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Ocular and Systemic Safety of Mirabegron Treatment in Elderly People with Overactive Bladder

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Abstract

Objective: We aimed to test ocular and systemic safety of mirabegron medication in the treatment of overactive bladder in elderly patients.

Method: A total of 74 patients (40 male, 34 female) with symptoms of overactive bladder admitted to the urology clinic were included in the study. Patients over 60 years old were included. Patients were followed-up for 3 months. Symptom scores (according to OAB-V8 form), intraocular pressure (IOP) readings of right and left eyes, systolic and diastolic blood pressures of the patients were recorded before and after the treatment. At the end of 3 months, all values were re-evaluated and compared with pre-treatment data.

Results: Mean age was 69.48±7.8 years. The symptom score was found to be 18.67 ± 9.87 before the treatment and 9.83 ± 2.71 after 3 months of the treatment (p=0.0001). Right eye mean IOP value was 16.06 ± 2.62 mmHg before treatment and 15.85 ± 2.31 mmHg after treatment (p=0.341). Left eye mean IOP value was 15.96±2.35 mm mmHg before treatment and 15.94±2.21 mm after treatment (p=0.855). Systolic blood pressure measurements were 128.91±11.76 mmHg before treatment and 128.43±11.95 mmHg after the treatment (p=0.110). Diastolic blood pressure measurements were 81.94±9.83 mmHg before the treatment and 81.31±10.14 mmHg after the treatment (p=0.071).

Conclusion: Treatment of overactive bladder with mirabegron 50mg/day is well tolerated and safe in elderly patients.

Keywords: Overactive bladder; β3-adrenoreceptor agonist; Oculer safety.

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Yaşlı Hastalarda Aşırı Aktif Mesane Tedavisinde Mirabegron Tedavisinin Oküler ve Sistemik Güvenliği

Öz

Amaç: Yaşlı hastalarda aşırı aktif mesane (AAM) tedavisinde mirabegron tedavisinin sistemik ve oküler güvenliğini test etmeyi amaçladık.

Yöntemler: Çalışmaya üroloji kliniğine başvuran ve aşırı aktif mesane semptomları olan 34 kadın, 40 erkek toplam 74 hasta dahil edildi. 60 yaş üzeri hastalar alındı, ortalama yaş 69.48±7.8 saptandı. Günlük 50 mg mirabegron verildi. Hastalar 3 ay takip edildi. Hastaların tedavi öncesi ve sonrası; semptom skoru, sağ göz ve sol göz intraoküler basınçları (İOB), sistolik ve diastolik kan basıncı değerleri kaydedildi. 3. ayın sonundaki değerler ile tedavi öncesi değerler karşılaştırıldı. İkili hipertansif ilaç kullanan ve tansiyon değeri 155/95' in üzerinde olan hastalar çalışma dışı bırakıldı.

Bulgular: Semptom skoru tedavi öncesi 18.67±9.87 saptanırken, 3 aylık tedavi sonrasında 9.83±2.71 saptandı (p=0.0001). Sağ göz IOB değerleri tedavi öncesi 16.06±2.62 mmHg iken tedavi sonrası 15.85±2.31 mmHg saptandı (p=0.341). Sol göz IOB değerleri tedavi öncesi 15.96±2.35 mmHg iken tedavi sonrası 15.94±2.21 mmHg saptandı (p=0.855). Sistolik kan basıncı değerleri tedavi öncesi 128.91±11.76 mmHg iken tedavi sonrası 128.43±11.95 mmHg saptandı (p=0.110). Diastolik kan basıncı değerlerine bakıldığında tedavi öncesi 81.94±9.83 mmHg iken tedavi sonrası 81.31±10.14 mmHg saptandı (p=0.071).

Sonuç: Yaşlı hastalarda aşırı aktif mesane tedavisinde oral mirabegron 50 mg/gün kullanımı IOB' ı arttırmamaktadır. Genel olarak güvenli ve iyi tolere edilebilen bir tedavidir.

Anahtar kelimeler: β3-Adrenoreseptör agonist, aşırı aktif mesane, oküler güvenlik, mirabegron.

INTRODUCTION

Overactive bladder (OAB) is a condition in which there is a feeling of urgent need to urinate (with or without incontinence), frequent urination, nocturia and urinary tract infection without an underlying pathology. When it becomes chronic, it may lead to serious problems in the quality of life of the patients and may lead to depression, emotional stress and social isolation. Its prevalence increases with age. Drugs that block muscarinic receptors on the bladder have been used for a long time to reduce detrusor muscle contractions and eliminate disturbing OAB symptoms. Antimuscarinic drugs stand for the main basis in the treatment of OAB and the most commonly used drugs. However, the side effects associated with these drugs limit the use, especially in elderly patients.

