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Urodynamic Parameters After Solifenacin Treatment in Men With Overactive Bladder Symptoms and Detrusor Underactivity

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Aims: To describe the changes in urodynamic parameters and to assess patients' perceptions of voiding difficulties and improvements in symptom bother after solifenacin treatment in men with overactive bladder (OAB) and detrusor underactivity (DUA). **Methods:** In this prospective study, 49 neurologically intact men were enrolled. DUA was defined as a bladder contractility index (BCI) <100. All subjects received 5 mg of solifenacin once a day for 120 days. A complete urodynamic study was carried out on the day before to the first dose of solifenacin and at day 120. **Results:** Solifenacin treatment resulted in a decrease in Q_{max} during UDS (−0.6 ml/sec; $P = 0.007$), $P_{det}Q_{max}$ (−6.4 cmH_2O; $P < 0.001$), BOOI (−7.5; $P < 0.001$), BCI (−3.8; $P = 0.001$), BVE (−4.4%; $P = 0.006$), and voided volume (−7.5 ml; $P = 0.09$). On the contrary, PVR (+6 ml; $P = 0.152$), and maximum cystometric capacity (+22.9 ml; $P = 0.001$) increased. The regression analysis suggested that changes in urodynamic parameters after solifenacin treatment were limited for BOOI (9.4%), $P_{det}Q_{max}$ (8.4%), and BCI (6.5%), with no significant impact on Q_{max} during UDS, BVE, volume voided and PVR. No significant change in subjective perception of voiding difficulties was found. The incidence of AUR was 2.2% and improvement in patient's experience of OAB symptoms bother after solifenacin treatment was observed. **Conclusions:** Solifenacin treatment results in changes of urodynamic parameters. These changes, however, seem not to be of clinical significance as suggested by the lack of subjective deterioration in voiding difficulties and by the low incidence of AUR. *Neurourol. Urodynam. 28:52–57, 2009.* © 2008 Wiley-Liss, Inc.

Key words: acute urinary retention; detrusor underactivity; LUTS; solifenacin; voiding disorders

INTRODUCTION

The International Continence Society (ICS) defines overactive bladder (OAB) syndrome as "urgency, with or without urge incontinence, usually with frequency and nocturia."[1] Epidemiological evidence indicates that symptoms of OAB are common and likely affect up to 50–100 millions of person worldwide. Detrusor underactivity (DUA) occurs in men of all ages. DUA is defined as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span.[1] DUA may influence the clinical presentation and impede the therapy of disorders as common and as disparate as idiopathic detrusor overactivity (IDO) and benign prostatic hypeplasia (BPH). Patients with DUA comprise up to 17% of all men with lower urinary tract symptoms (LUTS)[2] and some of them have concomitant urodynamically confirmed IDO.[3] LUTS include OAB symptoms and voiding symptoms. Although this latter are more prevalent in men with DUA or bladder outlet obstruction (BOO), OAB symptoms are generally more bothersome and, thus, they represent an important target in the management of men with DUA or BOO and OAB. Currently, treatment of OAB is focused on controlled relaxation of the detrusor muscle. Antimuscarinic agents are used in the treatment of OAB, and it has been shown to decrease episodes of leakage, decrease the number of voids per day, and increase patients' quality of life.[4] Solifenacin is an effective muscarinic receptor antagonist with selectivity for M_3 receptor in the urinary bladder.[5] In clinical studies, solifenacin treatment resulted in significant reductions in urgency and other symptoms of OAB with acceptable level of side-effects.[5] However, antimuscarinic therapy could be associated with worsening of voiding difficulties in men with voiding disorders such as BOO or DUA. Although Abrams et al.[6] suggest that anticholinergic drugs might be safely used in men with BOO, current clinical guidelines do not recommend the routinely use of anticholinergics in these patients. Nevertheless, the use of anticholinergics in such men remains attractive and studies are required to establish the safety that this treatment has for men with OAB and low detrusor contractility. In the current study, we described the changes in urodynamic parameters and in subjective perception of voiding symptoms after solifenacin treatment in a cohort of men with OAB and DUA. Additionally, the incidence of AUR and the subjective improvement of OAB symptoms were also reported.

