Unexpected outcome (positive or negative) including adverse drug reactions

Ganfort, a blinding drug to the physician

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Correspondence to Dr Mohammed Majid Akhtar, gogetmajid@gmail.com**Summary**

Ganfort eye drops are indicated for adult patients with open-angle glaucoma who have poor response to topical β -blockers or prostaglandin analogues. They contain 0.3 mg of bimatoprost (a prostaglandin) and 5 mg of timolol (β -blocker). The authors present a case of a 45-year-old man with glaucoma presenting with shortness of breath. On admission, he had a normal heart rate, pulse oximetry and examination. Despite being of low risk stratification using the Wells score and the Modified Geneva Score for pulmonary emboli, CT pulmonary angiogram scan subsequently showed extensive bilateral multiple large pulmonary emboli. This case demonstrates that the systemic absorption of ocular β blockers is extremely high and it bypasses the first pass metabolism. Therefore, even one drop of Ganfort into each eye once a day was sufficient to disguise the tachycardia of a large pulmonary emboli.

BACKGROUND

- ▶ Timolol had a very high systemic absorption that was not appreciated for a topical eye drop.
- ▶ The risk stratification scoring systems upon which most hospital protocols are based, incorrectly predicted that this patient was low risk.
- ▶ Topical eye drops should be noted in any patients admitted to hospital.

CASE PRESENTATION

A 45-year-old man presented to accident and emergency for investigation of his shortness of breath. He was previously fit and well apart from a diagnosis of glaucoma for which he was on Ganfort eye drops. He noted gradually increasing shortness of breath over 2 weeks with an associated decrease in his exercise tolerance to 20 metres. There was no associated chest pain, phlegm, haemoptysis, cough, orthopnoea, fever or travel history. He was a non-smoker with no history of asthma or chronic obstructive airway disease. He was afebrile, with a heart rate of 85 beats per min (regular), blood pressure 134/81, saturations of 97% with respiratory rate of 22 indicating mild tachypnoea. Otherwise cardiac and respiratory examinations, bloods including clotting and chest radiograph were unremarkable. However, his electrocardiogram did show pathological T wave inversion in leads V2–V4. The gentleman went on to have a CT pulmonary angiogram that showed extensive bilateral upper and lower zone filling defects in keeping with multiple large pulmonary emboli. Furthermore there was almost complete occlusion of the left inferior pulmonary artery with evidence of right heart strain.

OUTCOME AND FOLLOW-UP

The patient was initiated on warfarin and heparin and his exercise tolerance has subsequently improved to normal.

DISCUSSION

In the case of a young gentleman admitted with dyspnoea, differentials of pulmonary, cardiac or neurological dysfunction should be considered. Pulmonary dysfunction may occur as a result of infection, obstructive airway disease or damage to the lung parenchymal. Changes in the preload,

after-load or cardiac output are common cardiac causes of dyspnoea. Neurological causes of dyspnoea including traumatic or degenerative nerve conditions are rare, but important differentials.

In this case, the T-wave inversion on ECG pointed to a diagnosis of right heart strain secondary to pulmonary emboli. It should be noted that each drop of Ganfort eye drops contains 0.25 mg of timolol. Pulmonary emboli may be painless and in young/fit patients; a compensatory tachypnoea may result in normal oxygen saturations. Tachycardia occurs as a result of activation of the sympathetic system and is one of the most common signs elicited in pulmonary embolism.¹ Tachycardia is a component of the widely used Wells clinical prediction scoring system for pulmonary emboli and is given even greater weighting in the revised Geneva scoring system for pulmonary emboli.² However, in this case, the tachycardia was obscured as a result of timolol use, resulting in the patient being classified as 'low risk' for both scoring systems.

Timolol is a non-selective β -adrenergic receptor blocker. Large systemic absorption of timolol occurs as a result of excess fluid passing down the naso-lacrimal duct and onto the nasal mucosa. Ocular administration of timolol also bypasses the first pass metabolism. Thus when measured in the blood after ophthalmic administration, the systemic bioavailability of timolol reaches up to 78% and ophthalmic delivery of the drug has been shown to be just as effective as intravenous delivery.³

In a recent study of 20 healthy volunteers randomised to receive either timolol twice daily or artificial tears for 2 weeks, it was noted that chronic timolol administration resulted in reduced maximal heart rate at rest and during exercise, despite being at often undetectable levels in the blood.⁴

Since this study, there have been numerous case reports of the adverse side effects of timolol. Timolol has been noted to cause severe orthostatic hypertension or symptomatic bradycardia.⁵ It has been noted that this bradycardia can be particularly significant when timolol is combined with verapamil.⁶ Finally, timolol has been noted to cause bronchospasm in asthmatics and patients with chronic obstructive pulmonary disease.⁷ The effects of timolol in an individual is heavily dependent on the presence or absence of the P-450 enzyme CYP2D6.⁸

In conclusion, this is the first case report of timolol obscuring the diagnosis of pulmonary emboli with potentially adverse side effects. Timolol given as part of Ganfort eye drops has a very high absorption into the systemic circulation. Ophthalmic delivery of the drug is as effective as intravenous delivery. Like all β -blockers there are significant side effects including bradycardia, syncope and bronchospasm. Physicians must be aware that the reflex sympathetic tachycardia response in patients may be blunted, thus making a diagnosis of pulmonary emboli more challenging. The use of timolol or any topical β -blocker should be noted in any patient admitted to hospital.

Learning points

- ▶ Topical timolol has high systemic absorption.
- ▶ Timolol eye drops cause relative bradycardia.
- ▶ Pulmonary emboli risk scoring systems such as the Revised Geneva Score or the Wells score may not be reliable if patients are using topical timolol for glaucoma.

Competing interests None.

Patient consent Obtained.

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