

CASE REPORT

Insidious-onset, non-wheezing carteolol-induced asthma in an atopic patient without asthma history

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SUMMARY

Carteolol, a non-selective beta-antagonist with a potential risk of severe bronchial constriction in patients with asthma, is one of the most commonly prescribed medication for managing ocular pressure in glaucoma. We present a case of a 24-year-old woman with a history of atopy but no known asthma who presented an insidious onset of clinical manifestations compatible with drug-induced asthma after the initiation of carteolol for ocular hypertension control. The patient developed progressive chest tightness and dyspnoea for 2 months before the pulmonary function test revealed a positive bronchoprovocation response. She reported significant improvement of respiratory symptoms within 2 weeks after the discontinuation of carteolol, and a negative provocation response was later confirmed by repeat pulmonary function test. In conclusion, eye drops with non-selective beta-antagonising effect can induce asthmatic symptoms in patients without a previous diagnosis of asthma and should be administered with caution in patients with associated risk factors.

BACKGROUND

Adrenergic beta-antagonist eye drops have been well established for management of ocular

hypertension in glaucoma by reducing aqueous humour production from ciliary body. Although applied topically, minor systemic absorption of this preparation can occur through common routes including conjunctiva and nasolacrimal system¹ and can sometimes lead to severe adverse reactions including life-threatening bronchial constriction.² Therefore, the prescription of non-selective beta-antagonists to patients with asthma are generally avoided due to the concern of acute exacerbation. Nevertheless, issues regarding the risk in prescribing these preparations to patients with only associated risk factors of asthma, including atopic dermatitis or allergic rhinitis, have not been addressed in the literature, despite that beta-antagonists have been considered safe for allergic patients without a diagnosis of asthma. Here, we report the case of a 24-year-old woman with a history of atopy but without asthma and who had an insidious onset of drug-induced asthma by carteolol eye drops.

CASE PRESENTATION

A 24-year-old Asian woman with a history of allergic rhinitis, urticaria and eczema presented to the outpatient clinic of ophthalmology and was diagnosed with ocular hypertension. The initial intraocular pressure was 17.8 mm Hg on the right side and 19.0 mm Hg on the left side. Both fundus colour photography and optical coherence tomography revealed borderline-elevated cup-to-disc ratio for bilateral eyes. Average retinal nerve fibre layer thickness measured 96 µm on the right side and 90 µm on the left, with decreased thickness of the superior hump of the left eye noticed (figure 1). Due to a family history of glaucoma and no previously documented asthma, elective carteolol solution was prescribed for control of ocular hypertension.

One week after starting carteolol, she began to notice progressive upper chest tightness without radiation accompanied by a non-productive cough. She visited a pulmonary medicine clinic after 2 months use of eye drops. Increased breathing difficulty was complained of, with feelings of airway expansion being restricted. No accompanying nasal symptom was reported. There was no specific aggravating or relieving factor identified, and she denied exposure to any inhaled agents or unusual environment. Due to previously known allergy to house dust mites, she constantly uses dust mite-proof mattress and denied any change in her household surroundings and sanitation. On questioning of her current medication use, carteolol was not mentioned out of her negligence. She also

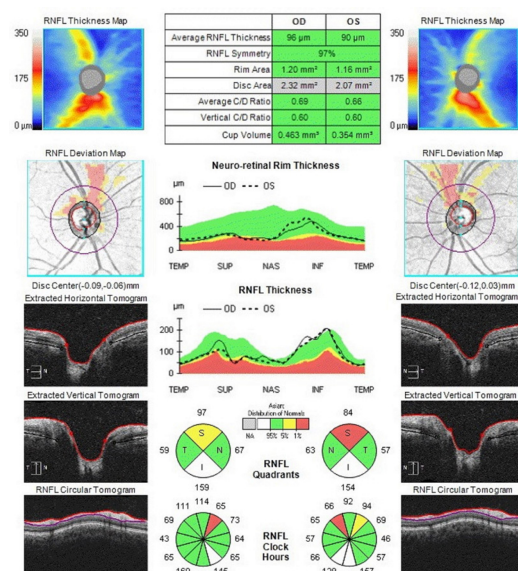


Figure 1 Retinal nerve fibre layer thickness map measured by Cirrus HD-OCT. C/D ratio, cup-to-disc ratio; HD-OCT, high-definition optical coherence tomography; OD, oculus dexter; OS, oculus sinister; RNFL, retinal nerve fibre layer.



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Figure 2 Chest radiograph of the patient.

recalled similar episodes of mild chest tightness with dyspnoea lasting for 35 days that happened in the past when the weather was colder with a frequency of fewer than once per year.

