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Feasibility of mirabegron in the treatment of overactive bladder in patients affected by Parkinson's disease: A pilot study

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Abstract

Background: We investigated the effectiveness and safety of mirabegron oral treatment in a group of patients with Parkinson's disease (PD) and overactive bladder (OAB), refractory to antimuscarinics.

Materials and methods: Thirty patients with PD and refractory OAB were prospectively included in the study. At baseline, motor symptoms, severity of disease and cognitive status were assessed with the Hoehn–Yahr Scale, the Unified Parkinson's disease Rating Scale, the Mini Mental State examination and the Montreal Cognitive Assessment. At baseline, urinary symptoms, satisfaction with treatment and the impact of urinary incontinence on quality of life (QoL) were assessed with the 3-day voiding diary, the Visual Analogue Scale (VAS), the Incontinence–QoL questionnaire and urodynamics. Patients started assuming mirabegron 50 mg tablets once daily. Evaluation of urinary symptoms and related questionnaires, motor symptoms, severity of PD and uroflowmetry with postvoid residual volume measurement were then repeated at the 3- and 6-month follow up. Side effects were also noted.

Results: At baseline, the most frequently reported urinary symptoms were: urinary urgency (present in all the patients), urge urinary incontinence in 28/30 (93.3%) and increased daytime urinary frequency in 25 (83.3%) patients. At the 3-month follow up, 7 out of the 30 patients achieved a complete urinary continence. Significant improvements in VAS and Incontinence–QoL scores were observed in 24 patients. These benefits were maintained for the whole observation period. Four patients discontinued treatment due to poor efficacy, and two due to the cost of the drug.

Conclusions: Mirabegron is a safe and effective treatment in patients with PD and OAB refractory to anticholinergics in the short-term follow up.

Keywords: mirabegron, Parkinson's disease, overactive bladder

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of the central nervous system following Alzheimer's disease, associated with loss of dopaminergic neurons.[1]

In addition to motor symptoms, patients with PD often show nonmotor symptoms such as sleep disorders, neuropsychiatric alterations, sensory symptoms and autonomic disorders.[2]

Neurogenic lower urinary tract dysfunction (NLUTD) is one of the most common autonomic disturbances in PD patients, the incidence being estimated as 55–80%. NLUTD in PD is often caused by urinary storage symptoms, characterized by the 'overactive bladder' (OAB) syndrome, with nocturia being the most frequently reported urinary symptom.[3] The conventional treatment of OAB in neurogenic patients is represented by antimuscarinic medications, which alleviate urinary urgency,

urge urinary incontinence (UUI), increased daytime urinary frequency and nocturia. Indeed, the use of antimuscarinics in OAB patients has been reported frequently associated with adverse effects, especially dry mouth, constipation and impaired ocular accommodation.[4–5] Moreover, poor persistence and adherence rates with antimuscarinics have been generally reported in the real-life, long-term treatment of OAB, due to their limited efficacy and intolerable adverse effects, with discontinuation rates at 2-year follow up particularly higher in the older patients.[6] In addition, especially in PD patients, antimuscarinics must be used with caution for the cumulative total anticholinergic load prescribed for different comorbidities.[7]

Mirabegron, a β3-adrenoceptor agonist mediating detrusor smooth muscle relaxation represents an alternative class of agents in the treatment of OAB, demonstrating efficacy as an antimuscarinic in reducing the frequency of micturition and incontinence but with substantially lower toxicity.[6] To date, no study investigated the efficacy and safety of mirabegron in the treatment of OAB symptoms in patients affected by PD.

To this aim, we assessed in a pilot study, the feasibility and potential impact of mirabegron on urinary symptoms, quality of life (QoL) and satisfaction with treatment in PD patients, in short-term follow up.

Patients and methods

This is a single-centre, prospective study, which was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee (CEAS No. 12396/18).

Patients were eligible for inclusion if they had a primary diagnosis of PD according to United Kingdom PD Society Brain Bank Criteria;[8] PD medications (including levodopa and dopaminergic agonists) were at stable doses before the beginning of mirabegron treatment.