In recent years, successful treatment of OAB with mirabegron, a selective β3-adrenoceptor agonist, has emerged as an important development in this regard. By activating β3-adrenoceptors on the detrusor muscle, mirabegron allows relaxation in the bladder and reduces OAB symptoms by increasing urine storage[1]. Studies have shown that mirabegron is well tolerated in patients and adverse effects are seen in lower incidence[2]. Advanced age, increased post-voiding residue and low urine flow rate are some causes of increased side effects of antimuscarinic drugs. Mirabegron is a safe option for these patients.

Anticholinergic drugs may increase IOP by narrowing the anterior chamber angle, causing pupillary dilatation and pushing the iris-lens diaphragm anteriorly[3]. Therefore, they are contraindicated in narrow-angle glaucoma. Since the β3-adrenoreceptor agonist mirabegron has no such side effects, it can be easily used in such patients.

METHOD

A total of 74 patients (40 male, 34 female) with symptoms of OAB admitted to the urology clinic between March 2017 and September 2018

were included in the study. Patients over 60 years old were included. Mean age was 69.48±7.8 years. The study was approved by the local Sanko University ethics committee. Symptom scores, intraocular pressure (IOP) readings of right and left eyes, systolic and diastolic blood pressures of the patients were recorded before and after the treatment. Overactive Bladder-Validated 8-question form (OAB-V8) was filled in by patients before the treatment (in Turkish)[4]. Daily urination frequency including nocturia and urge incontinence was recorded by patients. Patients were also referred to the ophthalmology clinic before the treatment. The patients underwent a detailed ophthalmologic examination including best-corrected visual acuity, slit-lamp biomicroscopy, fundus examination and 3-mirror gonioscopic examination. IOP of 21 mmHg was accepted as the upper limit. Patients with severe systemic hypertension (systolic blood pressure above 180 mmHg, diastolic blood pressure above 110 mmHg), patients with prolapse, history of incontinence surgery, urinary retention, bowel obstruction, patients with ocular disorders, history of glaucoma, previous ocular surgery and patients taking anti-glaucomatous medication were excluded. Common seen side effects of anticholinergic drugs such as blurred vision, constipation, dry mouth, headache, nausea and dyspepsia were questioned after the treatment. Mirabegron (50mg/day) was started orally, for 12 weeks. Patients were followed up monthly and side effects were recorded. At the end of 12 weeks, all values were re-evaluated and compared with pre-treatment data.

Statistical analyses were performed using the SPSS software version 15. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Paired Student's t-test was used to compare the measurements at two-time points (baseline and after 3 months). A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

13 patients were excluded from the study. Three of them had a history of glaucoma, 2 of them had systemic hypertension controlled by anti-hypertensive medication, 3 of them had a history of ocular surgery and 5 of the patients did not come to follow-up visits. A total of 74 patients completed the study. The mean age of the patients was 69.48 ± 7.8 (range 60-85). Daily urination frequency, nocturia and urgency values were significantly lower than the pre-treatment values ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). There was a significant difference in the symptom score before and after the treatment ($p=0.0001$). The mean IOP values of the right eye and the mean IOP values of the left eye were not significantly different before and after the treatment. There was no significant difference between systolic blood pressure and diastolic blood pressure before and after the treatment.(Table-1). The side effects in patients were shown in Table-2.

DISCUSSION

In our study, we tested the systemic and ocular reliability of mirabegron treatment and reported no negative effect. We did not find any other study about systemic and ocular effects of mirabegron treatment in patients with OAB.

Antimuscarinic agents are the most preferred and most commonly used drugs in the treatment of OAB. However, they are contraindicated in narrow-angle glaucoma because they may cause an increase in IOP. Therefore, we aimed to test the ocular safety of mirabegron in this study.

Table 1: Changes from baseline to end of treatment.

	Before treatment	After treatment	P
Symptom scores	18.67 ± 9.87	9.83 ± 2.71	0.0001
Urgency	6.16 ±4.34	3.96 ±2.24	<0.001
Frequency	12.36±2.48	7.34±3.56	<0.001
Nocturia	2.26 ±1.05	1.17 ±1.00	<0.001
IOP of right eyes(mm/Hg)	16.06±2.62	15.85±2.31	0.341
IOP of left eyes (mm/Hg)	15.96±2.35	15.94±2.21	0.855
Systolic blood pressures(mm/Hg)	128.91±11.76	128.43±11.95	0.110
Diastolic blood pressures (mm/Hg)	81.94±9.83	81.31±10.14	0.071

IOP: intra-ocular pressure

Table 2: Treatment-emergent adverse events.