INVESTIGATIONS

Her vital signs at presentation were stable, without desaturation or distress. No wheezing or altered breathing sound was observed during physical examination, and no abnormality was noticed on chest radiograph (figure 2). Complete blood counts and differential counts were all within normal limits, including an absolute eosinophil count of 127 cell/mL. Considering her history and current symptoms resembling asthma, pulmonary function test with methacholine test were arranged. Pulmonary function test revealed a mildly decreased forced vital capacity (FVC) of 2.80 L and a forced expiratory volume in one second (FEV₁) of 2.54 L that corresponded to 75.8% and 75.6% of the predicted values and a normal FEV₁/FVC ratio of 90.7%. Bronchoprovocation test turned positive with more than 20% decrease in both FVC and FEV₁ before methacholine reached 16 mg/mL. With the concomitant existence of the mild restrictive ventilatory defect and positive bronchoprovocation test, diagnosis of asthma was thus made.

On the next clinical visit, the patient mentioned about carteolol use started 2 months earlier, which was about 1 week before the onset of her respiratory symptoms. Putting together the clinical picture and the bronchoconstrictive effect of non-selective beta blockers, the pulmonologist suspected carteolol-induced asthmatic presentation. To further evaluate her atopic status and to exclude potential exposure to a previously unidentified environmental triggering factor, serum examination for possible allergens and IgE level were arranged. Elevated IgE level of 115 IU/mL was confirmed, and no other allergens besides previously known house dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*) were identified.

DIFFERENTIAL DIAGNOSIS

Taking into account the atopic history, current symptoms and findings of elevated IgE level and positive bronchoprovocation result after investigations, the conditions for a clinical diagnosis of asthma were fulfilled according to the Global Initiative for Asthma guidelines. Despite differential diagnosis, including gastro-oesophageal reflux disease and mitral valve prolapse, should also be considered in young women with chest tightness and dyspnoea, these diagnoses are not likely due to incompatible clinical presentation and the lack of supportive findings through history taking and physical examination.

As for the possible cause of sudden asthma onset in this patient, after excluding unidentified allergens by blood test and change in weathers, surrounding environments or personal hygienes by detailed history taking, an environmental trigger was considered not likely. Carteolol, therefore, became the most suspected cause considering its possible effect of bronchoconstriction, and the use of eye drops right before the onset of symptoms also supported drug-induced asthma chronologically.

TREATMENT

Carteolol was discontinued for the intention to diagnose by treatment, and inhaled bronchodilator for as-needed use was prescribed. No any other modification of daily activity, environmental exposure or medication was made.

OUTCOME AND FOLLOW-UP

After 5 days of eye drops withdrawal, significant improvement in respiratory status was noticed. The patient reported no inhaler use during this time, and the symptoms of chest tightness and cough reached complete remission after 2 weeks. To determine her underlying asthmatic status, repeat pulmonary function test and methacholine tests were arranged after 1 month of eye drops discontinuation under general health condition of the patient without any medication use. Both the FVC and FEV₁ values were similar to the last examination, while the result of methacholine test was negative with only 0.36% decrease in FVC and 3.16% decreased in FEV₁ at methacholine 16 mg/mL. As a result, her baseline was considered non-asthmatic, and the whole clinical picture was concluded as an episode of reversible asthma onset induced by the ophthalmic solutions. During another 2 months of follow-up, no more asthmatic presentation was reported by the patient.

DISCUSSION

Although most of the non-selective beta-antagonising solutions were validated with significant respiratory function impairment and increased asthma morbidity and mortality,³ there are still more choices of non-selective beta-antagonising medications compared with ocular-selective ones in clinical use. While physicians used to exclude the history of asthma before prescribing beta-antagonists to their patients, the possibility of underdiagnosis of asthma, most commonly due to an under-representation of respiratory symptoms to the physician by the patient due to lack of awareness,⁴ and susceptibility to asthma development, especially in high-risk populations with associated risk factors, might still be omitted. However, it is generally difficult for the ophthalmologists to identify these underlying problems in ophthalmology clinic, where patients would not be providing much information about their respiratory health. Thus, the risk of drug-induced asthmatic presentation on usage of bronchial-constrictive medications underlies.

Studies have demonstrated the epidemiological connection, genetic link and pathophysiological similarity between asthma and other atopic diseases.⁵ Multiple studies have also recommended that each condition should be evaluated in patients presenting either of the disorder due to the association of increased prevalence and significant comorbidity between the two.⁶ Being an important factor contributing to the development of atopy, elevated IgE level of higher than 100 IU/mL was also noticed to be associated with asthma, eczema and allergic rhinitis during childhood and in adolescents and older adults, which helps to provide further information about the respiratory status of the patient.⁷⁻⁹ Taking together a history of atopic diseases and laboratory result of high IgE level into consideration, our case should be identified with a high risk of asthma development or inducement. Adding up a history of previously suspicious respiratory symptoms, the possibility of underdiagnosed intermittent asthma should not be ruled out until proven otherwise, and the awareness of susceptibility to bronchial hyper-responsiveness should be raised.