Exclusion criteria were: a diagnosis of NLUTD in the presence of prostate enlargement or severe urogenital prolapse (pelvic organ prolapse quantification ⩾ stage II) with bladder outlet obstruction (BOO), or other potential confounding lower urinary tract (LUT) conditions. Furthermore, patients with uncontrolled hypertension, symptomatic orthostatic hypotension and symptomatic supine hypertension were excluded.

Neurologic examination. Neurologic examination included the Hoehn–Yahr (H&Y) Scale[9] and the Unified PD Rating Scale (UPDRS) motor section part III[10] to assess motor symptoms and severity of disease. Patients were tested under their anti-parkinsonian medication therapy, which remained unchanged during the whole observation period. In addition, the evaluation of the cognitive status was performed by using the Mini Mental State examination (MMSE)[11] and the Montreal Cognitive Assessment (MOCA).[12]

Urologic examination. Patients were instructed to fill in a 3-day voiding diary for daytime and nighttime urinary frequencies, and frequency of urinary urgency and UUI 30 days before starting mirabegron. In addition, patients were asked to indicate to what extent bladder problems limited their daily life activities on a modified Visual Analogue Scale (VAS) consisting of a 10 cm line marked with 'not at all' at the right end and 'very much' at the left end.[13] Visual ratings 'not at all' to 'very much' were then converted by the investigators to numerical values using a 0–10 scale. The impact of urinary incontinence on QoL was investigated with the Incontinence–QoL questionnaire (I-QoL),[14] as recorded by patients 30 days before commencing mirabegron treatment. The I-QoL is a 22-item tool that is easy to understand and complete when self-administered. The 22 items are divided into 3 domains: a domain (8 items) addressing the physical impact; another (9 items) capturing the psychological impact; and a 5-item domain capturing the social impact. For each domain, scores are calculated and a total score emerges from all 22 items. Scores range from 0 to 100, with a higher score indicating a better health status.[14] Patients underwent urodynamics to document the dysfunction of the LUT, and specifically, to detect detrusor overactivity and to exclude BOO. At the time of urodynamic examination, patients were free from urinary tract infections. Urodynamics were performed according to the International Continence Society (ICS) standards,[15] and included cystometry-at-physiologic-filling rate with body-warm fluid, and pressure–flow study, performed in the standing or sitting position. A simultaneous electromyographic (EMG) recording of the external urethral sphincter muscle activity was conducted. During cystometry, maximum cystometric capacity (MCC) and compliance, bladder filling sensation, the first volume and the maximum pressure at which the uninhibited detrusor contractions occurred and urinary incontinence episodes were recorded. For the

pressure–flow study, maximum flow rate, detrusor pressure at maximum flow rate and postvoid residual urinary volume (PVR) were recorded.

Patients commenced mirabegron 50 mg tablets once daily, after stopping their medications for OAB at least 2 months previously. We decided to administer mirabegron 50 mg instead of the lower dose, 25 mg, because 50 mg once daily is the most frequently adopted dose for clinical use, also in neurogenic patients. Furthermore, we wanted to avoid the risk of an unsatisfactory response due a reduced dosage in patients who have been nonresponsive to a previous treatment with anticholinergics.

Follow up. At the 3- and 6-month follow up, neuro-urologic evaluation, VAS, I-QoL questionnaire and uroflowmetry were performed again.

Comorbidities and side effects. Presence of comorbidities such as hypertension, cardiovascular, lung and osteoarticular diseases were also noted. Patients were asked to record on a daily chart, both blood pressure and pulse rate, with measurements performed at the beginning of treatment, 1 week after, and at 3 and 6 months' follow up. In addition, other side effects possibly related to the use of mirabegron (i.e. headache, palpitation, urticaria, nasopharyngitis, articular pain, urinary tract infection) were also evaluated.

The primary outcomes of the study were: (a) patients' persistence rate with mirabegron treatment at the 3- and 6-month follow up; (b) the change from baseline in the mean number of voids in 24 h, mean number of urgent micturition episodes in 24 h, mean number of UUI episodes in 24 h, at 3 and 6 months' follow up, and the comparison of these changes between responders and nonresponders; and (c) presence of side effects inducing treatment discontinuation at 3 and 6 months' follow up.

The secondary endpoints included improvement in I-QoL scores and in VAS scores at 3 and 6 months' follow up.

Statistical analysis

Statistical analysis was performed with SPSS version 17 for Windows (IBM Corp, Armonk, NY, USA). Descriptive statistics were performed to summarize the clinical and demographic characteristics. Student's *t* test and the Mann–Whitney *U* test were performed to compare continuous parametric and nonparametric variables, as appropriate. Continuous variables were reported as mean ± standard deviation (SD). All values in the text and tables are expressed as mean ± SD. Statistical tests were conducted with a significance level of 0.05. Spearman correlations were used to test for the strength of linear association between variables, along with the Wilcoxon and Mann–Whitney tests.

Results

Initially, 41 patients (17 males and 24 females) with refractory OAB to antimuscarinics were screened for the study but 11 were excluded due to: recurrent urinary tract infections in 5 cases, prostate enlargement in 4 (one of which with bilateral kidney dilatation) and uncontrolled blood hypertension in 2. A total of 30 patients (19 females and 11 males) were finally included in the study. Age was 72.4 ± 9.8 years; disease duration was 8.2 ± 4.2 years (Table 1). All patients were refractory to at least two antimuscarinics previously taken for 4 months. These medications have been stopped in all cases due to intolerable side effects, mainly dry mouth and constipation, but also because of the emergence of cognitive alterations. Out of 30, 24 patients completed the study. The neurologic characteristics of the patients are showed in Table 2. As noted, the neurologic impairment, as shown by the mean values of H&Y scale and UPDRS, was mild, and the cognitive status, as detected by MOCA and MMSE, was slightly affected. We did not detect any significant difference between males and females with regards age, disease duration and scores of H&Y and UPDRS. Again, MOCA and MMSE evaluations did not significantly differ between male and female PD patients.

Urologic complaints. At baseline, the most frequently reported urinary symptoms were urinary urgency, experienced by all the patients, and UUI detected in 28/30 (93.3%) patients. Twenty-seven (90%) patients complained of nocturia and 25 (83.3%) had increased daytime urinary frequency. All the patients voided spontaneously and only five presented with mild dysuria. Urodynamic investigation showed detrusor overactivity in all cases, with reduced MCC and high detrusor pressure during bladder filling (Table 3). On pressure–flow study, five patients (three males and two females) presented with high detrusor pressures at maximum flow rate (higher than 25 cm H_20) and low

Table 1. Demographics of 30 patients affected by Parkinson's disease with refractory NLUTS, treated with oral mirabegron, 50 mg/day.

Patients, *n* (M/F)	30 (M: 11/F: 19)
Age, years, mean ± SD	72.4 ± 9.8
Disease duration, years, mean ± SD	8.2 ± 4.2
Number of antimuscarinics previously used, mean ± SD	3.6 ± 2.1
Number of comorbidities, median (range)	3 (1–5)
Type of comorbidities	*Hypertension
	*Hypercholesterolemia
	*Ischaemic encephalopathy
	*Chronic lung diseases
	*Osteoarticular diseases
	*Hypothyroidism
	*Affective disorders
Comorbidities/patient, *n*	1: 6 patients
	2: 4 patients
	3: 10 patients
	4: 2 patients
	5: 8 patients

F, female; M, male; NLUTS, neurogenic lower urinary tract symptoms; SD, standard deviation.

Table 2. Neurologic characteristics of 30 patients affected by Parkinson's disease with OAB, treated with oral mirabegron, 50 mg/day.

