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MDPI

*Case Report*

# Betaxolol Ophthalmic Solution as Alternative Treatment for Patients with Timolol Allergy: A Case Report

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**Abstract:** Background: To establish if an allergy towards all β-blockers, as a group, should be assumed, if an allergic reaction is observed while using one specific β-blocking agent. Case presentation: The non-selective β-blocker timolol caused a severe allergic ocular reaction in a non-atopic patient with advanced primary open-angle glaucoma. Results: A patch test confirmed timolol allergy. No allergic reaction to other anti-glaucomatous topical drugs was observed, and treatment with the selective β-blocker betaxolol was successfully initiated. Conclusion: Allergy to the non-selective β-blocker timolol does not necessarily predict allergy to the selective β-blocker betaxolol, and betaxolol should therefore not be excluded as an alternative treatment.

**Keywords:** betaxolol; timolol; β-blocker; allergy

## 1. Introduction

Drug allergies are a class of unpredictable adverse reactions that are not related to the pharmacological effect of a drug, and can occur at subtherapeutic doses. Drug allergies encompasses a variety of immuno-modulated hypersensitive reactions, which can be stimulated by the administration of drug compounds, such as timolol [1] (Figure 1). Most clinically relevant unpredictable adverse drug reactions are type I and type IV allergies. Type I allergy, mediated by immunoglobulin E (IgE) antibodies, occurs rapidly within minutes to hours. Type IV allergy, mediated by T-lymphocytes is delayed, and appears up to several hours or days after exposure [2]. Drug allergies are structure-specific, which means that an allergic reaction to a drug does not necessarily cause cross-reactivity with another similar drug, even if they derive from the same class and share the same functional groups.

Topical β-blockers exert their ocular hypotensive action by blockade of the sympathetic nerve endings in the ciliary body, causing a decrease in the production of aqueous humor. They can be either non-selective or selective for β1-adreneric receptors [3]. Timolol is a non-selective β-blocker, inhibiting both β1- and β2-adrenergic receptors, while betaxolol is a β1-selective β-blocker. Common to all β-blockers is that they all contain an aryl-oxy-isopropanol-amine chain (Figure 1).

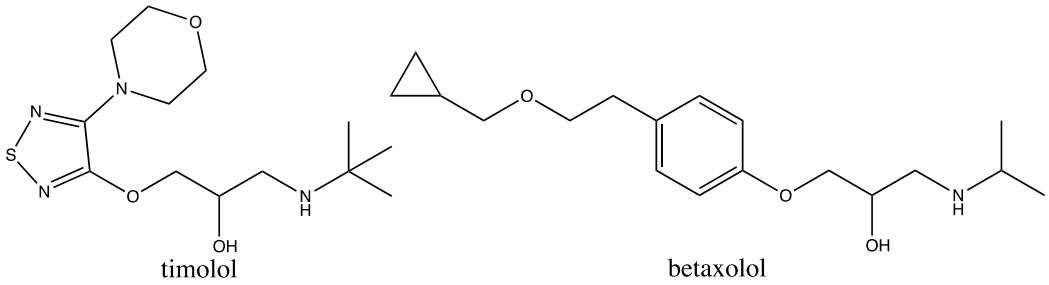


**Figure 1.** Chemical structure of timolol and betaxolol, illustrated by ChemDraw professional 19.0.

Here, we report a severe allergic ocular reaction to timolol in a patient where subsequent treatment with the β1-selective blocking agent, betaxolol, was successful and presented no allergic reaction.

## 2. Case Presentation

A 58-year-old non-atopic male experienced visual impairment on the right eye. Severe visual field losses (MD values of 25.5/24.5 db), total glaucomatous excavation of both optic nerve heads, severe loss of nerve fibers and retinal ganglion cells using Heidelberg OCT and intraocular pressure (IOP) of 38/40 mmHg were observed. Visual acuity was 0.2/0.6 and gonioscopy revealed open angles. The patient was diagnosed with advanced primary open angle glaucoma and immediate treatment with preservative free (PF) latanoprost (50 µm/mL) was initiated. The pressure was reduced to 25/25 mmHg. Due to insufficient IOP-lowering effect of PF latanoprost (50 µm/mL), a combined treatment of timolol (5 mg/mL)/dorzolamide (20 mg/mL) and PF latanoprost (50µg/mL) was initiated. This combination lead to a satisfactory IOP of 14/14 mmHg, without fluctuations. At a control visit after four months, no significant progression in lowering IOP was observed. After six months, the patient experienced increasingly red and irritated conjunctiva as well as periorbital dermatitis. Due to suspected preservative allergy, the patient was changed to PF timolol/dorzolamide. As the redness and irritation remained unchanged, PF timolol/dorzolamide was discontinued. Hereafter, timolol gel (1mg/mL) was initiated, while PF latanoprost (50 µm/mL) was continued. Few days after initiation of timolol gel (1mg/mL), the patient went to the emergency room with severe allergic symptoms, including angioedema (Figure 2A). Timolol gel was discontinued and the IOP increased to 22/24 mmHg.