MATERIALS AND METHODS

Experimental Design and Patients Recruitment

This is a prospective study with pre- and post-test design conducted at the Urology Department of the University of L'Aquila. All men assessed in our urodynamic unit who were studied with urodynamic study (UDS) from December 2005 to December 2006 were screened for the study. Our institutional

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review board approved the protocol. Following informed consent, all subjects underwent a detailed clinical evaluation, including full history, physical examination (general, abdominal, rectal and neurological) bladder diary and questionnaire, non-intubated uroflowmetry, urinanalysis with culture when required, cytology in men with suspected carcinoma. Neurologically intact men aged ≥40 years were eligible whether they had (1) urinary frequency (eight or more micturitions per 24 hr) and urgency (strong and sudden need to urinate), with or without urgency incontinence (one or more episodes per 24 hr), and (2) concomitant urodynamic evidence of DUA. Previous acute urinary retention (AUR) was not considered exclusion criteria. Low detrusor contractility was defined as a bladder contractility index (BCI) of less than 100.[7] BCI was obtained according to the following formula: $P_{det}Q_{max} - 5Q_{max}$. Exclusion criteria included urinary tract infection, prostate surgery, bladder stone, urogenital tumors, use of indwelling catheter or self-catheterization program, treatment within 3 weeks of enrollment with any anticholinergics or α1-adrenergic antagonists, treatment with 5α-reductase inhibitors within 6 months of enrollment, any condition for which antimuscarinics were contraindicated.

Intervention

All enrolled men received 5 mg of Solifenacin once a day for 120 days. The solifenacin administration was started the day of enrolment (Baseline). Medications (30 days supply) were dispensed during each study visit. Patients were instructed to tape any medications not taken back into the blister pack, to account for any selective adherence. During follow-up visits, blister-packed medications were counted, including medications not taken. Follow-up started on the first day of treatment. Patients were followed up every 30 days. All adverse events (AEs) were recorded. AEs were noted by direct observation and spontaneous patient report, and classified as mild (not interfering with usual function), moderate (interfering to some extent with usual function), or severe (interfering significantly with usual function). Solifenacin is a trademark of Astellas Pharma, Inc., Nihonboshi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan. For this study solifenacin was kindly provided by Dr. Carmine Presutti (Astellas Pharma S.p.A, Italy).

Urodynamic Protocol

All enrolled patients underwent a multichannel UDS (Urobenchmark 2000/3, SI.EM., Milan, Italy) performed from a single investigator (P.R). A complete UDS had been carried out on the day before to the first dose of solifenacin (baseline) and at day 120. For our purpose, the following measurements were manually extracted from each study trace: Q_{max} obtained during UDS, $P_{det}Q_{max}$, PVR, maximum cystometric capacity, and volume voided. BOO index (BOOI) was obtained according to the following formula: $P_{det}Q_{max} - 2Q_{max}$. BVE was calculated using the formula, bladder voiding efficacy (BE) = (Volume Voided × 100)/maximum cystometric capacity. The UDS was conducted with normal saline at non-physiological filling rate (30 ml/min). A 6 Fr dual-lumen urethral catheter and a 9 Fr rectal balloon catheter were used. Bladder storage function during UDS was assessed according with the ICS recommendations. Terminology used was conform to the definitions recommended by the ICS, except where specifically noted.[8]

Study Outcomes

Primary endpoints. As primary endpoints, we estimated the changes from baseline to day 120 of voiding function after solifenacin treatment. For this purpose, the following urodynamic variables were assessed: Q_{max} obtained during UDS, $P_{det}Q_{max}$, BVE, BCI, BOOI, volume voided, and PVR.