Sex	Age (years) (mean ± SD)	Disease duration (years) (mean ± SD)	Hoen &Yahr score (mean ± SD)	UPDRS score (mean ± SD)	MOCA score (mean ± SD)	MMSE score (mean ± SD)
F = 19	73.4 ± 8.9	7.6 ± 3.9	2.7 ± 0.8	30.5 ± 13	22.5 ± 5.3	25.5 ± 4.6
M = 11	67.3 ± 9.6	8.8 ± 4.5	2.3 ± 1.1	27.3 ± 10	23.3 ± 3.2	23.2 ± 3.2

F, female; M, male; MMSE, Mini Mental State examination; MOCA, Montreal Cognitive Assessment; OAB, overactive bladder; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

maximum flow rate due to a reduced relaxation of the external urethral sphincter; nevertheless, they did not present with high postvoid urinary residual volume (Table 3). At baseline, the mean ± SD value of the I-QoL was 39 ± 28.4. At the 3-month follow up, seven (23.3%) patients achieved a complete urinary continence, as observed in the 3-day voiding diary. At the same timepoint, significant decreases in the daily frequency of urinary urgency and UUI episodes were observed in 24 patients, as compared with baseline (from 9.7 ± 3.6 to 6.2 ± 2.9 and from 4.2 ± 2.1 to 2.9 ± 1.3,

Table 3. Urodynamic characteristics of 30 patients affected by Parkinson's disease at screening visit and then treated with oral mirabegron, 50 mg/day.

MCC (ml)	195.3 ± 62.5
UDC first volume (ml)	140.21 ± 142.3
UDC max pressure (cm H_2O)	33 ± 22.9
$P_{det}Q_{max}$ (cm H_2O)	69.8 ± 184.4
Q_{max} (ml/s)	13.3 ± 7.1
PVR (ml)	23 ± 31.2

Values are expressed as mean ± SD.
MCC, maximum cystometric capacity; UDC max pressure, maximum pressure of uninhibited detrusor contractions; $P_{det}Q_{max}$, detrusor pressure at maximum flow rate; Q_{max}, maximum flow rate; PVR, postvoid residual urinary volume; SD, standard deviation.

respectively, $p < 0.001$). Also, daytime and nighttime urinary frequencies significantly improved (from 9.2 ± 1.6 to 5.6 ± 2.9, and from 4.4 ± 2.1 to 2.1 ± 1.3, respectively, $p < 0.001$). A significant improvement was observed in the mean ± SD value of the I-QoL (from 39 ± 28.4 to 66.8 ± 29.2, $p = 0.01$). Six patients stopped taking mirabegron due to poor efficacy (four cases) or because of the cost of the drug (two cases). Most importantly, the mean VAS score and the mean I-QoL score significantly improved, from 3.8 ± 0.9 to 6.7 ± 1 and from 25 ± 2.1 to 82 ± 1.4, respectively ($p < 0.001$). With uroflowmetry, we did not detect any significant difference between the maximum flow rate and PVR before and after mirabegron treatment. At the 3-month follow up, when comparing satisfaction with treatment and the I-QoL between patients with both normal detrusor pressures and maximum flow rates during voiding and those with increased detrusor pressures and low flow rates, we did not observe any significant difference in VAS score (6.8 ± 0.9 *versus* 6.2 ± 1.1, respectively; $p = 0.2$) or value of the I-QoL (66.2 ± 29.6 *versus* 65.6 ± 31.8, respectively; $p = 0.3$). At the 6-month follow up, the favourable results related to urinary symptoms, VAS and I-QoL scores, and persisted in all the 24 patients (Table 4).

Comorbidities

All patients had ⩾1 comorbidity (range: 1–5) and the most frequently reported were osteoarticular disease and affective disorders (anxiety and depression). All these comorbid conditions were chronic diseases under pharmacological treatment (Table 1).

Comparison between responders and nonresponders to treatment

Overall, 4 out of the 30 patients (3 females and 1 male) stopped taking mirabegron at the 3-month follow up due to poor effectiveness. When analysing the clinical characteristics at baseline of these patients, we were able to observe that they presented with a significantly longer duration of the neurological disease, and with a trend to a significantly worse H&Y score, as compared with responders (Table 5).

