

Timolol eye drops for the management of acute migraine.

Notes for Prescribers.

Background

Beta Blockers have a wide array of actions, all of which are not fully understood. Oral Beta Blockers are used first line for the prevention of migraine although their mechanism of action is not known. Timolol is a non-selective oral beta blocker licenced for the prevention of migraine with a maximum daily dose of 20 mgs for migraine. (60mg for hypertension). Timolol eye drops are widely used for the management of glaucoma. 0.5% drops contain 5mg/ml and cost £1.50.

Case studies have suggested that eye drops can be beneficial in the management of acute migraine¹ and this has been confirmed by one randomised crossover trial². (There is also one small series of cluster headache presentations that have responded to Timolol drops³).

How does Timolol work in acute migraine?

Oral Beta Blockers have a high first pass metabolism and the gastric stasis that occurs in migraine inhibits their absorption. Absorption of eye drops is predominantly in the nasal mucosa via drainage in the nasolacrimal duct, but some conjunctival absorption occurs. Peak plasma levels of Timolol drops (one drop of 0.5% solution in each eye) are much lower than oral doses, 0.5 - 2ng /ml compared with 50-100 ng/ml for oral doses. Timolol eye drops achieve peak plasma levels in 10 minutes compared with two hours after an oral administration.

How Timolol eye drops work in acute migraine is not known. It may be that receptor sites are upregulated with regular beta blockade and become less responsive. Alternatively, there may be a "pharmacodynamic" effect, i.e. a specific intervention that is delivered de novo at an appropriate time in the evolution of a disease process even though it may be relatively small⁴.

How is Timolol used?

One drop of 0.5% solution is placed in each eye with the head tilted back and followed by blinking to facilitate the passage of drops into the lacrimal duct. If there is no action after 10 minutes this can be repeated. There is no reason why other acute medication can't be used at the same time if it is beneficial to do so.

In theory, drops should be used at the earliest onset of aura or pain if there is no aura. Timolol should not be used in people already on Beta Blockers and if these are in use for migraine prevention they should be stopped before using drops.

What are the side effects of Timolol?

Systemic side-effects can occur and are similar to oral side effects⁵. The most commonly reported are bronchospasm followed by bradycardia and hypotension. Contra indications are the same as for oral Beta Blockers.

Timolol drops should be stopped at least five days before an eye pressure check for glaucoma.

Prescribing off licence.

A number of preparations used in migraine, e.g. Amitriptyline, Sodium Valproate and Candesartan are widely used off licence. The patient should be made aware that this is an off licenced indication.

The GMC states that agents may be prescribed outside of their product licence when there is no suitably licenced medicines that will meet the patients need⁶.

References

¹ Migliazzo, Carl V, and John C Hagan 3rd. "Beta blocker eye drops for treatment of acute migraine." *Missouri medicine* vol. 111,4 (2014): 283-8.

² Kurian A, Reghunadhan I, Thilak P, Soman I, Nair U. Short-term Efficacy and Safety of Topical β -Blockers (Timolol Maleate Ophthalmic Solution, 0.5%) in Acute Migraine: A Randomized Crossover Trial. *JAMA Ophthalmol.* 2020;138(11):1160–1166.

³ Prusinsky A. Possibility of timolol use for immediate alleviation of Horton's cluster headache. Preliminary report. *Neurologia I Neurochirurgia Polska.* 1980;14(2):191–193.

⁴ Kernick D. Migraine - new perspectives from chaos theory. *Cephalalgia* 2005;25;561-566.

⁵ Munroe WP, Rindone JP, Kershner RM, D'Arcy PF. Systemic Side Effects Associated with the Ophthalmic Administration of Timolol. *Drug Intelligence & Clinical Pharmacy.* 1985;19(2):85-89.

⁶ Good practice in prescribing and managing medicines and devices. London: GMC, 2021. Available at: www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf