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Does Mirabegron the β3 Agonist Frequently Used in the Treatment of Overactive Bladder Really Affect the Respiratory System Negatively ? A Prospective Study

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ABSTRACT

Objective: Overactive bladder syndrome (OAB) has been defined by the International Continence Society (ICS) as feeling a sudden urge to urinate that mostly runs its course with increased daytime urination and waking up during the night to urinate. we aimed to contribute to the literature by investigating the effects of mirabegron treatment on the respiratory system in patients diagnosed with OAB.

Methods: The study was conducted on 63 patients diagnosed with OAB.A single dose of 50 mg tablets per day was prescribed to patients diagnosed with OAB to achieve standardization. Treatment was continued for three months. Spirometry and body plethysmography were performed to objectively evaluate the respiratory functions of patients with OAB.

Results: The spirometry and body plethysmography showed that the FVC value was 102.51 ± 16.99 L before, 101.77 ± 14.17 L at the first month, and 100.52 ± 15.98 L at the third month after mirabegron treatment. There was no statistically significant difference between the FVC value before mirabegron treatment and the FVC value measured at the first month after treatment, between the FVC value measured at the first month of treatment and the third month of treatment, and between the FVC values measured before treatment and the third month of treatment (p=0.805, p=1.000, p=1.000, respectively).

Conclusion: Our study results show that mirabegron, a β3 agonist, has no negative effect on

Keywords: β3 agonist; Mirabegron; Overactive Bladder; Respiratory; Spirometry

Introduction

Overactive bladder syndrome (OAB) has been defined by the International Continence Society (ICS) as feeling a sudden urge to urinate that mostly runs its course with increased daytime urination and waking up during the night to urinate. It may be accompanied by urine leakage before reaching the toilet following a sudden urge to urinate (Abrams et al., 2009). The symptoms of OAB are quite disturbing and sometimes seriously impair the patients' quality of life. The frequency of OAB has been reported at rates as high as 17%. The rate has been reported as 7-27% in males and 9-43% in females. OAB is thought to be a disorder resulting from loss of inhibition or increase in excitation mechanisms in the detrusor muscle during filling or emptying of the bladder. Specific receptors and neurotransmitters are involved in the physiology of the urothelium and detrusor and thus in the pathophysiology of the development of overactive bladder. The main ones are adrenergic, cholinergic, non-adrenergic and non-cholinergic receptors, interstitial cells and nerves that provide bladder afferent activity (Milsom et al., 2001).

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In studies that have examined the pathophysiology of OAB, all three beta-adrenoceptor subtypes (β1, β2, β3) have been shown in the detrusor muscle and the urothelium. The β3 subtype constitutes 97% of the beta-adrenoceptors in the bladder. Mirabegron is used in the treatment of OAB as it increases the urine storage of the bladder through its potent and selective agonism of β3 adrenoceptors (Nomiya & Yamaguchi, 2003; Yamaguchi & Chapple, 2007). Studies have also shown that beta-adrenoceptors are present not only in the bladder, but also in the adipose tissue, heart, vascular system and the skeletal muscles (Yamaguchi & Chapple, 2007). According to our knowledge, there are no studies in the literature examining the interaction of the β3 agonist mirabegron, which is widely used in OAB treatment, with these receptors on striated respiratory muscles and the effect of mirabegron on the respiratory system in this patient group.

In this study, we aimed to contribute to the literature by investigating the effects of mirabegron treatment on the respiratory system in patients diagnosed with OAB.

Methods

Study Design: The diagnosis of OAB was made according to the overactive bladder criteria accepted by the ICS. The patients received mirabegron treatment for three months. Spirometry and body plethysmography were performed before, one month after, and three months after the initiation of mirabegron treatment to assess the respiratory functions. The results were statistically analyzed and compared.

Study population: The study was begun with 88 patients diagnosed with OAB. Six patients in whom mirabegron was ineffective in the follow-ups, three patients who voluntarily wished to leave the study, nine patients who did not attend follow-ups, two patients who could not comply with the pulmonary function tests and three patients who could not complete the body plethysmography due to claustrophobia, were excluded from the study. The mirabegron treatment was discontinued in one patient who developed hypertension and one patient who complained of palpitation during the follow-up. These patients underwent the consultation of the cardiology polyclinic for further testing and treatment. The study was completed with 63 patients in total.

Patients under 18 years of age, those previously diagnosed with uncontrolled hypertension, those with chronic chest diseases such as chronic obstructive pulmonary disease (COPD) and asthma, those with severe kidney and liver failure, and with a history of chronic drug use that may interact with mirabegron were excluded from the study.

