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ORIGINAL ARTICLE

Effects of ospemifene on overactive bladder in postmenopausal women with vulvovaginal atrophy

E. Russo, G. Misasi, M. M. Montt-Guevara, A. Giannini and T. Simoncini

Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

ABSTRACT

Objective: Overactive bladder (OAB) is a complex and multifactorial syndrome associated with urinary frequency, urgency and incontinence. The menopause-associated hormonal changes play a role in the development of this condition. Vaginal estrogens are effective in improving OAB in postmenopausal women (PMW) with vulvovaginal atrophy (VVA). Ospemifene is a selective estrogen receptor modulator licensed for the treatment of VVA. This study aimed to evaluate the effects of ospemifene on OAB symptoms in PMW with VVA.

Methods: Forty PMW suffering from OAB and VVA received oral ospemifene (60 mg/day) for 12 weeks. All patients were assessed with a urodynamic study, a 3-day bladder diary and validated questionnaires (International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form [ICIQ-UI SF] and International Consultation on Incontinence Questionnaire – Overactive Bladder [ICIQ-OAB]) at enrollment and at the end of the study.

Results: Cytometric capacity, bladder compliance and verbal sensory threshold responses during bladder filling were improved after treatment. The voiding diary showed a significant reduction of daily voids, urge urinary incontinence episodes and nocturnal events. The median overall scores of the ICIQ-UI and ICIQ-OAB were also significantly improved.

Conclusions: Our study suggest that treatment with ospemifene in PMW suffering from OAB is associated with a reduction of OAB symptoms due to a decreased bladder sensitivity and with an improvement in quality of life.

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Overactive bladder; vulvovaginal atrophy; aging; menopause; selective estrogen receptor modulator; ospemifene

Introduction

The menopausal transition and the related estrogen withdrawal are frequently linked to the development of vulvovaginal atrophy (VVA) and of lower urinary tract symptoms (LUTS), including urinary incontinence, urgency, frequency and recurrent urinary tract infections [1]. Such association of symptoms is referred to as the genitourinary syndrome of menopause [2].

Overactive bladder (OAB) is a multifactorial syndrome [3] characterized by urgency with or without urinary incontinence, frequency and nocturia [4] that often emerges across the menopausal transition [5]. Urinary urgency is certainly the key and the most bothersome OAB symptom. As defined by the International Continence Society (ICS), urgency is 'the complaint of a sudden compelling desire to pass urine which is difficult to defer' [4]. Many conditions that are frequently encountered at midlife in women can also favor the development of OAB, such as the metabolic syndrome [6], affective disorders [7], urinary microbiota changes [8] or subclinical autonomic nervous system dysfunction [9]. OAB has a profound personal and socioeconomic impact. The prevalence of female OAB is estimated to range between 2% and 53% and increases with age, affecting 19.1% of women over 65 years of age [10].

Estrogen deprivation has been mechanistically linked in many ways to OAB and urinary urgency. Estrogen loss leads to activation of the Rho-kinase pathway, which is important for the development of detrusor overactivity (DO) [5,11]. Estrogen withdrawal is also linked to increased acetylcholine release in the bladder, to changes in urothelial afferent signaling and to increased connexin-43 expression [5,11]. These changes are thought to increase the sensitivity of the bladder urothelium and hence OAB.

A large body of evidence supports the use of topical estrogens for the treatment of urinary urgency in postmenopausal women (PMW) with OAB [12–15]. In the recent past, new therapeutic concepts for the treatment of VVA have been introduced, but the potential impact on the lower urinary tract has yet to be explored. Ospemifene is a selective estrogen receptor modulator that has approval for the treatment of moderate to severe symptomatic VVA in PMW [16,17]. Ospemifene acts as an estrogen agonist in the vaginal tissue without estrogenic effects on the breast and the

CONTACT Tommaso Simoncini tommaso.simoncini@unipi.it Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, 56126 Italy

endometrium [17]. The impact of ospemifene on postmenopausal LUTS has not yet been systematically investigated.

This study aims to assess the impact of ospemifene on OAB in women with VVA.

