
Timolol Eyedrop-Induced Fatal Bronchospasm in an Asthmatic Patient

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Timolol ophthalmic preparation is a nonselective β -adrenergic receptor blocking agent commonly used in the treatment of many types of glaucoma, as well as for routine presurgical lowering of intraocular pressure. Timolol, however, is readily absorbed from the conjunctiva and nasal mucosa into the systemic circulation and may cause systemic side effects^{1,2} including bronchospasm, which may be severe^{3,4} or even fatal.⁵ It is well known that systemic application of β -blocking agents is contraindicated in patients with asthma. It is not generally appreciated, however, that timolol ophthalmic eye-drops should be used with caution or even avoided in patients with bronchospastic disease.¹

To further emphasize the risk involved in the use of this preparation in the presence of obstructive lung disease, this report describes the occurrence of fatal bronchospasm in an asthmatic patient following topical use of ophthalmic timolol.

Case Report

A 70-year-old woman was hospitalized for cataract extraction. She had a history of asthma, which in the recent several years had been asymptomatic, essential hypertension, and mild diabetes mellitus. Her medications at admission included methyldopa, 250 mg three times a day, and sustained-release theophylline, 300 mg twice a day. Physical examination revealed a mildly obese patient with no respiratory distress. Her pulse was 88 beats per minute and regular, and her blood pressure was 150/80 mm Hg. The lungs were clear to auscultation, and the heart sounds were normal without murmurs. Ocular examination revealed bilateral cataracts. Other physical

findings were unremarkable. Routine hematological and biochemical blood tests were normal except for a mildly elevated level of blood glucose. Chest roentgenogram showed mild cardiomegaly and normal lung fields. The electrocardiogram demonstrated sinus rhythm with no arrhythmias or ischemic changes.

Before being taken to the operating room, two drops of 0.5% timolol maleate were administered to the patient's right eye for routine presurgical lowering of intraocular pressure. About 30 minutes later she was found to be cyanotic and in severe respiratory distress. Her pulse was weak and fast, but regular, and breathing efforts were associated with audible wheezing. Cardiorespiratory arrest ensued before treatment for the rapidly progressive bronchospasm could be started. Cardiorespiratory resuscitation, followed by mechanical ventilation, endotracheal epinephrine, and intravenous bronchodilators and steroids, succeeded in partially reversing the bronchospasm; nevertheless, the resulting severe irreversible brain damage, most probably from prolonged severe hypoxemia, led to death 2 days later.

Discussion

It is certainly a tragedy when a patient hospitalized for minor surgery dies. Airway reactivity in those with asthma differs from patient to patient and, indeed, even in the same patient on repeated testing. A delicate balance exists between adrenergic-mediated bronchodilation and cholinergic bronchoconstriction. Any pulmonary β -adrenergic blockade in these patients would shift the autonomic balance toward the cholinergic response, resulting in further bronchoconstriction.

Timolol is readily absorbed from the conjunctiva and nasal mucosa (by drainage through the lacrimal duct) into the systemic circulation, bypassing the liver, where the drug is normally metabolized; consequently, a high concentration of this nonselective β -adrenergic blocking

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agent may reach the bronchopulmonary circulation.^{1,2} When administered systemically, timolol is approximately eight times more potent than propranolol hydrochloride¹ and has a duration of action of about 24 hours.⁶ A dose of 2 drops 0.5% timolol, as the patient received, may result in a significant concentration of the drug in the systemic circulation,^{1,2,7} producing undesirable effects lasting several hours in a susceptible host. These systemic adverse effects are well known,^{8,9} and one of the most severe and potentially dangerous side effects is the exacerbation of airflow obstruction.⁵ Because of this reaction, topical as well as systemic use of β -adrenergic receptor blocking agents is not advisable in patients with asthma or in patients with chronic obstructive lung disease.

Timolol ophthalmic preparation may cause other significant and potentially dangerous side effects. It has been reported to cause bradycardia, syncope, hypotension, congestive heart failure, second-degree to third-degree heart block, central nervous system disturbances, and sexual impotence.⁸⁻¹⁰

Betaxolol is a potent and a selective β -adrenergic blocking agent that is as effective as timolol in decreasing intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension when administered in eyedrop form.¹¹⁻¹³ Although several previous studies demonstrated that topical betaxolol has no significant adverse effects on respiratory function in patients with pulmonary disease,^{11,14} exacerbation of obstructive airway disease may occur,¹⁵ indicating that its cardioselectivity is not absolute.

The case presented emphasizes the need for greater awareness of the medical history and physical findings of each patient before prescribing or using topical β -adrenergic antagonists. β -Adrenergic blocking agents should be avoided in patients with bronchospastic diseases, even

when they are asymptomatic. Should the use of these agents be unavoidable, a selective β_1 -adrenergic blocking agent or an initial lower dose is recommended, with careful monitoring for undesirable side effects, to avoid similar unexpected tragedies.

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