Secondary endpoint. As secondary endpoints, we estimated the changes, from baseline to day 120, in patient perception of voiding symptoms assessed by the four items of International prostate symptom score (IPSS) voiding symptoms, in number of urge urinary incontinence (UUI) episodes per week, in patient perception of treatment benefit assessed by "Patient Perception of Bladder Condition" (PPBC), in number of urgency episodes per 24 hr and in number of micturitions. Additionally, the incidence of AUR after solifenacin treatment was also recorded.

Statistical analysis. Statistical analysis was performed using SPSS 11.0 (SPSS, Inc., Chicago, IL) software. An alpha value threshold of 0.01 was used. All statistical tests were two-tailed. Continuous variables were normally distributed (Shapiro-Wilk test $P < 0.01$) and were presented as mean and CI 99% and analyzed using a Student *t*-test for paired data. General Linear Model with weighted least-squares analysis for maximum cystometric capacity was curried out to evaluate the impact of solifenacin treatment on UDS parameters.

RESULTS

Study Flow Chart, Clinical-Demographic Characteristics and Adverse Events After Solifenacin Treatment

Between December 2005 to December 2006, 290 men were assessed in our urodynamic unit and 49 of them were enrolled in the study. The participation rate was 16.8% (49/290 subjects). In Table I, we describe the baseline characteristics of all patients, the incidence of AEs and the number of patients discontinuing before completing the study. The incidence of AUR after solifenacin treatment was also assessed. One man (2.2%) reported AUR after 23 days of solifenacin treatment, underwent catheterization, and dropped out of the study.

Urodynamic Parameters Before and After Solifenacin Treatment

In Table II, we show urodynamic parameters before (baseline) and after solifenacin treatment (day 120). Urodynamic parameters in subjects at baseline showed that the mean value of Q_{max} during UDS was 7.8 ml/sec (CI 99% 7.3–8.2 ml/sec), $P_{det}Q_{max}$ 47.9 cmH_2O (CI 99% 44.6–51.1 cmH_2O), BOOI 33.9 (CI 99% 29.6–38.3), BCI 83.8 (CI 99% 81.4–86.2), BVE 67.8% (CI 99% 63.8–71.8%), PVR 130 ml (CI 99% 114.3–146.2 ml), volume voided 239.1 ml (CI 99% 209.4–268.8 ml), maximum cystometric capacity 352.3 ml (CI 99% 296.3–408.2 ml). The same urodynamic parameters at day 120 demonstrated that the mean value of Q_{max} during UDS was 7.2 ml/sec (CI 99% 6.5–7.9 ml/sec), $P_{det}Q_{max}$ 41.5 cmH_2O (CI 99% 37.9–45.1 cmH_2O), BOOI 26.4 (CI 99% 21.9–30.8), BCI 80 (CI 99% 77.3–82.7), BVE 63.4% (CI 99% 57.8–68.9%), PVR 136.2 ml (CI 99% 115.4–157.2 ml), volume voided 231.6 ml (CI 99% 194.3–268.2 ml), maximum cystometric capacity 375.3 ml (CI 99% 326–425.6 ml).

Changes in Urodynamic Parameters After Solifenacin Treatment

In Table II, we report the mean changes in urodynamic parameters after solifenacin treatment. Solifenacin treatment resulted in a slight decrease in Q_{max} during UDS (mean changes −0.6 ml/sec; CI 99% −1.1 to 1.4 ml/sec; $P = 0.007$), $P_{det}Q_{max}$ (mean changes −6.4 cmH_2O; CI 99% −8.7 to −4.0 cmH_2O, $P < 0.001$), BOOI (mean changes −7.5; CI 99%

TABLE I. Clinical Characteristics, Adverse Events, and Patients Discontinuing Treatment

