CASE REPORT

Topical timolol for treatment of epistaxis in hereditary haemorrhagic telangiectasia associated with bradycardia: a look at CYP2D6 metabolising variants

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SUMMARY

A 59-year-old man presented to the emergency department with lightheadedness. He had started intranasal administration of ophthalmic timolol for the prevention of epistaxis associated with hereditary haemorrhagic telangiectasia approximately 3 weeks earlier with excellent response. His heart rate was about half its normal rate, an ECG revealed sinus bradycardia, and it was determined he had significant cardiac issues in his family history. Essentially all other tests were normal. The discontinuation of the intranasal use of timolol resolved any further episodes of lightheadedness and bradycardia. It was determined through genetic testing that he is an intermediate metaboliser of CYP2D6, the main enzyme contributing to the metabolism of timolol. This explains the development of the bradycardia after intranasal timolol use. The metabolising variants of CYP2D6 need to be considered when prescribing medications metabolised by this enzyme, so possible adverse effects can be avoided.

BACKGROUND

Epistaxis is a very common problem that affects approximately 90% of patients with hereditary haemorrhagic telangiectasia (HHT), with its severity ranging from a social nuisance to life-threatening haemorrhages.¹ Surgery was the mainstay for these life-threatening haemorrhages, until recently, when the vascular endothelial growth factor (VEGF) inhibitor bevacizumab has shown promise as a medical treatment for HHT-related epistaxis.²

Topical timolol is used in the treatment of superficial haemangiomas in infants,^{3 4} and so has been theorised to be a viable option in the treatment of epistaxis in patients with HHT due to its effects on VEGF. Olitsky^{1 5} used topical timolol to treat epistaxis in patients with HHT both a rapid and persistent response; hence, topical timolol was used in our patient with HHT for the treatment of epistaxis with a good response. However, he developed symptomatic bradycardia, as he was an intermediate metaboliser of CYP2D6. Timolol is primarily metabolised by CYP2D6.⁶ This case highlights the importance that one needs to be aware of the pharmacogenetic variants of CYP2D6, as it may increase the possibility of adverse effects, such as bradycardia.

CASE PRESENTATION

A 59-year-old man with a history of HHT presented to the emergency department with symptoms of lightheadedness. Approximately 3 weeks earlier, he had started intranasal administration of 0.5% timolol eye drops—three drops to each nostril three times a day—for prevention of epistaxis, with excellent response. His family history is significant for pacemaker placement in his father at age 59 and sudden death in his paternal grandfather in his early 30s and a paternal aunt at age 66. He had no other significant medical history. The only medications he was taking at the time of presentation, other than topical timolol, were cholecalciferol and ω -3 fatty acids.

Initial evaluation revealed his heart rate to be 49 bpm (his normal heart rate usually runs in the 80s), while his blood pressure was normal at 130/78 mm Hg. The remainder of the examination was unremarkable. An ECG revealed sinus bradycardia with right bundle branch block (RBBB; figure 1).

He was admitted to the hospital. Routine blood tests (complete blood count, comprehensive metabolic panel and thyroid stimulating hormone) were all normal. A CT scan of the head was performed to rule out any intracranial pathology for the current symptom of lightheadedness, which was negative. A two-dimensional echocardiogram revealed a left ventricular ejection fraction of 68%, and normal left and right ventricular systolic function with no regional wall motion or valvular abnormalities. A tilt table test was normal.

The timolol eye drops were suspended, and he was placed on telemetry. He was also continued on supportive therapy, consisting of intravenous fluids and fall precautions.

The patient did not have any further episodes of lightheadedness after discontinuation of the intranasal timolol eye drops. Repeat ECG showed normal sinus rhythm with RBBB (figure 2). Considering the symptomatic bradycardia and significant cardiac history in the family, pacemaker placement was discussed. However, due to the temporal relation between the intranasal timolol eye drop administration and the symptoms, he was referred first for genetic studies to evaluate for CYP2D6 activity. Genetic testing revealed that he is an intermediate metaboliser of CYP2D6 (*1/*4), which explains the reason for the bradycardia after topical β -blocker usage. He did not have any further episodes of bradycardia after the discontinuation of topical timolol.

