Respiratory Adverse Effects of Timolol, Betaxolol and Carteolol

TIMOLOL, BETAKSOLOL VE KARTEOLOUÛN RESPIRATUAR YANETKİLERİ

Turgut YILMAZ*, Nuray AKYOL*, Mehmet Hamdi MUZ**

* Department of Ophthalmology, Medical School of Fırat University,
** Department of Chest Diseases, Medical School of Fırat University, Elazığ, TURKEY

Summary

Purpose: We evaluated the adverse effects of the three b adrenoceptor blocking eye drops: nonselective timolol, bl selective betaxolol and partial agonist carteolol, to the respiratory functions.

Patients and methods: 20 otherwise healthy open angle glaucoma patients receiving topical b blockers were put on timolol, betaxolol and carteolol eye drops sequentially, each for 4 weeks. After each period, respiratory functions have been examined. Forced expiratory volume 1 (FEV1), Forced vital capacity (FVC), Forced expiratory flow 25%-75% (FEF 25%-75%) and peak expiratory flow rate (PEFR) have been obtained. One-way ANOVA with SPSS for Windows 6.0 used for statistical analysis.

Results: Forced expiratory volume in one second and forced expiratory flow 25%-75% values with timolol were higher than the ones with betaxolol ($p<0.05$) They were not found significantly different when betaxolol-carteolol and timolol-carteolol groups compared. Differences in forced vital capacity, forced expiratory volume in one second/forced vital capacity and peak expiratory flow rate measurements for any group were not statistically significant.

Conclusion: Timolol may cause more severe impairment than betaxolol on pulmonary functions. Protection gained with partial agonist activity is equivocal.

Key Words: Beta blocking agents, Respiratory adverse effects, Pulmonary functions

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Özet

Amaç: Bu çalışmanın amacı, beta-blokör göz damlaları olan nonselektif timolol, Bl selektif betaksolol ve parsiyel agonist etkili karteololün pulmoner fonksiyonlar üzerine olan etkilerini araştırmaktır.

Hastalar ve yöntem: Başka bir sağlık problemi olmayan ve herhangi bir topikal 13 blokör kullanan 20 primer açık açılı glokom hastasına 4 'er haftalık sürelerle timolol, betaksolol ve karteolol damlaları sırası ile uygulandı. Her bir ilaç uygulanımı periyodunu takiben hastalara solunum fonksiyon testleri yapıldı ve FEVİ (forced expiratory volume 1), FVC (forced vital capacity), FEF%25-75 (forced expiratory flow %25-75) ve PEFR (peak expiratory flow rate) parametreleri elde edildi. Sonuçların istatistiksel değerlendirmesi SPSS for windows 6.0 programında tek yönlü varyans analizi ile yapıldı.

Bulgular: Timolol kullanımı sonunda, FEVİ ve FEF%25-75 değerleri betaksolol dönemine kıyasla daha düşük bulundu ($p<0.05$). Timolol-karteolol ve betaksolol-karteolol dönemleri arasında bu parametreler açısından anlamlı bir fark yoktu. FVC, FEVİ/FVC ve PEFR parametreleri açısından karşılaştırıldıklarında 3 grup da birbirinden farklı bulunmadı.

Sonuç: Timolol, pulmoner fonksiyonlar üzerinde betaksolole göre daha fazla yan etkiye sahiptir. Parsiyel agonist aktivitenin koruyucu etkisi ise tartışmalıdır.

Anahtar Kelimeler: Beta-blokör ilaçlar, Pulmoner fonksiyonlar, Pulmoner yan etkiler

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Glaucoma is a common disease in the elderly affecting approximately 6% of those over 75 years (1). Ophthalmic b adrenoceptor blockers are widely used for the reduction of intraocular pressure (IOP) in patients with glaucoma. Currently, in our country there are 5 topical b adrenoceptor blockers approved for lowering IOP; timolol maleate, betaxolol, carteolol, levobunolol and metipranolol. A11 b adrenoceptor blockers have been absorbed into the systemic circulation and may cause unwanted cardiovascular, pulmonary, central nervous system and metabolic effects (2). Systemic adrenoceptor block-

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Correspondence: Turgut YILMAZ
Department of Ophthalmology
Medical School of Fırat University,
Elazığ, TURKEY

ing effects have been reported rarely following cardioselective b blocker betaxolol while non-cardioselective drugs resulted in systemic adrenoceptor blockade in healthy volunteers and glaucoma patients with previous unremarkable cardiovascular and pulmonary examination (2,3).

Broncospasm-related respiratory complications are the most important adverse effects due to P blockers. p_2 adrenergic tone is essential for the maintaining of open airways. The p_2 receptors blockade may contract the smooth muscles in the pulmonary bronchi and lead to bronchospasm and airway obstruction (2). The cardioselective P adrenoceptor blockers are assumed that they minimize p_2-mediated bronchoconstriction and airway obstruction. Respiratory adverse effects may also be detected with the drugs with partial P agonist properties. The intrinsic sympatomimetic activity of the carteolol may help to reduce systemic adverse effects (3). The evidence supporting this claim is certainly not absolute, with some studies showing no increased protection from adverse effects (2,4).

