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# Bronchospasm after timolol administration

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Dear Editor,

Timolol is a non-selective β-adrenergic receptor-blocking agent [1]. It is topically administered in patients suffering from open-angle glaucoma or ocular hypertension. Among this patient population, timolol is usually prescribed alongside prostaglandin analogues [2]. The prevalence of glaucoma increases with age. Most patients treated with timolol for glaucoma are of advanced age and may have various comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease (COPD), and arterial hypertension [3]. Notably, in the female population with COPD, the prevalence of open-angle glaucoma is significantly higher than in the general population [4]. Timolol's systemic absorption and central nervous system penetration can lead to several side effects, including bradycardia, bronchospasm, increased fatigue, or confusion [5]. We would like to present two cases where timolol administration resulted in severe, life-threatening bronchospasm, followed by hypoxic cardiac arrest in patients with COPD and asthma.

A 76-year-old female patient with a well-known history of COPD underwent eye surgery due to senile cataract. The patient had no episodes of exacerbation in everyday life. The chronic medication with long-acting β-mimetic and long-acting muscarine antagonist was well titrated. The patient ceased smoking after a diagnosis of COPD years ago. Prior to that, she had a 50 pack-year history of smoking. Phacoemulsification with intraocular lens implantation was performed under regional anaesthesia in an outpatient regime. At the end of the surgery, 0.5% timolol was administered in the dose of one drop into the conjunctival sac. After discharge from the hospital, on the way home the patient suffered from shortness of breath and developed a cardiac arrest. Cardiopulmonary resuscitation (CPR) was initiated immediately by a witness and was continued by the emergency service. After 17 minutes of CPR, spontaneous circulation was restored, and the patient was transferred to a tertiary hospital to the intensive care unit. Upon admission, bronchospasm was diagnosed. The usual treatment of COPD exacerbation was initiated, including betamimetics, muscarine agonists, corticosteroids, xanthines, leukotriene antagonists, magnesium sulphate, and artificial lung ventilation with the need to use rescue protocols such as ketamine infusion, adrenalin infusion, and muscle relaxation. On the 5$^{th}$ day of admission, the patient regained full consciousness and was extubated. The patient had no neurological deficit. On the 7$^{th}$ day, the patient was discharged to the ward.

A 66-year-old female patient with a recent history of asthma-COPD overlap (ACOS) underwent eye surgery due to senile cataract. Despite the diagnosis, the patient was still an active smoker (40 pack-years). The patient suffered from frequent exacerbation of ACOS symptoms with an average need of 3 doses of short-acting β-mimetics per day. Because of the recent diagnostics, titration of inhalation long-acting β-agonists and corticosteroids for ACOS was still ongoing. The patient probably had insufficient plasmatic drug levels at the time of surgery. The same surgery as in the previous case was performed.

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At the end of the surgery, one drop of 0.5% timolol was applied to the conjunctival sac of the eye. After discharge from the hospital, the patient started to feel shortness of breath. The emergency service was activated. However, upon arrival, the patient developed a cardiac arrest. Telephone-assisted CPR was immediately performed by the witness for 3 minutes and continued by the emergency service for another 4 minutes. Spontaneous circulation was restored after 7 minutes of CPR. After that, the patient was transferred to a tertiary hospital intensive care unit. Severe bronchospasm was diagnosed upon admission. Standard treatment of bronchospasm was initiated as in case 1. The patient did not recover consciousness. The hospital stay was complicated with epileptic seizures, myoclonic seizures, and pneumonia with septic shock. On the 7$^{th}$ day, multiorgan failure developed. Because of a predicted poor neurological outcome and multiorgan failure on the 20$^{th}$ day, the treatment regime was changed to palliative care. The patient died on the 20$^{th}$ day of admission.

Timolol is a non-selective β-adrenergic antagonist. Commonly it is used for the treatment of high intraocular pressure [2, 3]. Because of its systemic absorption and central nervous penetration, timolol has several known side effects such as bronchospasm, fatigue, and bradycardia [5]. Timolol-induced bradycardia is a well-described phenomenon in the literature [6-9]. However, there are only a few cases documented where topical timolol induced bronchospasm [10-13]. Charan [11] documented two cases where the forced expiratory volume at one second ($FEV_1$) decreased by 25% in one patient and 47% in another patient after administration of two drops of 0.25% timolol in the conjunctival sac. Both patients had a history of well-compensated asthma. After timolol discontinuation, the $FEV_1$ returned to its original values in both patients [11]. In concordance with Charan's [11] findings is another documented case presented by Holtman [12]. He described the increased incidence of bronchospasm in asthma patients after topical administration of timolol. Notably, in the case presented by Holtman [12], discontinuation of timolol led to a decreased incidence of bronchospasm episodes in the patient. In our unique cases, administration of timolol led to life-threatening bronchospasm with subsequent hypoxic cardiac arrest. Compared to Charan [11] and Holtman [12], bronchospasm in our cases was more severe and developed in a very short time. We believe this could be due to increased systemic absorption in the operated eye and therefore easier absorption of the drug with higher plasmatic levels of timolol. It is well documented that higher plasmatic levels of timolol, morbidity and noncompliance lead to a higher incidence of side effects [14]. To our best knowledge, there is only one paper regarding fatal respiratory side effects of timolol, by Nygaard [10], published in 1997. It documents 17 cases that occurred in Norway in the period 1986-1995. There was a majority of patients with cardiac side effects and only 6 patients with respiratory adverse events. Interestingly, according to Nygaard [10], elderly patients are at greater risk of timolol's side effects compared to the general population. Our cases highlight the urgency of spreading awareness of timolol's respiratory side effects and their potentially fatal consequences. We agree with Nygaard [10] that timolol's side effects are probably severely underreported despite timolol being regularly used for almost 40 years now.

