

Timolol eye drops induced bradycardia

噻嗎洛爾滴眼液引致的心搏徐緩

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We report a 25-year-old man with bradycardia after administration of ophthalmic timolol. The patient was asymptomatic, and his bradycardia resolved after stopping the eye drop. He was discharged after a four-hour observation. This case demonstrated that topical timolol eye drop may cause systemic adverse reaction. The use of timolol and its possible side-effects are discussed. (*Hong Kong j.emerg.med.* 2010;17:71-74)

本文報告一名 25 歲男子施用噻嗎洛爾滴眼液後出現心搏徐緩。該名病人並無任何症狀，停用滴眼液後，心跳率回復正常，經四小時觀察後離院。此個案顯示噻嗎洛爾滴眼液可引致全身性的不良反應。本文討論噻嗎洛爾滴眼液之使用與潛在的副作用。

Keywords: Bradycardia, ophthalmic solutions, timolol

關鍵詞：心搏徐緩、滴眼液、噻嗎洛爾

Introduction

Topical ophthalmic solution may be overlooked as a cause of systemic adverse reaction. One typical example is ophthalmic timolol. Timolol is a common anti-glaucoma agent,¹⁻³ a non-selective beta-adrenergic receptor blocking drug. When applied topically on the eye, timolol has the action of reducing intraocular pressure, possibly related to the decreased aqueous humour secretion from the ciliary epithelium. Beta-blocking ophthalmic agents are generally safe but it can be absorbed systemically. There are case reports

that implicate the occurrence of bronchospasm, heart block, congestive heart failure or central nervous system dysfunction after the instillation of topical timolol eye drop.⁴⁻¹⁵

We report the development of sinus bradycardia in a healthy young patient due to topical administration of timolol maleate. The bradycardia resolved spontaneously after four hours of close observation.

Case report

A 25-year-old gentleman suffered from right eye injury during a football game three weeks ago in April 2007. His right eye injury was complicated by post-traumatic cataract after the contusion. He was scheduled to receive an operation for his right eye condition with day surgery. During the pre-operative assessment, the patient was found to have a slow heart rate of around 40 beats per minute (bpm). The operation was withheld and the gentleman was immediately brought from the day surgery centre to the emergency department (ED) for assessment.

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Despite his bradycardia, direct enquiry revealed the absence of significant symptoms. The patient had no palpitation, dizziness, nor chest pain. He enjoyed good past health and did not have history of cardiac disease or bradycardia. His current medications included 0.5% timolol (1 drop twice daily to the right eye), levofloxacin and 1% prednisolone acetate eye drops, oral acetazolamide and potassium chloride (slow releasing) tablets. Actually, the patient had used the above medications for eight days and the 0.5% timolol eye drop had been applied to his right eye five hours prior to his attendance at the emergency department.

The blood pressure measured in the emergency department was 112/68 mmHg and the pulse rate was 38 bpm. The patient was fully alert without any distress or signs of heart failure. The electrocardiogram (ECG) on ED presentation showed sinus bradycardia, PR interval of 163 msec, QRS interval of 98 msec and QTc interval of 351 msec (Figure 1). The chest X-ray and blood tests including complete blood count, renal function, liver function, thyroid function (TSH, T4), and cardiac enzymes (troponin T and creatine kinase) were unremarkable.

The patient was monitored in the ED observation room. He remained asymptomatic during observation. His pulse rate returned to 59 bpm spontaneously four

hours later. ECG was repeated (four hours later) and it showed sinus rhythm without bradycardia. The patient was discharged with advice on cessation of timolol. The patient remained in good condition and the follow-up revealed no recurrence of bradycardia.

Discussion

Ophthalmic timolol is a common drug to lower the intraocular pressure.¹⁻³ It is used commonly to treat glaucoma and traumatic cataract with secondary rise in intraocular pressure. Timolol is a non-selective beta-adrenergic receptor antagonist for blocking beta 1 and 2 adrenergic receptors.⁴

Ophthalmic timolol is licensed for the treatment of glaucoma and ocular hypertension, and the recommended dose is 1 drop of the 0.25% solution into the affected eye(s) twice daily. If the response is inadequate, then 1 drop of 0.5% strength twice daily in the affected eye(s) can be administered (Product Information BETIMOL® ophthalmic solution, 2004). The therapeutic dose is 0.125-0.25 mg LA bd.

The systemic bioavailability and pharmacokinetics of ophthalmic timolol are comparable to intravenous administration of timolol.¹⁶ In contrast to the low