Performing pulmonary function tests (PFT) is one of the objective methods to assess respiratory adverse effects of these drugs. Commonly used expiratory flow rate measurements provide data on the integrity of airways and the severity of the airway impairment (5). FVC (Forced vital capacity) is the volume of the gas that can be exhaled as forcefully and rapidly as possible after a maximal inspiration. In obstructive lung disease, FVC is reduced due to air trapping (5). Forced expiratory volume timed (FEVt) is the maximum volume of the gas that can be exhaled over a given time period. Forced expiratory volume in one second (FEV1) is the most commonly used measurement. In obstructive conditions, the time necessary to forcefully exhale a certain volume is increased and FEV1 is decreased. Forced expiratory flow 25%-75% (FEF 25%-75%) is the average flow rate during the middle 50% of an FVC measurement. It is also known as the maximum mid-expiratory flow rate (MMFR) and commonly used to assess to status of medium sized airways in obstructive conditions. It progressively decreases with age and correlates well with the FEV1. The MMFR is a more sensitive indicator of the airway obstruction than the FEV1. Peak expiratory flow rate (PEFR) is the maximum flow rate that can be achieved (5,6). It also shows the status of medium and small sized airways which are mostly impaired in p_2 mediated bronchoconstriction.

The aim of this study was to compare the pulmonary functions during the use of each t)f the three p blocking agents; cardioselective betaxolol, noncardioselective timolol and partial agonist carteolol.

Patients and Methods

A group of primary open angle glaucoma were recruited from the glaucoma unit of Firat University Ophthalmology Clinic. They were all on a single-drug regimen and receiving a topical b adrenoceptor blocker for keeping their IOPs regulated. They were all ambulant, compliant with their regimen and non-smokers. The patients were excluded in the beginning if they had a history of cardiopulmonary disease, they were on systemic b adrenoceptor blocking agents and broncodilatators or were unwilling about follow-ups and tests. Then they undergone a respiratory system examination including a postero-anterior chest x-ray, and 20 of them which was found unremarkable at the end of examination selected as the study group.

The study was carried as sequentially in three longitudinal groups and all patients lead the same sequence. All patients received topical timolol 0.5% bid first. The patients who were using another medication just changed to timolol maleate. A prior washing period have not been introduced for not causing an IOP peak. Then they switched to betaxolol 0.5 % bid and lastly carteolol 2% bid. Each of these periods took 4 weeks. At the end of each period, all patients were investigated for subjective symptoms related to respiratory system and pulmonary function tests were obtained with microcomputerized spirometry (SPiROSIFT 500, Fukuda Denshi, Japan). All tests performed by the same technician at 22-24 °C room temperature as the patients on sitting position and their nose closed. The tests performed after 3 hours of the morning dose by which the drugs were at thenmaximum serum concentrations. All results were corrected by age, height and weight of the patients. FVC, FEV1, FEF25%-75%, PEFR were measured

for each patient and the ratio of FEV1/FVC was calculated.

Measurements were displayed in two pattern: Actual measurements as liters (raw data) and corrected measurements as which the % of the normal age-, height- and sex-matched values (predicted data). All data were put forward as the mean±SD. Analysis of variance (ANOVA) were used to evaluate the effects of the three drugs. For any analysis of variance approaching significance, Tukey B test is used to determine the groups which were significantly different from each other. All computations and comparisons were done with SPSS for Windows; version 6.

Results

12 of our patients were female and 8 male. Their ages were between 52 and 77 years (mean 61.3 ±12.31). Mean weight of the male patients were 75.25 kg, and mean weight of the female ones were 69.50 kg (mean for the all patients were 72.2±11.8). Their mean heights were 1.62±0.11 meters. All patients were free from symptoms related to respiratory system.

Raw data and predicted values of pulmonary function tests for timolol, betaxolol and carteolol groups were displayed at Table 1 and Table 2. Mean actual measurements for FEV1 were increased by 12% when the patients were switched from timolol maleate to betaxolol eye drops. This difference were statistically significant ($p<0.05$). FEV1 predicted values were also significantly different between timolol and betaxolol groups ($p<0.05$). No statistically significant difference were determined between betaxolol-carteolol and timolol-carteolol groups, for both FEV1 raw data and predicted values.

Both raw data and predicted values for FVC showed no statistically significant differences in any of the groups. Differences between FEV1/FVC ratios were also not found statistically significant.

FEF25%-75% mean actual measurements increased by 17.8% when patients switched from timolol to betaxolol. This change was statistically significant ($p<0.05$). Predicted values of FEF25%-75% for these two groups were also significantly different ($p<0.05$). The differences between the timolol-carteolol and betaxolol-carteolol groups were found statistically insignificant.