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Figure 1 ECG revealing sinus bradycardia with right bundle branch block.

DISCUSSION

Epistaxis is a very distressing, and recurrent, symptom affecting approximately 90% of patients with HHT.¹ Surgery remained the mainstay of treatment for severe epistaxis, until recently when the VEGF inhibitor bevacizumab showed successful results in HHT-related epistaxis.² This is due to the fact that VEGF levels are elevated in patients with HHT, and play a role in the development of nasal telangiectasia.⁷

Topical timolol has been used to treat superficial haemangiomas in infants.^{3 4} Although the mechanism is unclear, it may be related to vasoconstriction, endothelial cell apoptosis and

decreased VEGF expression.⁸ The initial response to timolol may be secondary to its vasoconstrictive properties, while longer term effects may be due to the endothelial cell apoptosis and decreased VEGF expression.⁵ Therefore, it was theorised that timolol could be a good treatment option for epistaxis in patients with HHT. And, advantages of topical timolol, compared with bevacizumab, include greater availability of the medication without the need for compounding, ease of application and decreased cost.⁵

Timolol is a non-selective β -blocker, largely eliminated by the liver and primarily metabolised by CYP2D6, with a minor contribution from CYP2C19.⁶ The contribution of CYP2D6 and

Figure 2 Repeat ECG showing normal sinus rhythm with right bundle branch block.

CYP2C19 to timolol metabolism was estimated to be >90% and <10%, respectively.⁶ Ocular administration of timolol has been associated with systemic adverse effects, such as bradycardia,^{6 9 10} with β -blockade observed even at low-plasma concentrations of timolol (~ 1.0 ng/mL).¹⁰ A change in heart rate is the most striking effect of the systematically absorbed fraction of ophthalmic timolol, with 0.5% aqueous formulations presenting greater effects than 0.1% hydrogel formulations.¹⁰

The pharmacokinetics of timolol are dependent on the genotype of this polymorphic enzyme.^{6 11–14} Differences in the enzyme activities lead to four major phenotypes: poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizers.^{6 15–17} In a study by Nieminen *et al*,¹⁰ it was noted that there was 2.5-fold higher plasma area under the curve in PMs than in EMs after application of timolol 0.5% aqueous eye drops. In addition, application of timolol eye drops intranasally gave rise to higher plasma concentrations and greater β -blockade in PMs than in EMs.^{6 10} These findings demonstrate a gene-concentration/effect relationship for timolol.

The finding of a null variant (*4) of CYP2D6 in our patient is expected to lead to a slower metabolism of timolol, which could account for his subsequent bradycardia; however, the dosage used and the bioavailability of the drug may also contribute significantly. The daily dosage in this case was three drops three times a day per nostril ($0.065 \text{ mL} \times 18 = 1.2 \text{ mL}$) of a 0.5% solution (0.5 mg/mL) or a total of 6 mg/day. When taken orally, timolol is typically prescribed at 10 mg twice daily, so the dosage used by our patient was not excessive; however, the route of administration (nasal drops) was unique. The nasal mucosa is known to be an efficient route for drug delivery,¹⁸ and the thin, close to the surface, large telangiectasias associated with HHT may enhance the systemic uptake of drugs. Thus, the CYP2D6 genotype of this patient, combined with intranasal administration, may have both led to this serious adverse drug reaction.

Learning points

- Intranasal administration of timolol is very effective in the treatment of epistaxis in hereditary haemorrhagic telangiectasia (HHT).
- Understand the pharmacogenetic variants of CYP2D6, as well as drug–drug interactions, involving CYP2D6.
- While prescribing pharmacotherapy to patients with HHT, especially medications that are metabolised through CYP2D6, like timolol, remember the variants of CYP2D6 as it may increase the possibility of adverse effects.

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