While there were multiple reports of asthma exacerbation induced by topical beta blockers in asthmatic patients, reports of ophthalmic solutions-induced asthmatic symptoms in diagnosis-free patients are limited. Among various non-selective beta-antagonising eye drops, carteolol, which has intrinsic sympathomimetic activity, is considered having the least chance of bronchial constriction.¹⁰ Despite a relatively rare risk of asthma inducement by carteolol, after excluding other possible triggering factors by a detailed history and serum examination, we considered drug-induced asthma as the most compatible answer toward the case's clinical presentation. The significant improvement in respiratory symptoms and a negative bronchial provocation test after the discontinuation of carteolol also supported our judgement. Although the diagnosis would be most convincing with a positive result from rechallenge test of this drug, after discussion with the patient and under safety concern, the decision of not performing the rechallenge approach was made. A repeat pulmonary function test was performed instead, and a non-asthmatic result also implied a drug-induced reversible asthmatic episode by validating her asthma-free baseline.

About the predictivity of asthma status by a positive methacholine result, in spite of the high sensitivity and significant correlation with respiratory symptoms,¹¹ false-positive results can still be caused by hyper-responsiveness of reactive airways, which might be normal variants or a manifestation of asymptomatic asthma. Some prospective studies have also demonstrated that airway hyper-responsiveness revealed by methacholine test helps predict future symptoms onset and development of a clinical diagnosis of asthma.^{12 13} For this population, the possibility of asthmatic presentation when exposed to triggering factors should be kept in mind. Even with a negative baseline methacholine test result, a positive response might still be observed after medication use in patients prone to asthma development, as what happened to our case. Therefore, to determine patients with increased risk of airway hyper-responsiveness after starting medication with bronchial constrictive effect, the arrangement of bronchoprovocation test could be considered in patients with risk factors of asthma development, either with or without a previously positive provocation response, before treatment begins.

For management of asthma elicited by ophthalmic solutions, discontinuation of the triggering medication would be the most important in initial management besides other means according to the treatment guideline for asthma. Significant improvement should be expected later if the medication is indeed the

triggering factor for the asthmatic status, as in our case, a nearly complete remission of her respiratory symptoms was noticed after 2 weeks of carteolol withdrawal without any bronchodilator use. Evaluation of the necessity of ocular hypertension treatment should be performed again by the ophthalmologist, and selection of alternative medications should be considered if continuous treatment is demanded. As for prevention of asthma development in patients with treatment-needed glaucoma or ocular hypertension, prescription of non-selective beta-antagonist should be performed with caution on patients with atopy or suspected respiratory symptoms. In any case, the definite mean to prevent adverse respiratory events in high-risk patients is to choose alternative medications without bronchial constrictive effect, for example, prostaglandin analogues or carbonic anhydrase inhibitors.

To improve clinical care of patients with atopy or risk factors for asthma in need of non-selective beta-antagonists use, prospective clinical trials are still required to provide further information about potential respiratory hazard by beta-antagonising eye drops and to help establish the evidence level to guide clinical practice on this particular patient group.

Patient's perspective

I didn't really think it was anything big when the symptoms first occurred since I could recall several times of similar things happened in the past, except that they never lasted that long and the feelings of breathing difficulty was never that obvious. And I had never expected just once of eye drops in the morning to bring such adverse effect! Especially since the ophthalmologist had asked me about my history before prescription and I was one hundred per cent sure that I didn't have asthma, which was also why I forgot to tell the internal medicine doctor about the drug when he asked me if there was any current medication use. It was kind of frustrating when the doctor initially told me that I had a positive asthma test result. I've been used to allergic rhinitis and skin rashes but I never thought that I might be receiving another atopic diagnosis after growing up, and asthma sounds more terrible than the others. It was a relief to know later that my symptoms were all because of the eye drops instead of my having asthma. I'm glad that the doctor found the cause before my condition got worse. There's no doubt that I will try my best to refrain from using medications with similar effects to the eye drops in the future, and, if I'm revisiting any clinic, I might consider sharing this adverse experience with my doctors more voluntarily to make sure that the same thing won't happen again.

Learning points

- ▶ Eye drops with non-selective beta-blocking function have the potential of inducing symptoms of asthma in patients without a previous diagnosis.
- ▶ Patients without asthma but with a history of atopy should be alerted to possible respiratory condition after receiving these eye drops.
- ▶ Bronchial provocation test for patients with risk factors of asthma development could be considered before treatment is started after a discussion with the patients.

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