Methods

Study population

This is a prospective open-label intervention trial on 40 consecutive patients referred to our center between February 2019 and May 2021 with VVA and concomitant OAB. Eligibility criteria were postmenopausal status with moderate to severe VVA, not on local hormonal therapy, no abnormal uterine bleeding, negative urinalysis for infection, clinical diagnosis of OAB and/or urodynamic diagnosis of DO. Patients with contraindications for selective estrogen receptor modulator therapy, urodynamic stress or mixed urinary incontinence, neurological diseases or abnormal uterine bleeding and suspected or confirmed lactose allergy were excluded from this study.

Eligible patients received oral ospemifene 60 mg/day for 12 weeks. Patients underwent a complete urodynamic evaluation before and after treatment. Urodynamic assessment was carried out using Urobank Maestro (HC ITALIA) with a double lumen 6–7 F catheter. Subjective OAB symptoms were measured using validated questionnaires before and after treatment: 3-day bladder diary, International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) and International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB). All patients were monitored for discomfort, medication compliance and side-effects during the treatment by weekly telephone calls.

Eligible patients gave their written informed consent in accordance with the Declaration of Helsinki. The study was carried out under the recommendations of the Good Clinical Practice (ICH/GCP). The Regional Ethics Committee approved the protocol for Clinical Trials, Tuscan Northwest Wide Area (Approval Number: 12770).

Table 1. Demographic characteristics of patients.

Characteristic	n = *40*
Age (years)	60.45 ± 6.36
FMP (years)	50.93 ± 3.24
Years since FMP (years)	9.45 ± 6.08

Data are presented as mean ± standard deviation. FMP, final menstrual period.

Urodynamic assessment

The urodynamic assessment allows testing several aspects of low urinary tract function. Urodynamics includes uroflowmetry, cystometry and pressure-flow study. The cystometric evaluation aims to assess the bladder's ability to store urine and any bladder activity during the filling phase. Bladder sensitivity is evaluated by the verbal sensory thresholds that identify the different intensities of the patient's desire to void during bladder filling: the first sensation of filling, the normal desire to void and the strong desire to void. Bladder capacity (cystometric capacity) is calculated as the maximum tolerable volume of saline that can be infused, while bladder compliance is a measure of bladder elasticity.

Statistical analysis

Categorical variables were represented as frequencies and percentages. Continuous variables were checked for normal distribution using the D'Agostino–Pearson normality test. In accordance, normal continuous variables were represented as mean ± standard deviation and those with non-normal distribution were represented as medians and interquartile range.

To evaluate pre-treatment and post-treatment outcome, categorical variables such as DO and the pathologic score were analyzed using Fisher's exact test. To evaluate continuous variables, a one-tailed paired Wilcoxon test was used. For all comparisons, $p < 0.05$ was considered statistically significant.

Results

The mean age of the patients was 60.5 ± 6.4 years (Table 1). Of the 40 participants, three patients dropped out because of adverse effects during therapy (migraine and muscle aches).

Urodynamic parameters are presented in Table 2. Treatment with ospemifene was associated with a

Table 2. Urodynamic parameters ($n = 37$).

Parameter	*Baseline*	*12-week follow-up*	p-*Value*
Q_{max} (ml/s)	19.0 (16.0 – 22.5)	19.0 (17.0 – 24.0)	0.006
Q_{ave} (ml/s)	10.0 (8.5 – 12.0)	11.0 (9.0 – 13.0)	0.005
First sensation of filling (ml)	120.0 (98.0 – 132.5)	146.0 (130.0 – 180.0)	<0.001
Normal desire to void (ml)	200.0 (142.0 – 230.0)	230.0 (190.0 – 256.3)	<0.001
strong desire to void (ml)	270.0 (240.0 – 331.0)	308.0 (260.0 – 360.0)	<0.001
Cystometric capacity (ml)	350.0 (308.0 – 390.0)	390.0 (305.0 – 420.0)	<0.001
Bladder compliance (ml/cm^3 H_2O)	47.0 (39.5 – 68.0)	56.0 (41.0 – 70.0)	<0.001
$P_{det}Q_{max}$ (cm^3 H_2O)	33.0 (28.0 – 35.0)	33.0 (30.0 – 35.0)	ns
MUCP (cm^3 H_2O)	55.0 (46.5 – 60.0)	56.0 (45.5 – 60.0)	ns
Functional length (mm)	1.9 (1.7 – 2.0)	1.9 (1.7 – 2.0)	ns
Detrusor overactivity (*n*, %)	8.0 (21.62%)	8.0 (21.62%)	ns

Data presented as median (interquartile range). To analyze the outcomes after treatment, a one-tailed paired Wilcoxon test was performed. Detrusor overactivity was analyzed with Fisher's exact test. $p < 0.05$ was considered significant. Q_{max}, peak flow rate; Q_{ave}, average flow rate; $P_{det}Q_{max}$, detrusor pressure at maximal flow; MUCP, maximum urethral closure pressure; ns, not significant.