We documented two unique cases where timolol administration into the conjunctival sac led to bronchospasm with subsequent hypoxic cardiac arrest in patients with ACOS and asthma. These cases demonstrate the urgent need to be aware of timolol's systemic side effects, not only cardiac ones, but also respiratory. They underscore the importance of exercising extreme caution when treating elderly patients suffering from asthma or COPD with timolol.

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## REFERENCES

1. Dunn M. Timolol-induced bronchospasm. JAMA 1982, 247: 27-28. DOI: https://doi.org/10.1001/jama.247.1.27.
2. Hoy SM, Keam SJ, Keating GM. Travoprost/timolol. Drugs Aging 2006; 23: 587-599. DOI: https://doi.org/10.2165/00002512-200623070-00005.
3. Zimmerman TJ, Leader B, Golob DS. Potential side effects of timolol therapy in the treatment of glaucoma. Ann Ophthalmol 1981; 13: 683-689.
4. Lee JS, Kim YJ, Kim SS, Park S, Choi W, Bae HW, Kim CY. Increased risk of open-angle glaucoma in non-smoking women with obstructive pattern of spirometric tests. Sci Rep 2022; 12: 16915. DOI: https://doi.org/10.1038/s41598-022-21225-0.
5. Nanda T, Rasool N, Callahan AB, Stamper RL, Odel JG. Ophthalmic timolol hallucinations: a case series and review of the literature. J Glaucoma 2017; 26: e214-e216. DOI: https://doi.org/10.1097/IJG.0000000000000712.
6. Abbas SA, Hamadani SM, Ahmad U, Desai A, Kitchloo K. Ophthalmic timolol and hospitalization for symptomatic bradycardia and syncope: a case series. Cureus 2020; 12: e7270. DOI: 10.7759/cureus.7270.
7. Mäenpää J, Pelkonen O. Cardiac safety of ophthalmic timolol. Expert Opin Drug Saf 2016; 15: 1549-1561. DOI: 10.1080/14740338.2016.1225718.
8. Elikowski W, Fertała N, Zawodna-Marszałek M, Gaca-Wysocka M, Bolewski A. Bradycardia during optical timolol therapy: its delayed remission after timolol discontinuation and unexpected further relapse. Polski Merkur Lekarski 2022; 50: 25-29.
9. Abbas SA, Hamadani SM, Ahmad U, Desai A, Kitchloo K. Ophthalmic timolol and hospitalization for symptomatic bradycardia and syncope: a case series. Cureus 2020; 12: e7270. DOI: 10.7759/cureus.7270.
10. Nygaard HA, Høvding G. Adverse effects of local use of beta-blockaders in glaucoma. A literature review and a survey of reports to the adverse drug reaction authority 1986-95. Tidsskr Nor Laegeforen 1997; 117: 2019-2021 [Article in Norwegian].
11. Charan NB, Lakshminarayan S. Pulmonary effects of topical timolol. Arch Intern Med 1980; 140: 843-844.
12. Holtmann HW, Holle JP, Glänzer K. Alteration of bronchial flow resistance due to timolol 0.25% in bronchial asthma (author's transl). Klin Monbl Augenheilkd 1980; 176: 441-444. DOI: https://doi.org/10.1055/s-2008-1057475 [Article in German].
13. Vonwil A, Landolt M, Flammer J, Bachofen H. Bronchoconstrictive side effects of timolol eye drops in patients with obstructive lung disease. Schweiz Med Wochenschr 1981; 111: 665-669 [Article in German].
14. Uusitalo H, Niño J, Tahvanainen K, Turjanmaa V, Ropo A, Tuominen J, Kähönen M. Efficacy and systemic side-effects of topical 0.5% timolol aqueous solution and 0.1% timolol hydrogel. Acta Ophthalmol Scand 2005; 83: 723-728. DOI: https://doi.org/10.1111/j.1600-0420.2005.00562.x.