PEFR mean actual measurements increased by 10.51% when patients switched from timolol to betaxolol. This was statistically insignificant. The differences between predicted values of PEFR for these two groups were also not found statistically significant. The differences between the timolol-carteolol and betaxolol-carteolol groups were also not statistically significant.

Discussion

Our data provide important information regarding the respiratory adverse effects of the b adrenergic blocking agents on glaucoma patients.

Table 1. Pulmonary function tests raw datas for timolol, betaxolol and carteolol groups.

	FEVl(lt)	FVC(lt)	FEV1/FVC	FEF25%-75%(lt)	PEFRQt/s))
Timolol	1.84±0.23	2.19±0.41	0.90±0.08	2.52±0.36	4.09±0.66
Betaxolol	2.06±0.29	2.13±0.61	0.94±0.16	2.97i0.60	4.52±1.27
Carteolol	2.01±0.14	2.15±0.59	0.86±0.19	2.76±0.55	4.40Ü.19

Table 2. Pulmonary function tests predicted values for timolol, betaxolol and carteolol groups.

	FEV1(%)	FVC(%)	FEV1/FVC(%)	FEF 25%-75%(%)	PEFR(%)
Timolol	72.85±8.43	74.14±7.56	98.94i7.84	80.7Ü9.94	63.42i3.64
Betaxolol	88.28±10.51	79.71±7.06	103.0Ü11.41	108.7Ü18.87	68.85i9.38
Carteolol	85.71±7.82	78.14il0.20	101.56i9.73	95.28il4.69	65.42ilO.04

These agents, in spite of their similar antiglaucomatous activity, differ from each other regarding their respiratory side effects. In our study, we compared three different b blocking agents from the point of view of respiratory adverse effects, and found the nonselective b blocking agent timolol as the most unreliable one. When our patients switched from timolol to the cardioselective b blocking betaxolol, FEV1 increased by means of 12% and PEFR 25%-75% increased by means of 17.8%. These increments were statistically significant and in our opinion, they have showed the reversal of b2 mediated airway obstruction. In spite of its insignificance, quite an important increment of 10.51% were seen in the PEFR values due to the switching. These changes, along with no significant impairment in FVC demonstrate temporary airway obstruction without air trapping. Similar increments reported in otherwise healthy glaucoma patients in a randomized crossover study. When changing timolol to betaxolol, an increase of 8% and 13% reported in FEV1 and PEFR respectively (3). In another study, a group of glaucoma patients with no pulmonary disease were examined with spirometry while they switched from nonselective timolol to betaxolol or pilocarpin. 11.45% and 18% increments were reported in FEV1 and PEFR values respectively (1) . These studies support our results which show a slowdown instead of a decrease in the airflow.

Chronic obstructive pulmonary disease are more common in the elderly, and glaucoma is also diagnosed mostly in this age group. Nonselective p blocking agents not only cause unrecognized or unsuspected respiratory side effects among otherwise healthy glaucomatous patients, but also exacerbate preexisting pulmonary disease (7). In another study, 26% decrease in FEV1 is reported with timolol in the asthmatic patients (8). Several clinical studies have suggested a greater safety potential for topical administration of betaxolol, a cardioselective b blocking agent in glaucoma patients with coexisting pulmonary disease as compared with the nonselective p blocking agent timolol (9,10). Betaxolol was reported to cause no exacerbation of pulmonary symptoms or deterioration in measured pulmonary function tests in asthmatic patients (11). However, other authors make this suggestion equivocal with their reports (12,13). Hugues et al (7) also reported that betaxolol were similarly and significantly lower FEV1 in the same manner with the timolol and carteolol in the patients with chronic bronchitis (7).

Carteolol, a nonselective b blocking agent with partial agonist activity, may theoretically cause less cardiovascular and respiratory impairment. "In our study, carteolol group showed a statistically insignificant increment of 8.5% in FEV1 in comparison with timolol group. Again insignificant, FEF25%-75% increased by means of 9.52% and PEFR increased by means of 7.58% in the carteolol group when compared with the timolol group. We think these increments are clinically significant. In spite of there is some suggestion that b blockers with intrinsic sympatomimetic activity are less likely to cause bronchospasm (2,14), quite a big pile of reports indicate no increased protection with carteolol from adverse effects (4,7). Diggory et al reported no significant changes in pulmonary functions between timolol and carteolol groups in a randomized, double masked study of glaucoma patients with no history of broncospasm (3). At the same study, betaxolol showed to cause significant improvement in FEV1. In our study, carteolol seems to have an advantageous effects over timolol regarding pulmonary functions; but these were found statistically insignificant.

Regarding the results of this study and the predators, it is advisable to choose cardioselective eye drops as first line drug when a treatment by adrenoreceptor blocking agent is indicating, in an otherwise healthy patient to prevent the risk of bronchoconstriction. Inspite of their insignificant difference with non selective blocking timolol, partial agonist carteolol seems to be safer than its.

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