Table 3. Comparison of the parameters related to voiding diary and questionnaires ($n = 37$).

Parameter	*Baseline*	*12-week follow-up*	p-*Value*
Median number of voids (24 h)	10.0 (8.0 – 12.0)	8.0 (8.0 – 9.0)	<0.001
Urge urinary incontinence (24 h)	7.0 (5.0 – 8.0)	5.0 (5.0 – 6.5)	<0.001
Median number of nycturia events	3.0 (2.0 – 4.0)	2.0 (2.0 – 3.0)	<0.001
ICIQ-UI SF (score 0–21)	15.0 (14.0 – 15.0)	12.0 (10.5 – 13.5)	<0.001
Pathologic (score > 11)	37.0 (100%)	23.0 (62.16%)	<0.001
Frequency	4.0 (3.0 – 5.0)	3.0 (2.5 – 4.0)	<0.001
Quantity of leaks	4.0 (2.0 – 4.0)	2.0 (2.0 – 4.0)	<0.001
Quality of life	8.0 (7.0 – 9.0)	6.0 (5.0 – 7.0)	<0.001
ICIQ-OAB (score 0–16)	11.0 (9.0 – 12.0)	8.0 (6.0 – 9.5)	<0.001
Frequency of voiding	3.0 (2.0 – 3.0)	1.0 (1.0 – 2.0)	<0.001
Nocturia	3.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	0.016
Urgency voiding	3.0 (3.0 – 3.0)	2.0 (2.0 – 3.0)	<0.001
UUI	2.0 (2.0 – 3.0)	2.0 (1.0 – 2.5)	0.009

Data presented as median (interquartile range) or *n* (%). To analyze the outcomes after treatment, a one-tailed paired Wilcoxon test was performed. The pathologic score was analysis with Fisher's exact test. $p < 0.05$ was considered significant. ICQ-UI SF, International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form; ICQ-OAB, International Consultation on Incontinence Questionnaire – Overactive Bladder; UUI, Urge Urinary Incontinence.

significantly increased volume of saline needed to trigger the first sensation of filling, normal desire to void as well as strong desire to void (Table 2). Maximum bladder capacity and compliance were also significantly increased after treatment with ospemifene (Table 2).

While all of the patients had OAB symptoms, only eight had a urodynamic DO at baseline. These eight women showed similar improvements in the previously described cystometric parameters, but they still had DO after treatment with ospemifene (Table 2).

At uroflowmetry, which assesses how urine is emitted, no clinically significant modifications were found upon treatment with ospemifene (Table 2).

The urodynamic modifications were accompanied by consensual improvements in the LUTS perceived by the patients, as indicated by the voiding diary and questionnaires. The median number of voids during the day and during the night (nocturia) and the median number of episodes of urinary urgency were all significantly decreased after treatment with ospemifene (Table 3). The scores in total and in every single item of the questionnaires exploring quality-of-life impairment related to urinary incontinence and OAB were statistically improved after treatment with ospemifene (Table 3).

Discussion

Our study shows that PMW suffering from VVA and OAB symptoms experience improvements in urinary frequency and urgency, nocturia and urinary incontinence after 12 weeks of treatment with ospemifene. This finding is relevant since LUTS are a common and bothersome consequence of the menopausal transition, and there is a lack of effective therapeutic strategies to address this need.

There is no single form of OAB but, rather, several phenotypes based on the underlying mechanisms and pathophysiological cofactors. Menopausal estrogen withdrawal is one of these contributing factors and should be considered in developing personalized treatments for OAB [3].