The flow chart of the patients included in and excluded from the study has been presented in Figure 1.

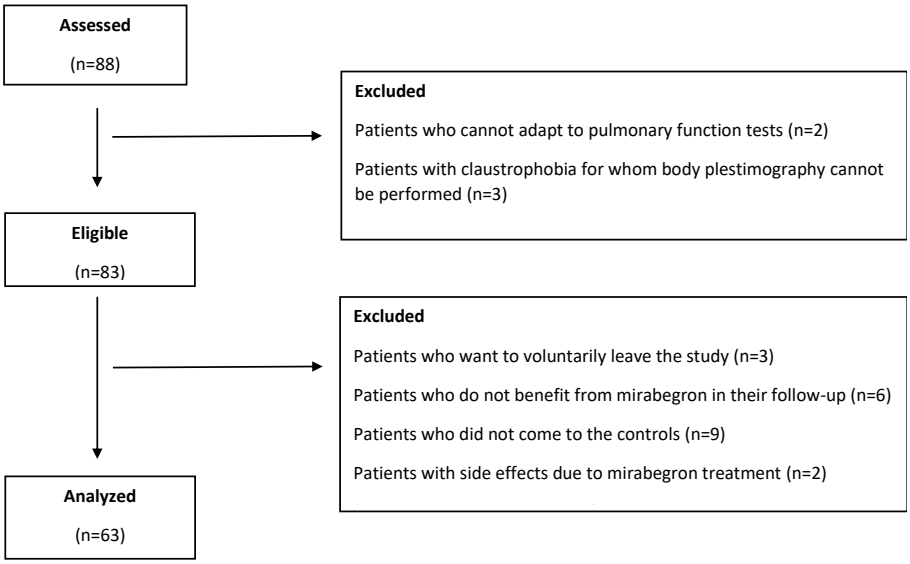

Figure 1. The flow chart of the patients included in and excluded from the study

Mirabegron treatment: A single dose of 50 mg tablets per day was prescribed to patients diagnosed with OAB to achieve standardization. Treatment was continued for three months. During the study, the response to treatment was measured using the Urogenital Distress Inventory (UDI-6) form.

Assessment of Respiratory Functions

Patients diagnosed with OAB underwent spirometry and body plethysmography to obtain an objective assessment of the respiratory functions.

Spirometry: Spirometry (device brand: Vyaire Vyntus PFT) was performed to identify disorders in lung functions and their severity in patients diagnosed with OAB. Each patient underwent a pulmonary function test in accordance with the American Thoracic Society/European Respiratory Society guidelines and the European predictive values (Miller & Enright, 2012; Quanjer et al., 1993). Using spirometry, the functional vital capacity (FVC), the forced expiratory volume in first second (FEV1), the FEV1/FVC ratios, the peak expiratory flow rates (PEF), and the forced expiratory flow between 25%-75% of vital capacity (FEF25-75) were measured.

Body plethysmography: Patients diagnosed with OAB underwent lung volume and capacity measurements by body plethysmography (device brand: Vyaire Vyntus BodyBox) based on the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (Wanger et al., 2005). The residual volume (RV) of the lungs, the total lung capacity (TLC) and the functional residual capacity (FRC) of the lungs that could not be measured by spirometry were measured by body plethysmography.

Statistical Analysis

The continuous variables were shown as mean and standard deviation. The groups' respiratory function test results based on time periods were compared using the paired sample t-test. P values lower than 0.05 were considered statistically significant.

Results

The study was conducted on 63 patients diagnosed with OAB. Of the 63 patients, 42 (66.7%) were male and 21 (33.3%) were female. The patients' average age was 41.0 ± 13.2 years and the average BMI was calculated as 25.5 ± 3.91 kg/m2. The demographic characteristics of the patients have been presented in Table 1.

Table 1. Demographic characteristics of the patients

Number of patients		63
Mean age ± SD, (year)		41.0 ± 13.2
Mean BMI ± SD, (kg/m^2)		25.5 ± 3.91
Gender, n (%)	Male	42 (66.7)
	Female	21 (33.3)

