need of repeated injections, and for anesthesia in patients with incomplete SCI are limitations of this therapy. A new β-3adrenoreceptor agonist (Mirabegron) has recently been introduced as an option in the treatment of overactive bladder.[7] Improved incontinence and relevant reduction in pad use and daily micturition frequence were observed.[8] Because of the different mechanism of action, and thus the potential of less side effects, this agent seems to be a promising drug also in the treatment of NDO in patients with SCI. Aim of the study was to evaluate the efficacy and tolerability of mirabegron in patients with SCI.

MATERIALS AND METHODS

In a retrospective chart analysis, we included all consecutive patients, treated with mirabegron 50 mg for a period of at least 6 weeks between September 2014 and March 2015. Demographic data, mode of bladder management, previous NDO therapy and urodynamic results before and after treatment were evaluated. Side effects, satisfaction and effectiveness of the therapy were evaluated. Patients with previous injection of onabotuliuntoxin were included, if the last injection was at least 12 month before mirabegron treatment. After antimuscarinic treatment, all patients received mirabegron 25 mg once daily, which was adapted to 50 mg after 2 weeks. Frequency of bladder evacuation and incontinence episodes were documented in a voiding diary prior and after the therapy. The urodynamic investigation was conducted according to ICS guidelines, a symptomatic urinary tract infection was excluded before urodynamic testing. The statistical analysis was performed with SPPS (SPSS, IBM, Armonk, NY, USA): all values are given as mean and s.d. The Komolgorov Smirnnov Test was used to test the normal distribution. All relevant parameters

Neuro-Urology, Swiss Paraplegic Center, Nottwil, Switzerland
Correspondence: Professor Dr J Pannek, Neuro-Urology, Swiss Paraplegic Center, Guido A. Zäch Strasse 1, 6207 Nottwil, Switzerland.
E-mail: juergen.pannek@paraplegie.ch
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(frequency of bladder evacuation per 24 h, incontinence episodes per 24 h, maximum cystometric capacity, maximum detrusor pressure and compliance) revealed a normal distribution ($P>0.05$). Because of normal distribution of the values (Komolgorov Smirnow test), the Wilcoxon sign-ranked test was used. A P value <0.05 was considered significant.

RESULTS

Between August 2014 and March 2015, 17 patients (4 women, 11 men, mean age of 45 ± 15.5 years) with NDO were treated with mirabegron for a period of at least 6 weeks. Two patients were excluded from further analysis due to incomplete data. During the treatment phase, no antimusarinic drug was added. SCI was the main reason for NDO. The patients characteristics are listed in Table 1. Twelve of 15 patients received a previous antimuscarinic treatment (AM), whereas injections of onabotulinumtoxin were performed in 3 patients. Reasons for change of the AM therapy were lack of efficacy ($n=3$), or side effects ($n=12$, dry mouth and constipation). The duration of treatment with mirabegron was 6.9 ± 0.9 weeks.

Follow-up visit

Urodynamic data. We observed a significant decrease of the maximum detrusor pressure during the storage phase (45.8 vs 30 cm H_20, $P=0.018$). The maximum cystometric capacity increased from 365 to 419 ml, $P=0.084$, the compliance enlarged from 28 to 45 ml cm^{-1}, $P=0.069$) (Figure 1). Figure 2 showed an example of an urodynamic chart pre- and post treatment.

Clinical results. The frequency of bladder evacuation per 24 h (8.1 vs 6.4, $P=0.003$), and incontinence episodes per 24 h (2.9 vs 1.3, $P=0.027$) were significantly reduced. Nine out of 15 patients were satisfied with therapy, 4/15 reported side effects (3 aggravation of urinary incontinence, 1× constipation). After the follow-up visit nine patients continued with mirabegron, whereas six patients received another treatment (4× AM; 2× injection of onabotulinumtoxin).

The patients ($n=3$), who reported an aggravation of urinary incontinence during the therapy with mirabegron were analyzed, comparing the urodynamic parameters pre and post therapy. This patient revealed a decrease of maximum cystometric capacity from 345 to 263 ml ($P=0.65$), an increase of maximum detrusor pressure during storage phase from 47 to 55 cm H2O ($P=0.59$) and reduction of the compliance from 47.6 to 36.3 ml cm^{-1} H2O ($P=0.91$).