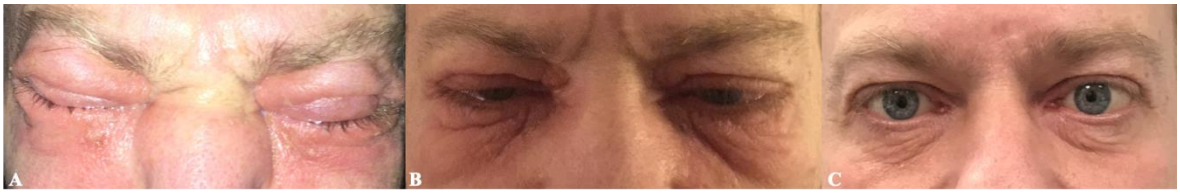


**Figure 2.** This illustration represents the subject after ocular treatment with timolol (1 mg/mL), (**A**), the subject after a patch test with timolol (**B**) and the subject after treatment with betaxolol (5 mg/mL) (**C**).

An acute patch test was performed to establish that the cause of the allergic reaction was due to timolol, and to rule out any cross-reactivity with other glaucomatous drugs. A positive patch test reaction to timolol was observed (Figure 2B), while no allergic reaction was observed to prostaglandin analogues (latanoprost) carbon anhydrase inhibitors (dorzolamide and brinzolamide), sympathomimetics (brimonidine tartrate and apraclonidine), parasympathomimetic (pilocarpine), or the selective-1 β-blocking agent, betaxolol. Treatment with betaxolol (5 mg/mL) was initiated, with a resulting IOP of 10/12 mmHg, without significant fluctuations throughout the day. Combined treatment with betaxolol administered twice daily and PF latanoprost (50 µm/mL) once a day was well tolerated (Figure 2C). Periorbital dermatitis was treated successfully with topical tacrolimus 0.1% twice daily for a week. The patient has given his written informed consent for publication of this case report and accompanying images.

## 3. Discussion

Ophthalmic β-adrenergic antagonistic agents are commonly used in the treatment of glaucoma, because of their effectiveness in reducing IOP [3]. Although the majority of published data suggests similar IOP reduction between betaxolol and timolol [4–6], the use of betaxolol in Denmark is uncommon. We investigated the number of betaxolol prescriptions based on the number of timolol prescriptions per year in Denmark in the period 1996 to 2018 (Figure 3) and found that betaxolol is used at an increasingly lower rate than timolol (Figure 3).

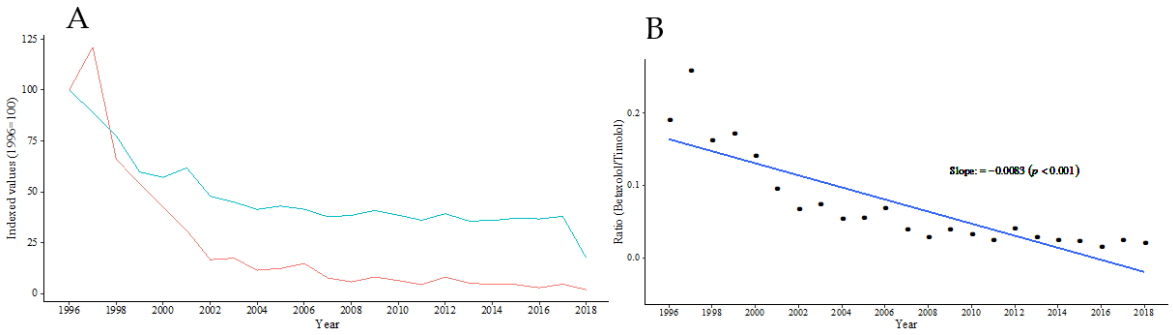


**Figure 3.** (**A**) The figure shows the evolution of the indexed number of prescriptions of betaxolol (red line) and timolol (blue line) per years in Denmark in the period 1996 to 2018, with 1996 as the index year, in which the values are normalized to 100. (**B**) Depicts the evolution of the relative number of prescriptions of betaxolol to timolol per year in Denmark in the period from 1996 to 2018. The black dots represent the exact ratios and the blue line and grey area represents the best linear fit (using OLS) and the 95% confidence intervals, respectively. The figure establishes a significantly negative trend in the ratio with a negative slope of −0.0083 per year, $p < 0.001$ (blue line). All data is drawn from the Danish Registry of Medicinal Products Statistics, which contains data on all prescriptions dispensed in Denmark since 1995. For methods see [7]. Anatomical Therapeutic Chemical system codes used: betaxolol: S01ED02; timolol: S01ED01.

Previous reports [7–14] have extensively described the detrimental effects of ophthalmic timolol. In accordance with our case report, a previous study based on a study population of 448 patients, have shown that 2.6 % of patients treated with timolol presented with allergic reactions [8]. However, most studies reporting allergic dermatitis in response to timolol treatment, also report cross-sensitivity with other known β-blockers such as betaxolol or other glaucoma eye drops [9–14]. In the present case, allergy was only present after treatment with timolol. Comparing the structural elements of β-blockers timolol and betaxolol with other known anti-glaucomatous β-blockers (levobunolol, metipranolol, carteolol), none other than timolol contains a morpholin-4-yl-1,2,5-thiadiazol scaffold, which is why that the allergic reaction observed in the present patient is caused by this scaffold.

## 4. Conclusions

Our findings emphasize that physicians should not assume allergy towards all β-blockers as a group, if an allergic reaction is only observed while using one specific β-blocking agent. Therefore, further evaluation of a patient showing signs of drug allergies, should be conducted to determine if the allergy is limited to a specific β-blocker.

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## Abbreviations

IOP Intra Ocular pressure
PF Preservative free

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