Side effects

No consistent variation in blood pressure or pulse rate have been detected during all follow ups and no serious adverse effect was reported. No patient stopped taking the pharmacological agent due to adverse effects.

Discussion

LUT symptoms (LUTS) are among the most frequently reported nonmotor symptoms in PD patients, with OAB symptoms being the most common. LUTS in PD patients are reported to be associated with poorer QoL, falls and admission to care.[16] Similar to the treatment of OAB in the general elderly population, to date, after behavioural therapy, antimuscarinics are the main treatment for OAB in PD patients. However, limitations are frequent, including nonresponse, constipation and cognitive impairments.[17] Alternative strategies can be represented by mirabegron oral treatment, or botulinum toxin intradetrusor injections in selected cases.

In this pilot study, we show that mirabegron, a β-3 receptor agonist inducing detrusor muscle relaxation, was associated with reporting fewer urinary symptoms in the majority of OAB patients with PD who were refractory to the conventional treatment with antimuscarinics. Herein, we clearly demonstrate for the first time that mirabegron was not only able to improve urinary symptoms in PD patients but also many aspects of their QoL. Only few recently published studies reported on the beneficial effect of mirabegron in

Table 4. Urological results before, and at 3 and 6 months after oral treatment with mirabegron (50 mg/day) of 24 patients affected by Parkinson's disease with OAB.

	Baseline	3 months' follow up	6 months' follow up	*p*
Daytime urinary frequency	9.2 ± 1.6	5.6 ± 2.9	5.8 ± 2.5	$p < 0.001$
Night-time urinary frequency	4.4 ± 2.1	2.1 ± 1.3	2.0 ± 1.5	$p < 0.001$
Daily frequency of urinary urgency episodes	9.7 ± 3.6	6.2 ± 2.9	6.4 ± 3.1	$p < 0.001$
Daily frequency of UUI episodes	4.2 ± 2.1	2.9 ± 1.3	3.1 ± 1.6	$p < 0.001$
Q_{max} (ml/s)	13.3 ± 7.1	13.6 ± 5.3	13.9 ± 5.5	$p < 0.008$
PVR (ml)	23 ± 31.2	23.1 ± 30	24.3 ± 31.1	$p < 0.008$

Daytime, night-time urinary frequency, urinary urgency and UUI: episodes/ day (mean ± SD values).
OAB, overactive bladder; UUI, urge urinary incontinence, Q_{max}, maximum flow rate, PVR, postvoid residual urinary volume; SD, standard deviation.

Table 5. Comparison between responder and nonresponder Parkinson's disease patients, treated with mirabegron 50 mg/day at the 3-month follow up.

	Responders $n = 24$	Nonresponders $n = 4$	*p*
Neurological disease duration, years	7.9 ± 4.1	12.5 ± 3.7	$p = 0.04$
Hoehn–Yahr score	2.5 ± 0.9	3.3 ± 1.1	$p = 0.068$

Values are expressed as mean ± SD.
SD, standard deviation.

controlling OAB symptoms in patients with neurogenic diseases. In one study performed in 44 patients with central nervous system disorders,[18] mirabegron low dosage effectively decreased urgency symptoms, but among the included patients only six were affected by PD. Three previously published studies (two prospective, randomized controlled trials, and one retrospective analysis) reported the results of mirabegron 50 mg once daily, in patients with spinal cord injury and multiple sclerosis.[19–21] In two of these studies, patients received mirabegron 25 mg once daily, which was adapted to 50 mg after 2 weeks.[20,21] As a result, mirabegron 50 mg once daily improved both urodynamic variables and patient-reported outcomes in patients with Neurogenic Detrusor Overactivity (NDO), with a good safety profile. A more recent study showed favourable effects of mirabegron 50 mg once daily also in paediatric patients with neurogenic bladder due to spina bifida.[22]