OAB symptoms are part of the so-called genitourinary syndrome of menopause, that includes all the changes in the uro-genital district linked to the hormonal modifications happening at this age. A common feature of such problems is that they are progressive and worsen with aging and increasing time from last menstrual period. Early and continued hormonal intervention is critically important to prevent worsening of VVA [18]. In parallel, there is solid evidence that estrogen replacement is effective in ameliorating urge urinary symptoms and incontinence in PMW [19].

Strategies able to stop or reverse urogenital aging may be effective in the treatment of genitourinary syndrome of menopause with prevalent OAB symptoms [13,15]. To this extent, menopause physicians should identify those women who develop LUTS at the menopausal transition who could be candidates for hormonal interventions.

Nowadays, new approaches for the treatment of VVA, including the orally available selective estrogen receptor modulator ospemifene, have entered the therapeutic arena.

Preliminary evidence suggests that treatment of VVA with ospemifene results in improved OAB symptoms [20–23]. Moreover, a recent study showed that treatment with ospemifene in women with mixed urinary incontinence undergoing mid-urethral sling placement resulted in a significant improvement in terms of mean number of daily voids, urgent micturition events and nocturia events, and better scores in OAB quality-of-life questionnaires [23]. These results are consistent with our findings.

We also observed improvements in objective urodynamic parameters indicating a decreased bladder sensitivity and an increased capacity and compliance that explain the change in subjective perception of urgency and in the voiding behavior. Similar results on urodynamic parameters were found by Schiavi et al. in women with mixed urinary incontinence undergoing surgery [23].

OAB has long been attributed to increased and uncontrollable detrusor muscle contractility (indicated as DO) [24]. More recently, evidence for a pathogenetic role of a dysfunction of the urothelium, the urethra and the central and peripheral nervous system is emerging [3,25]. Dysfunction of these districts is more specifically linked to altered bladder sensation and sensory urgency that turn into an early perception of bladder filling and into an earlier and eventually

urgent desire to void [4]. Sensory urgency is hypothesized to be an early step in the development of OAB, with DO being a later phenomenon in the spectrum of the disease [26].

Our present results indicating that ospemifene improves bladder sensitivity might support the concept that hormonal modulation in perimenopausal women and PMW with OAB symptoms might act in the preliminary phases of the cascade, leading to later overt OAB. Hence, ospemifene could be a therapeutic option in PMW with early forms of OAB.

In the presence of an overt myogenic dysfunction of OAB characterized by phasic involuntary detrusor contractions, the use of vaginal estrogens is supported by level 1 evidence [5,15]. In our series of patients only 22% had DO at baseline. No urodynamic changes in terms of DO and detrusor pressure were found after treatment, suggesting that ospemifene does not act on detrusor contractility. This contrasts with previous studies on this topic [23,27]; however, the low incidence of DO in our population makes it difficult to reach conclusive evidence.

OAB and urge urinary incontinence are mostly managed with anti-muscarinic agents that are characterized by significant dose-related side-effects that often limit patients' adherence, with more than 85% of women stopping the treatment over 12 months [28]. To this extent, the contribution to improved bladder sensitivity brought by the addition of estrogen or ospemifene to these drugs could be important to achieve a synergistic effect and to lower discontinuation rates [15,29,30].

The strengths of our study are the prospective design and the urodynamic characterization of OAB before and after treatment. An intrinsic limitation of the study is the expected improvement in VVA-related symptoms due to ospemifene, which might be a confounder in the identification of the changes in urinary symptoms by women.

In conclusion, our study demonstrates that women with menopause-associated OAB benefit from treatment with ospemifene, showing improved bladder sensitivity and subjective and objective measures of OAB. This seems to result from a modulation of bladder afferent signaling.

This finding is important as OAB is a common problem that is largely underestimated and underdiagnosed. Menopause physicians should be aware of OAB and be knowledgeable of its pathophysiology in order to identify those women who are candidates for an early and continued therapy to treat this condition.

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ORCID

E. Russo http://orcid.org/0000-0001-8920-3899
G. Misasi http://orcid.org/0000-0002-4056-9328
M. M. Montt-Guevara http://orcid.org/0000-0002-8648-3845
A. Giannini http://orcid.org/0000-0003-0512-4435
T. Simoncini http://orcid.org/0000-0002-2971-0079

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