Table 1 Patients characteristics

Patients	Female 4
	Male 11
Age	45 ± 15.5 years
Underlying disease	Traumatic spinal cord injury 12
	Myelomeningocele 1
	Multiple sclerosis 1
	Tetraplegia (encephalomyelitis) 1
Duration of injury	15.4 ± 12.5 years
Lesion level	Cervical 3
	Thoracic 8
	Lumbar 2
	No defined lesion level 2
AIS score	AIS A 8
	AIS B 0
	AIS C 1
	AIS D 4
	No AIS score 2
Prevoius therapy	Antimuscarinics 12
	Onabotulinumtoxin 3
Bladder management	CIC 12
	Spontaneous 3
Side effects	No side effects 11
	Aggravation of urinary incontinence 3
	Constipation 1
Satisfaction with treatment	Satisfied 9
	Non-satisfied 6
Further treatment	Mirabegron 9
	Antimuscarinics 4
	Onabotulinumtoxin 2

DISCUSSION

According to our data, NDO treatment with mirabegron in patients with NLUTD due to SCI is feasible and well tolerated. We observed significant improvements in clinical and urodynamic data. Especially reduction of the maximum detrusor pressure, enlarging the maximum cystometric capacity and improvement of the compliance are crucial in patients with NLUTD, as the main goal of the treatment of NLUTD due to SCI is the protection of the upper urinary tract. According to the guidelines, first line treatment of NDO are antimuscarinics.[4] However, patient compliance is poor, often the therapy is discontinued due to side effects.[5] The new β-3 agonist mirabegron offers a new opportunity in the treatment of overactive bladder (OAB).[9,10] Until today, the studies available assessed the effect of mirabegron on urgency, urge incontinence and voided volume. Merely a single study investigated the effect in patients with NLUTD.[11] Corresponding to our data, the authors observed a reduction of incontinence episodes, improvement in urodynamic parameters and also in bladder deformity.[11] In contrast to our study, mirabegron was an additional therapy to antimuscarinic treatment in case of insufficient reduction of NDO. In our treatment concept, the antimuscarinic treatment was stopped and mirabegron therapy was initiated. Therefore, after a therapy duration of at least 6 weeks, we state, that the improvement in clinical parameters (reduction of bladder evacuation frequency and reduction of incontinence episodes) and urodynamic parameter are directly related to the treatment. To our best knowledge, this is the first analysis of mirabegron in patients with NDO due to SCI including urodynamic investigation. We observed an improvement in urodynamic parameters (increased maximum cystometric capacity, decreased maximum detrusor pressure during storage phase and improvement of the compliance). In a urodynamically controlled study in patients with idiopathic OAB, Matsukawa *et al.*,[12] also observed an improvement during the storage phase, whereas the voiding phase was not affected. The pathophysiology of NDO is completely different from idiopathic OAB. The term OAB is based on symptoms, a urodynamically proven detrusor overactivity is not mandatory. Furthermore, NDO in patients with SCI is due to defined neurological lesion, whereas in idiopathic OAB patients, the underlying pathology remains often unclear. Therefore the results are not comparable among these groups.

Regarding safety, we did not observe severe side effects. Three patients reported an aggravation of urinary incontinence, another patient presented increasing constipation. we do not have a good explanation for the aggravation of urinary incontinence. Analyzing the data of these three patients we observed an impairment of the urodynamic parameters. The reduction of