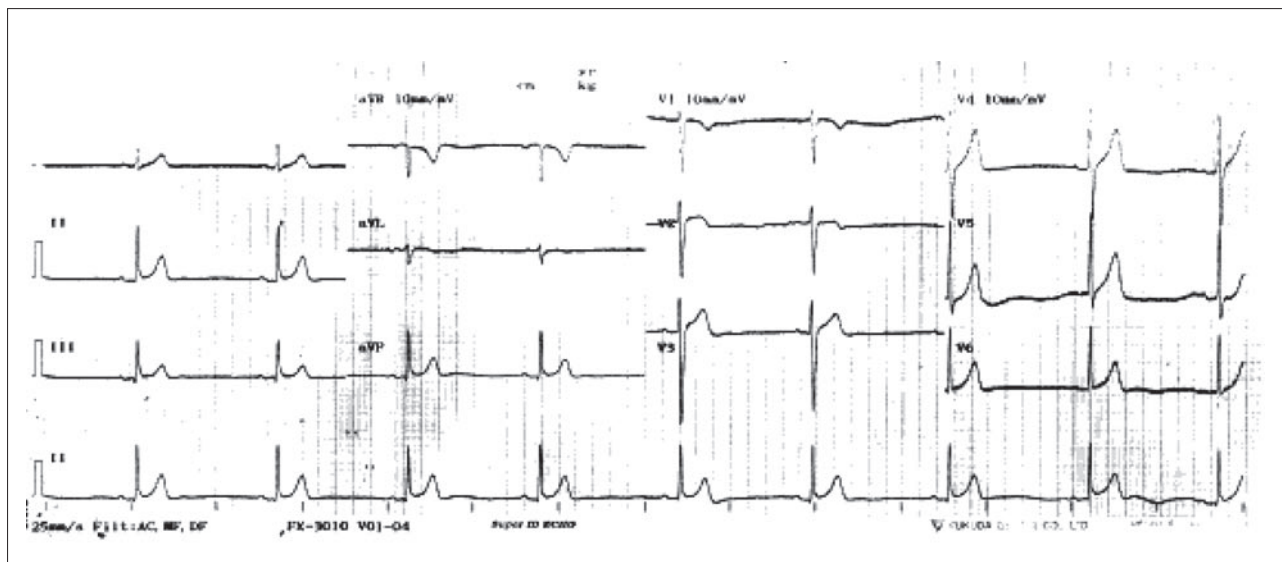


Figure 1. The ECG on arrival at the emergency department showing sinus bradycardia, PR interval 163 msec, QRS 98 msec and QTc interval 351 msec.

bioavailability of 61% after oral ingestion, the bioavailability after ophthalmic instillation is 78%.¹⁶ Timolol is absorbed into the systemic circulation rapidly and the maximum plasma level becomes detectable within 15 minutes after ophthalmic application.¹⁶⁻¹⁸ The average plasma concentration ranges from 0.46 ng/ml to 1.38 ng/ml after using aqueous solution.¹⁸ Timolol has a half life of 4-5 hours.¹⁸ It is metabolised by the polymorphism cytochrome P450 2D6 enzyme (CYP2D6) after systemic absorption.¹⁹ Its inactive metabolites are excreted primarily by the kidneys. A case report showed ophthalmic timolol was also excreted into human breast milk. The concentration in breast milk is approximately 6 times higher (5.6 ng/ml) than in serum (0.93 ng/ml).²⁰ In view of the systemic absorption after topical application, gel formulations of ophthalmic timolol have been developed to reduce systemic absorption and adverse effects. However, no differences were observed in heart rate suppressive effects between ophthalmic gel and aqueous formulations.^{21,22}

The exact mechanism whereby timolol reduces ocular pressure is not exactly known. The most likely mechanism is by decreasing the secretion of aqueous humour.²³ Although the drug is used topically, it is absorbed systemically and adverse systemic effects occur occasionally. Ophthalmic timolol has been proven to have systemic effects in terms of heart rate, blood pressure and respiratory functions. The heart rate is significantly suppressed from 15 minutes to 2 hours after ocular administration.^{16,18} The mean suppression in heart rate is 5-6 bpm in aqueous and gel formulations in the daytime.²²

There have been case reports of bradycardia,⁹⁻¹¹ complete heart block,^{12,13} variable degrees of atrioventricular block¹⁴ and respiratory arrest respectively that required resuscitation.¹⁵

The aetiology of sinus bradycardia is numerous. Sinus bradycardia can be caused by physiological conditions (well-conditioned athletes, during sleep, vagal stimulation), pharmacological uses (digoxin, narcotics, β -adrenergic antagonists, calcium channel blockers, quinidine) or pathological conditions (acute inferior

myocardial infarction, increased intracranial pressure, carotid sinus hypersensitivity, hypothyroidism, hypoxia and hypothermia).^{24,25} In this case, the young gentleman did not have history of cardiac disease and endocrine disease. Ophthalmic timolol-induced bradycardia was diagnosed clinically after excluding other causes of sinus bradycardia. The patient's heart rate returned to normal after stopping the medication.

The beta-adrenergic blocking effects of ophthalmic timolol may be longer and stronger in elderly patients than in younger ones.²⁶ Therefore, elderly patients should be monitored for a longer duration as compared with younger patients. Timolol maleate is contraindicated in patients with bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block and overt cardiac failure. If early signs of major adverse effects such as heart failure and bronchospasm are detected, ophthalmic timolol should be discontinued.

Conclusion

A case of clinical diagnosis of ophthalmic timolol-induced bradycardia has been presented. Despite the alleged safe profile of ophthalmic timolol, we should be alert that ophthalmic timolol may be a causative agent of bradycardia in patients receiving treatment for ocular hypertensive diseases. In the elderly or those with underlying medical illness, the systemic adverse effects may become significant. Emergency physicians should be alert to this possible association, and should discontinue ophthalmic timolol and treat the patients accordingly if bradycardia or other major adverse effects are identified.

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