Characteristics	
Age (years)	66.7 (64.2–69.1)
Race no. (%)	
Caucasian	49 (100)
Previous AUR, no. (%)	0 (0)
Previous treatment with anticholinergics, no. (%)	5 (10.2)
OAB symptoms, no. (%)	
8 or more micturation/24 hr	49 (100)
Urgency	49 (100)
1 or more UUI/24 hr	13 (26.5)
OAB duration, no. (%)	
>6 months	49 (100)
Adverse events, no. (%)	
Acute urinary retention	1 (2.2)
Dry month	
Mild	9 (20)
Moderate	3 (6.7)
Severe	1 (2.2)
Costipation	
Mild	2 (4.4)
Moderate	2 (2.2)
Severe	0 (0)
Blurred vision	
Mild	0 (0)
Moderate	0 (0)
Severe	0 (0)
Discontinuing, no. (%)	
Adverse events	
Acute urinary retention	1 (2.2)
Dry month	1 (2.2)
Consent withdrawal	1 (2.2)
Lost follow-up	0 (0)
Protocol violation	1 (2.2)

−10.5 to −4.6, $P < 0.001$), BCI (mean changes −3.8; CI 99% −6.7 to −0.9; $P = 0.001$), BVE (mean changes −4.4%; CI 99% −8.4% to −0.4%; $P = 0.006$), and voided volume (mean changes −7.5 ml; CI 99% −15.6 to −1.1 ml; $P = 0.09$). On the contrary, PVR (mean changes +6 ml; CI 99% 4–8.7 ml, $P = 0.152$), and maximum cystometric capacity (mean changes +22.9 ml; CI 99% 32.7–54.4 ml; $P = 0.001$) increased. We have further quantified the impact of solifenacin treatment on UDS parameters (Table III). We have explored this aspect by a General Linear Model weighted for maximum cystometric capacity. This analysis showed that Solifenacin treatment did not have a significant impact on urodynamic parameters such as Q_{max} during UDS ($\eta^2 = 0.019$; $P = 0.102$), BVE ($\eta^2 = 0.098$; $P = 0.063$), PVR ($\eta^2 = 0.006$; $P = 0.50$), and volume voided ($\eta^2 = 0.038$; $P = 0.081$). Differently, solifenacin treatment seemed to have a small impact on the other parameters. In particular, a decrease in $P_{det}Q_{max}$ ($\eta^2 = 0.098$; $P = 0.002$), BOOI ($\eta^2 = 0.084$ $P = 0.003$), and BCI ($\eta^2 = 0.065$ $P = 0.009$) of the 9.8%, 8.4%, and 6.5% were found, respectively. In Figure 1 we present the typical changes of the urodynamic curves before and after solifenacin treatment.

TABLE III. Quantification of Solifenacin Treatment on Urodynamic Parameters

Urodynamic variable	Adjusted η^2 [a]	*P*-value
Q_{max} during UDS	0.019	0.102
Pdet Q_{max}	0.098	0.002
BOOI	0.084	0.003
BCI	0.065	0.009
BVE	0.098	0.063
PVR	0.006	0.50
Voided volume	0.038	0.081

UDS, urodynamic study; BOOI, bladder outlet obstruction iondex; BCI, bladder contractillity index; BE, bladder voiding efficiency; PVR, post-void residul.
[a]General Linear Model weighted for maximum cystometric capacity.

Patient Perception of Voiding Difficulties

To evaluate the subjective perception of voiding difficulties after solifenacin treatment, we analyzed the IPSS symptom score of each of the four voiding items. Table IV gives the IPSS voiding symptoms score stratified for each single question. No significant change in subjective perception of voiding difficulties after solifenacin treatment was observed.

Clinical Efficacy of Solifenacin Treatment

In Table IV, we report the mean changes in subjective perception of OAB symptoms after solifenacin treatment. The number of urge incontinence episodes per week decreased significantly after treatment (mean changes −6.8; CI 99% −8.8 to −4.5) ($P < 0.001$) as well as the PPBC (mean changes −2.2; CI 99% −2.7 to −1.65) ($P < 0.001$). The number of urgency episodes per 24 hr (mean changes −2.0; CI 99% −3.02 to −0.77; $P < 0.001$) and the micturation per 24 hr (mean changes −2.82; CI 99% −3.52 to −2.12; $P < 0.001$) were also reduced after solifenacin treatment.