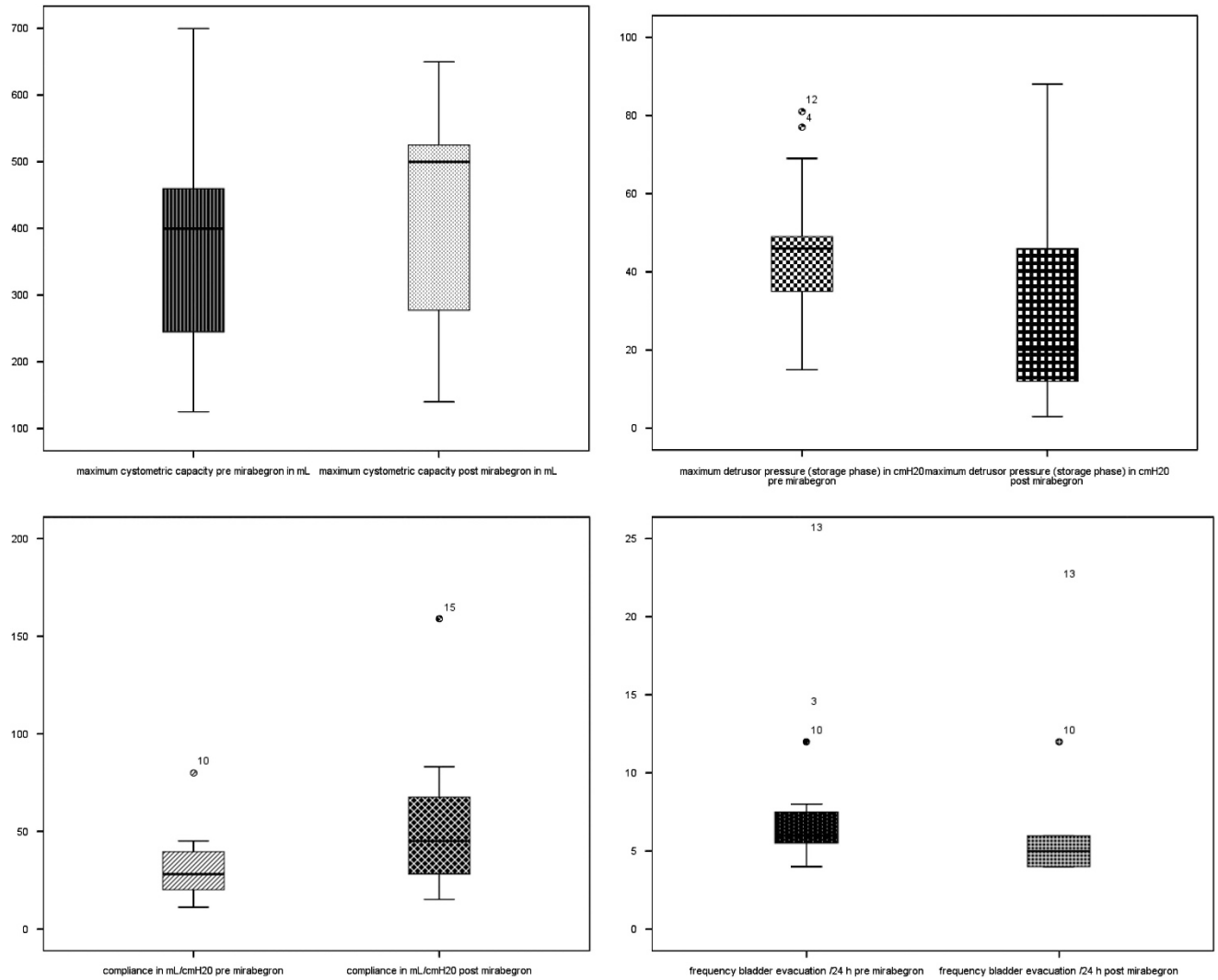

Figure 1 The urodynamic investigation revealed an increase in maximum cystometric capacity (NS), a decrease of maximum detrusor pressure during the storage phase (NS) and increase in the compliance. The frequence of bladder evacuation in 24 h decreased after a treatment period of 6 weeks.

cystometric capacity, increased detrusor pressure and reduction of compliance explain the worsening of the clinical symptoms. Probably, the initial antimuscarinic therapy was not sufficient, but was still able to improve the urodynamic parameters. In the follow-up the antimuscarinic effect was subsided, and the β-3 agonist was not potent to sufficiently improve the bladder dysfunction. In a phase IV study investigating safety and efficacy of mirabegron in patients with OAB, Yamaguchi observed adverse events in 23%, most of them mild or moderate. The most common side effect was constipation.[13] However, mirabegron was additional medication to a base line therapy with solifenacin. Potentially the additional antimuscarinic drug is also responsible for this side effect.

Nevertheless, a potential interaction of mirabgeron with β receptors in the intestine can explain the constipation in our patients who received only mirabegron.

In summary, mirabegron seems to be an novel therapeutic option to reduce NDO. Interestingly, some authors reported synergistic effects of a combination of mirabegron and an antimuscarinic drug in the treatment of OAB.[13] Because of the different mechanism of action (inhibition of the muscarinic receptor and activation or the sympathetic activity in the lower urinary tract (LUT)) this combination might be another future option to decrease the elevated detrusor pressures in patients with NLUTD due to SCI.

Limitations of our study are the retrospective character and the small number of patients. Nevertheless, we observed an improvement of clinical and urodynamic parameters in patients with NDO due to SCI. Therefore, this new agent might be an additional therapeutic option in these patients. Prospective randomized studies are required to investigate the efficacy and safety in this patients.