In the present study the therapeutic benefit of mirabegron 50 mg once daily was observed early at the 3-month follow up, with the majority of patients (24/30) presenting significant improvements in all the considered OAB symptoms and, worth noting, without any concomitant mild or moderate adverse effect. Moreover, patients' satisfaction with treatment, assessed by the VAS and the I-QoL, significantly improved. All these improvements persisted along the whole observation period and only four patients discontinued treatment due to lack of effect at the 3-month follow up. These four nonresponder patients differed from the

others for a significantly longer duration of the neurological disease, and for worse (but not significant) H&Y scores. In the present study, mirabegron 50 mg once daily was also effective in controlling OAB symptoms in five patients with a mild dysuria and a baseline BOO condition due to a nonrelaxing external urethral sphincter. The low PVR detected in these patients did not require the use of alpha-blocker medications.

These results appear to be of a great relevance, particularly in patients with NLUTD due to PD, in whom the use of anticholinergics, typically applied to treat urinary symptoms, can add to the anticholinergic burden of antiparkinsonian therapies. Indeed, many studies have found anticholinergic burden, defined as the cumulative anticholinergic potential resulting from polypharmacy,[23] to be a significant risk factor for falls and fractures, delirium[24] and cognitive impairment in elderly populations.[25] Patients may also be susceptible to anticholinergic effects due to the cholinergic dysfunction as part of the disease process. Crispo and colleagues found that patients with the highest anticholinergic burden were more likely to be diagnosed with a fracture and delirium compared with those not taking medications with anticholinergic effects.[26] For these reasons, mirabegron has recently emerged as a potentially safe and effective treatment for OAB in neurogenic OAB patients, with some preliminary evidence.[27] In a recent systematic literature review with a mixed treatment comparison of medical treatments for non-neurogenic OAB, mirabegron 50 mg appeared to be as efficacious as antimuscarinics in reducing the frequency of micturition incontinence and UUI episodes (with the exception of solifenacin 10 mg) but with significantly less side effects.[28] In the general older population, the few available data showed that the pharmacological agent induced a significant but modest reduction in the mean number of daily micturitions and incontinence episodes, compared with placebo, but without severe side effects.[29]

One possible concern regarding the use of a β3-agonist in PD patients is the possible presence of orthostatic hypotension or variability in blood pressure in the supine position (supine hypertension). Hypertension, on the other hand, has been the most commonly reported adverse event across the OAB phase III population, occurring in approximately 0.4–10% of patients receiving mirabegron 50 mg *versus* placebo, or 0.4% *versus* solifenacin.[30] However, in one of these studies, the mean increase in systolic and diastolic blood pressure associated with mirabegron 50 mg was ⩽1 mm Hg in OAB patients and was reversible upon treatment discontinuation.[31] Supine hypertension, described as 'a somewhat paradox situation', can be present in PD patients with advanced dysautonomia and orthostatic hypotension, and usually occurs in chronic autonomic failure.[32] None of our patients with mild neurologic impairment complained of symptomatic supine hypertension during treatment with mirabegron, although its exclusion could have been made only with a 24 h ambulatory blood pressure monitoring. Also, in the present study, mirabegron was well tolerated without any systemic side effects during follow up of all patients. In addition, it did not affect bladder emptying in PD patients, as already reported in the literature.

A possible limitation of our study is the lack of a placebo group; indeed, we performed a preliminary study wherein all patients acted as their own control. Thus, we could not account for any placebo effect related to the application of a new pharmacological agent.

Other limitations are the short-term follow up and the small number of patients included. Nevertheless, the favourable results of mirabegron treatment in the majority of our PD patients, who were previously compelled to stop anticholinergics due to side effects, support the possibility of a new, alternative and safe treatment for their OAB symptoms.

Conclusion

In this pilot study, we demonstrated the feasibility of mirabegron to control urinary symptoms in patients affected by PD and OAB refractory to conventional drugs in the short term. The lack of intolerable side effects to mirabegron in these patients refractory to antimuscarinics due to tolerability issues can be considered the most relevant advantage of this kind of treatment in patients with PD and OAB.

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Conflict of interest statement

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