TABLE II. Effects of Solifenacin Treatment in Relationship to Baseline Urodynamic Parameters

Urodynamic variable	Baseline	Day 120	Difference[a]	*P*-value[b]
Q_{max} during UDS (ml/sec)[c]	7.8 ml/sec (7.3–8.2)	7.2 (6.5–7.9)	−0.6 (−1.1–1.4)	$P = 0.007$
$P_{det}Q_{max}$ (cmH_2O)[c]	47.9 (44.6–51.1)	41.5 (3.7.9–45.1)	−6.4 (−8.7–−4.0)	$P < 0.001$
BOOI[c]	33.9 (29.6–38.3)	26.4 (21.9–30.8)	−7.5 (−10.5–−4.6)	$P < 0.001$
BCI[c]	83.8 (81.4–86.2)	80 (77.3–82.7)	−3.8 (−6.7–−0.9)	$P = 0.001$
BVE (%)[c]	67.8 (63.8–71.8)	63.4 (57.8%–68.9%)	−4.4 (−8.4–−0.4)	$P = 0.006$
PVR (ml)[c]	130 (114.3–146.2)	136.2 (115.4–157.2)	+6 (4–8.7)	$P = 0.152$
Voided Volume (ml)[c]	239.1 (209.4–268.8)	231.6 (194.3–268.2)	−7.5 (−15.6–−1.1)	$P = 0.009$
Maximum cystometric capacity (ml)[c]	352.3 (296.3–408.2)	375 (326–424.6)	+23 (13.5–33.4)	$P = 0.001$

BOOI, bladder outlet obstruction index; BCI, bladder contractillity index; BE, bladder voiding efficiency; PVR, post-void residual.
[a]Difference in mean changes from baseline to day 120.
[b]Student *t*-test for paired data.
[c]Mean and CI99%.