CONCLUSIONS

Mirabegron may evolve as an alternative in the treatment of NDO. We observed an improvement in urodynamic and clinical parameters. Further, placebo-controlled studies are necessary to verify these results.

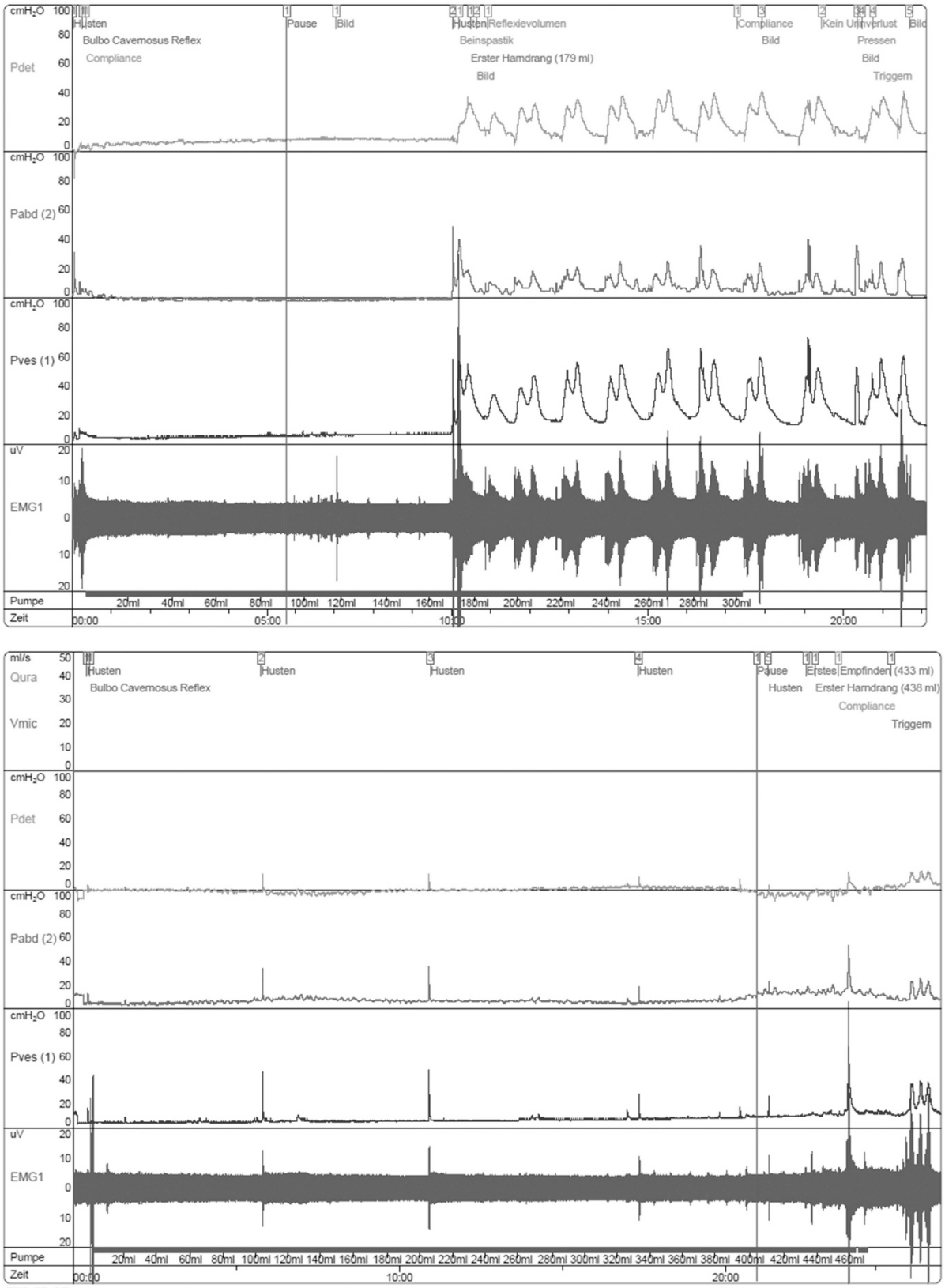

Figure 2 Urodynamic examination in patient with NLUTD dur to SCI pre treatement with Miragbegron and during the control 6 weeks later. A full color version of this figure is available at the *Spinal Cord* journal online.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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