SD, standart deviation; BMI, body mass index

The spirometry and body plethysmography showed that the FVC value was 102.51 ± 16.99 L before, 101.77 ± 14.17 L in the first month, and 100.52 ± 15.98 L in the third month after mirabegron treatment. There was no statistically significant difference between the FVC value before mirabegron treatment and the FVC value measured at the first month after treatment, between the FVC value measured at the first month of treatment and the third month of treatment, and between the FVC values measured before treatment and the third month of treatment (p=.805, p=1.000, p=1.000, respectively). The average FEV1 value measured before mirabegron treatment was 99.60 ± 15.86 L and was measured as 99.00 ± 13.32 L at the first month after treatment and as 99.46 ± 12.32 L at the third month. There was no statistically significant difference between the average FEV1 value before mirabegron treatment and the FEV1 value measured at the first month after treatment, between the FEV1 value measured at the first month of treatment and the third month of the treatment, and between the FEV1 values measured before treatment and at the third month of treatment (p=1.000, p=1.000, p=1.000, respectively). The FEV1/FVC ratio before mirabegron treatment was 101.42 ± 5.87 and it was 100.68 ± 5.07 at the first month after treatment and 100.68 ± 14.04 at the third month of treatment. There was no statistically significant difference between the average FEV1/FVC value before mirabegron treatment and the FEV1/FVC value measured at the first month after treatment, between the FEV1/FVC values measured at the first month and the third month of treatment, or between the FEV1/FVC values measured before treatment and at the third month of treatment (p=0.511, p=1.000, p=1.000, respectively). The FRC value was 110.12 ± 20.60 L before mirabegron treatment, 109.93 ± 18.57 L at the first month after treatment, and 109.52 ± 19.65 L at the third month of treatment. There was no statistically significant difference between the average FRC value before mirabegron treatment and the FRC value at the first month after treatment, between the FRC value at the first month of treatment and the third month of treatment, and between the FRC values measured before treatment and at the third month of treatment (p=1.000, p=1.000, p=1.000).

The results of the measurements performed by spirometry and body plethysmography on patients diagnosed with OAB have been presented in Table 2.

Table 2. Comparative analysis of the effect of mirabegron treatment on lung functions by months

Variables	Beginning (1)	1st month (2)	3rd month (3)	p-value*
Mean FVC ± SD (L)	102.51 ± 16.99	101.77 ± 14.17	100.52 ± 15.98	0.439 1 vs 2 0.805 2 vs 3 1.000 1 vs 3 1.000
Mean FEV_1 ± SD (L)	99.60 ± 15.86	99.00 ± 13.32	99.46 ± 12.32	0.700 1 vs 2 1.000 2 vs 3 1.000 1 vs 3 1.000
Mean FEV_1/FVC ± SD (%)	101.42 ± 5.87	100.68 ± 5.09	100.56 ± 14.04	0.651 1 vs 2 0.511 2 vs 3 1.000 1 vs 3 1.000
Mean PEF ± SD (%) (L/sn)	98.79 ± 16.82	98.39 ± 14.37	97.68 ± 20.50	0.779 1 vs 2 1.000 2 vs 3 1.000 1 vs 3 1.000
Mean FEF_{25-75} ± SD (L)	84.90 ± 20.21	85.04 ± 18.30	85.00 ± 21.91	0.977 1 vs 2 1.000 2 vs 3 1.000 1 vs 3 1.000
Mean FRC ± SD (L)	110.12 ± 20.60	109.93 ± 18.57	109.52 ± 19.65	0.897 1 vs 2 1.000 2 vs 3 1.000 1 vs 3 1.000
Mean RV ± SD (L)	98.81 ± 29.84	98.22 ± 25.71	100.00 ± 23.80	0.630 1 vs 2 1.000 2 vs 3 0.920 1 vs 3 1.000
Mean TLC ± SD (L)	97.92 ± 15.23	98.79 ± 12.26	100.20 ± 10.04	0.064 1 vs 2 0.514 2 vs 3 0.152 1 vs 3 0.130

SD, standart deviation; BMI, body mass index; FVC, functional vital capacity; FEV1; forced expiratory volume in first second, PEF, peak expiratory flow rates, FEF25-75, forced expiratory flow between 25%-75% of vital capacity, FRC, the functional residual capacity; RV, residual volume; TLC, total lung capacity,

*Repeated measures ANOVA

Discussion

This prospective cross-sectional study aimed to assess the effects of mirabegron widely used in the treatment of OAB on the respiratory system and to contribute to the literature. In this study we conducted on 63 patients, we determined that mirabegron had no negative effects on the respiratory system. To the best of our knowledge, this study will become the first in the literature to investigate the effect of mirabegron on the respiratory system in patients diagnosed with OAB.

OAB is defined as a feeling of urgency with or without urinary incontinence without a proven infection or metabolic etiology, which is generally accompanied by frequent urination and nocturia (Abrams et al., 2009). It is a costly chronic symptom complex prevalent among the

community that significantly affects the individual's quality of life (Chapple et al., 2020).