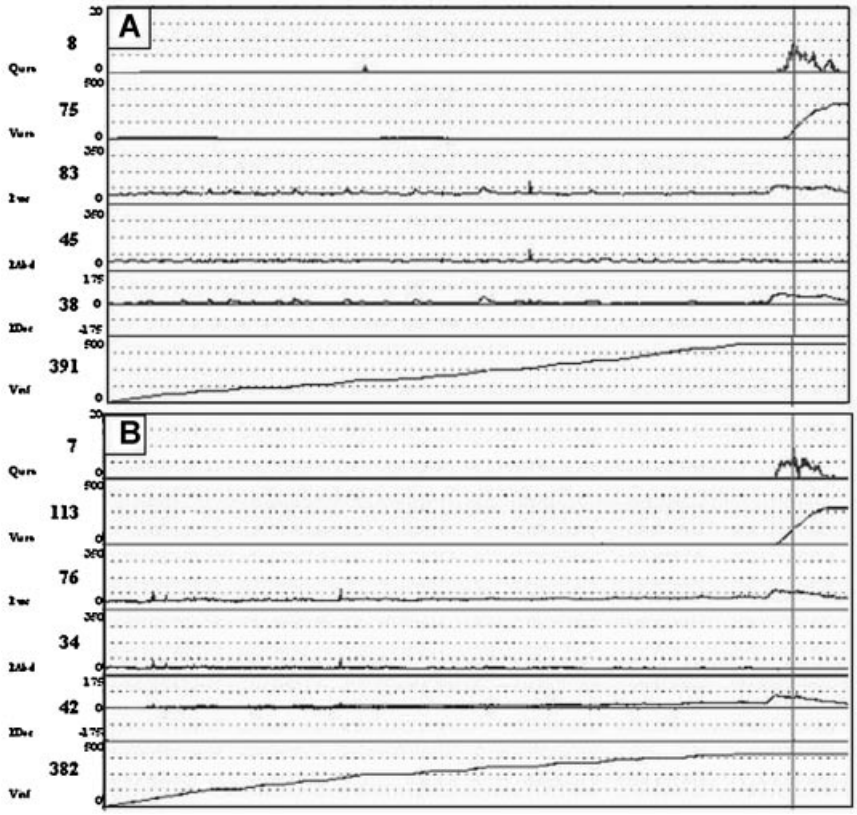

Fig. 1. Urodynamic studies at (**A**) baseline and (**B**) after solifenacin treatment in a 67-year-old man.

DISCUSSION

Approximately one-third of men with LUTS do not have BOO. In these cases OAB or DUA is often responsible for the complaints.[9] The two main treatment options for OAB syndrome are bladder retraining and anticholinergic drugs. The current level of concern is such that anticholinergics are not recommended in patients with OAB symptoms and voiding disorders.[10] Nevertheless, the use of anticholinergics remains attractive in this category of men. Results from previous studies seem to suggest a possible use for anticholinergics in men with LUTS and OAB.[11] Although significant concerns arise about validity of the data coming from these studies,[11] the apparent safety, in terms of AUR, of antimuscarinic drugs could be explained considering that these drugs act on the afferent nerves initiating the micturation reflex.[12] Additionally, being competitive antagonists, their action could be reduced during detrusor contraction when massive release of acetylcholine occurs.[13] Thus controlling OAB symptoms without aggravating voiding symptoms

TABLE IV. Patient Perception of Voiding Difficulties and Improvement in OAB Sysmptoms Bother After Solifenacin Treatment

	Symptoms score			
IPSS voiding symptoms	**Baseline[a]**	**Day 120[a]**	***P*-value[b]**	
Incomplete emptying	2.24 (2.01 to 2.47)	2.42 (2.14 to 2.71)	0.118	
Intemittency	1.68 (1.38 to 1.99)	3.51 (3.23 to 3.79)	0.486	
Weak urinary stream	3.35 (3.05 to 3.65)	3.51 (3.23 to 3.79)	0.164	
Hesitancy	2.15 (1.86 to 2.45)	2.29 (2.06 to 2.51)	0.110	
	Baseline[a]	**Day 120[a]**	**Difference[c]**	***P*-value[b]**
UUI/week (no.)	11.7 (79.8 to 13.4)	4.9 (3.2 to 6.7)	−6.8 (−8.8 to −4.5)	<0.0001
PPBC	4.75 (4.37 to 5.14)	2.55 (2.24 to 2.87)	−2.2 (−2.7 to −1.65)	<0.0001
Urgeny episodes/24 hr (no.)	5.2 (6.5 to 3.9)	3.2 (4.2 to 2.2)	−2.0 (−3.02 to −0.77)	<0.0001
Micturation frequency/24 hr (no.)	13.3 (12.6 to 14.1)	10.5 (9.8 to 11.2)	−2.82 (−3.52 to −2.12)	<0.0001

UUI, urge urinary icontinence; PPBC, patient perception of bladder condition.
[a]Mean and CI99%.
[b]Student *t*-test for paired data.
[c]Difference in mean changes from baseline to day 120.

is an important therapeutic goal in the management of these patients. In this regard, Abrams et al.[6] described the urodynamic findings of men with urodynamically proven BOO taking tolterodine or placebo. After 12 weeks, no clinically significant deterioration in BCI and PVR was found and no AUR in tolterodine group was reported. However several methodological criticisms have been pointed out for this study.[14]

In the current study, we measured the changes in urodynamic parameters and in subjective perception of voiding symptoms after solifenacin treatment in a cohort of men with OAB and low detrusor contractility. Additionally, the incidence of AUR and the subjective improvement of OAB symptoms after anticholinergic treatment were also reported.