Mirabegron (50mg/gün)
Drymouth3 (4.05 %)
Blurredvision1 (1.35%)
Headache3 (4.05 %)
Constipation4 (5.40%)
Dizziness2 (2.7%)
Dyspepsia2 (2.7%)
Peripheraledema3 (4.05%)
Nasalcongestion1 (1.35%)
Nausea2 (2.7%)

Mirabegron, a β3-adrenoreceptor agonist, is an effective, reliable new drug used in the treatment of OAB. Mirabegron shows its effect by activating β3-adrenoceptors on the detrusor muscle and increases urine storage by causing relaxation in the bladder[1].

Studies searching for the role and effects of β3-adrenoceptors in the eye are ongoing. In vitro studies have shown that beta-adrenergic relaxation in cattle iris sphincter muscle is provided by many beta-receptors, in particular, β3 receptor subtypes[5]. The β3-adrenoceptors were detected in conjunctival epithelial cells and rat conjunctiva[6]. In addition, it has been shown that it has a role in the control of retinal vascular tonus in rats and exists in choroidal and retinal endothelial cells[7,8].

In our study, there was a significant change in symptom score value after the treatment. Symptom score includes urgency, frequency and nocturia. A significant change was recorded in all of these values before and after the treatment. Side effects such as dry mouth, dizziness, constipation, high blood pressure, dyspepsia, peripheral edema, headache and nasal congestion were found to be compatible with the literature (Table-2)[2,9].

Many different drugs need to be used for accompanying comorbid diseases in the elderly. In such patients, care should be taken for drug interactions. Use of anticholinergic agents in elderly patients should be closely monitored because of cognitive side effects. Gray et al. reported that oxybutynin, an anti-cholinergic agent, medication increased cognitive side effects and cognitive impairment occurred in patients[10]. In the studies about darifenacin and fesoterodine medications in elderly patients, complaints about urination were found to be significantly decreased. However, dry mouth and constipation were the most common side effects[11,12]. In studies, mirabegron medication with a dose of 25-50 mg/day showed a significant difference in terms of efficacy compared to placebo while side effect was found to be similar to placebo indicating that it could be safely used in elderly patients[13]. In our study, no significant side effects were observed and it was observed that mirabegron was well tolerated by the patients.

Blurred vision is the most common side effect of anticholinergic drugs. Abrams found this rate as 4-6% in his study[14]. In our study, we observed blurred vision only in one patient.

Also, these drugs cause ciliary smooth muscle relaxation by pupillary dilation and may lead to an increase in IOP. There are many different studies investigating the effects of anticholinergic drugs on IOP. In a study with oxybutynin, acute angle-closure glaucoma was reported in a patient[15]. It is an eye emergency

and should be treated urgently as it may cause visual loss. Advanced age, female gender, family history, hypermetropia, anatomical factor (thick crystalline lens, plateau iris, narrow iridocorneal angle) are the risk factors causing drug-induced acute glaucoma[16]. In studies with solifenacin, there was no significant change in intraocular pressure in normal patients[17,18]. In our study, no such side effects were observed in the patients. Anticholinergic drugs are known to cause muscarinic blockage in lacrimal glands and reduce tear secretion. In a study, the rate of dry eye related to solifenacin succinate medication was reported to be 1.3%[18]. In this study, we did not evaluate tear film parameters, so we could not make a clear assessment of the dry eye.

EAU guideline is also recommended for the treatment of mirabegron ''Mirabegron 25 mg and 50 mg showed similar efficacy in UUI treatment in the population >65 yr and >75 yr when compared with the overall population and should be considered to treat UUI in elderly patients if additional antimuscarinic load is to be avoided.''[19].

Our limitations in this study are; the study has not a prospective design and patients with glaucoma were excluded from the study.

CONCLUSİON

Treatment of OAB with Mirabegron 50mg/day is effective as well as a safe treatment at the same time. After 3 months of treatment, it does not cause an increase in IOP. It is generally safe and well-tolerated. Since elderly patients have to use various medications due to their comorbidities, drug interactions and side effect potentials are higher in these patients. In our study, it was seen that mirabegron is well-tolerated and safe in elderly patients.

Authors' contributions

MS: analysis and interpretation of data, drafting of the manuscript., statistical analysis,wrote the manuscript. MS and BB: conception and design, acquisition of data, administrative, technical, or material support, supervision. All authors read and approved the final manuscript.

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