The initial treatment of OAB includes non-invasive approaches such as lifestyle changes (fluid management, weight loss, reducing the consumption of tea and coffee), bladder education (techniques to suppress urgency) and pelvic floor muscle exercises. The second line treatment is pharmacotherapy, and mirabegron or antimuscarinic agents are recommended (Nambiar et al., 2018). In studies investigating the pathophysiology of OAB, all three beta-adrenoceptor subtypes (β1, β2, β3) have been shown in the detrusor muscle and the urothelium. The β3 subtype constitutes 97% of the beta-adrenoceptors in the bladder (Nomiya & Yamaguchi, 2003; Yamaguchi & Chapple, 2007).

Mirabegron is a potent and selective agonist of β3 adrenoceptors (Song, Lee, Park, & Kim, 2021). Mirabegron, β3-adrenoceptors cause detrusor smooth muscle relaxation, reduce the afferent signals from the bladder, improve compliance during bladder filling and increase the bladder capacity (Athanasiou et al., 2020). The American Urological Association (AUA) and the European Association of Urology (EAU) guidelines recommend oral antimuscarinics or β3-adrenoceptor agonists (β3-agonists) as first-line pharmacological treatment for OAB (Lightner, Gomelsky, Souter, & Vasavada, 2019; Nambiar et al., 2018).

Since their discovery in the late 1980s, β3 adrenoceptors have been identified not only in the bladder, but also in several human tissues such as the myocardium, the retina, the myometrium, the adipose tissue, the gall bladder, the brain, the blood vessels and the skeletal muscles (Chapple et al., 2020; Schena & Caplan, 2019). In a case presentation of a patient with Parkinson's disease receiving baclofen and mirabegron treatment conducted by Malsin et al. in 2019, it was reported that the β3 agonism of mirabegron may have similar effects to baclofen overdose and act synergistically with baclofen and reduce the rigidity of respiratory muscles and cause deterioration of lung functions (Malsin, Coleman, Wolfe, & Lam, 2019). Despite this study, in an experimental study conducted by Abe et al., it was shown that the intravenous infusion of β3 agonists dose-dependently increased the glucose uptake in three types of skeletal muscle, brown adipose tissue, white adipose tissue, the heart and the diaphragm (Abe, Minokoshi, & Shimazu, 1993). In the study conducted by Puzzo et al., it was reported that β3 adrenoceptor activation had important anabolic effects on skeletal muscles. In the same study, it was also concluded that β3 agonist treatment may be an effective therapeutic strategy to improve muscle growth and strength in various diseases associated with muscle loss or degeneration (Puzzo et al., 2016).

In this study we conducted, to assess the respiratory systems of patients diagnosed with OAB, the patients underwent spirometry and body plethysmography before the initiation of mirabegron treatment, one month later and three months after the initiation of mirabegron treatment. We identified that there was no significant difference between the FVC, FEV, FEV FEV1/FVC, PEF, MFEF, FRC, RV, and TLC values before the initiation of mirabegron treatment and at the first and third month of mirabegron treatment. Contrary to the case presentation of Malsin et al., our results support the pathophysiological mechanisms in the studies conducted by Puzzo et al. and Abe et al. Although Malsin et al. hypothesized, based on a single case, that mirabegron might have a negative effect on the respiratory system in a patient with Parkinson's disease, the findings of our prospective, observational, and controlled study with patient follow-up support the mechanism of mirabegron's high selectivity for β3-adrenergic receptors and its low affinity for β3-adrenergic receptors in the respiratory tract.

In our study, findings were obtained suggesting that mirabegron treatment does not have a significant adverse effect on respiratory functions. We believe that these results may provide guidance to discharge during the treatment planning process for patients diagnosed with overactive bladder (OAB). However, further large-scale, prospective, and randomized clinical studies are needed to reach more definitive conclusions on this matter.

Our study's limitations can be listed as the low number of patients, exclusion of patients with chronic diseases and absence of a control group.

Conclusion and Recommendations

Our study results show that mirabegron, a β3 agonist, has no negative effect on the respiratory system in patients diagnosed with overactive bladder. Prospective randomized clinical studies with more extensive series are required to demonstrate mirabegron's effect on the respiratory system.

Ethics Committee Approval: Ethics committee approval for this study was received from Atatürk University ethics committee (Date: January 1, 2020, Number: 968968).
Informed Consent: Necessary consents were obtained from the patients
Peer-review: Externally peer-reviewed.
Author Contributions: Concept-AEC, Design-AU, Supervision-TA, Data

Collection or Processing-KO, Analysis-FA, Literature Review-AU, AG, Writing the Manuscript-AEC, Critical Review-OA, EYU, ŞA

Conflict of Interest: The authors have no conflicts of interest to declare.

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