Detrusor contractility declines with age.[15] The ICS Standardization Committee, in its 2002 report, did not define specific cutoffs for DUA.[8] For this reason we used cutoffs similar to those of other investigators.[7] Other urodynamic methods have been described for the assessment of bladder contractility during voiding.[3,16] Each method has its advantages and disadvantages, and controversy exists among experts regarding which method should be used. The ICS Committee did not state any preference for a certain method.[8] Here, we report a decrease in Q_{max} during UDS (−0.6 ml/sec), $P_{det}Q_{max}$ (−6.4 cmH20), BCI (−3.8), BVE (−4.4%), volume voided (−7.5 ml) and an increase in maximum cystometric capacity (+23 ml) and PVR (+6 ml) after solifenacin treatment. The results from this study seems further to provide some evidences that treatment with solifenacin of OAB in men with DUA is associated with an improvement in patient's experience of OAB symptoms bother. Additionally, results of PPBC scale demonstrate that patients perceived a significant improvement in their overall bladder condition. Although, urodynamic changes were statistically significant except for PVR and volume voided, the elementary question is if these differences were also clinically significant. A common misconception is that a statistically significant result is always of clinical significance. A statistically significant difference indicates only that the difference is real. It does not mean that the difference is large or important. Thus, it is important to assess the magnitude of treatment response and understand if it is also of clinical relevance. In order to quantify the magnitude of treatment response we have performed a regression analysis. One of the most important criticisms made to Abrams and co-workers was that quantification of changes in urodynamic parameters, such as Q_{max}, $P_{det}Q_{max}$, and BCI, were not adjusted for filling volume.[14] We believe that this is an important aspect and thus, by regression analysis, we have weighted each parameter for maximum cystometric capacity.

Although the minimally important difference in urodynamic parameters that could be considered meaningful for a patient has not been detected, changes in urodynamic parameters after a specific treatment should be interpreted considering also subjective measurable parameters. This methodological approach might provide a better picture of clinical impact associated with specific changes in urodynamic parameters. The regression analysis we have done indicates that of all urodynamic parameters only BOOI, $P_{det}Q_{max}$, and BCI had quantitatively appreciable differences. Once again, this does not mean that these changes are clinically significant and their meaning is not easily understandable. However the analysis of subjective perception of voiding difficulties, after solifenacin treatment, allow us to conclude that changes of this nature in urodynamic parameters do not appear to be of clinical significance in a population of men with OAB and DUA. In addition, this seems to be confirmed by the detection of a low incidence of AUR after solifenacin treatment and that is comparable to that observed in aged matched population with DUA.[3]

Our results should be analyzed in light of the potential limitations that the study has. The short study period and the relatively low number of patients are two important limitations. However, the use of a pre- and post-test design allowed us to reduce the number of men to be enrolled in the study and, at the same time, maintain a good statistical power. Additionally, this experimental design represents an attractive model since the comparisons were made "within subjects" rather than "between subjects." In this contest since in any research design, ideally, the experimenters could to attempt to control all outside variables except for the one(s) to be measured, we believe that there is no better control than oneself. Finally, the interpretation of efficacy parameters is partially limited by the lack of a placebo arm. Therefore, the present data may not allow conclusions regarding absolute benefits of solifenacin treatment in these patients. However, despite these limitations, the magnitude of subjective improvement in OAB symptoms is in good agreement with the results of studies on solifenacin.[5]

CONCLUSIONS

Our data suggest that 120 days of solifenacin treatment results in significant changes in BOOI, $P_{det}Q_{max}$, and BCI with no deterioration in subjective perception of voiding difficulties. Additionally, the results from this study seems to provide some evidences that treatment with solifenacin is also associated with an improvement in patient's experience of OAB symptoms bother. The incidence of AUR after active treatment was similar to that of aged matched population with DUA. To more definitively establish a role of anticholinergics in men with OAB and DUA, further studies should be performed with more patients and with sufficient follow-up.

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