Dear Dave

Dave and other members of the bpac[nz] team answer your clinical questions

Who is Dave?

Pharmaceutical Programme Manager Dave Woods is a graduate of Manchester University (B.Sc. [Hons]) and the University of Otago (MPharm). Dave has extensive experience in hospital pharmacy, drug information, rational use of drugs and quality assurance. He has published on a range of subjects and holds editorial positions for several international journals.

If you have a clinical question email it to dave@bpac.org.nz

My patient was started on timolol eye drops a week ago for glaucoma. He is now complaining of feeling tired and coldness in his hands and feet. Could this be due to the timolol eye drops, and how can the situation be managed?

It is known that drugs can be absorbed in to the systemic circulation from ophthalmic preparations such as eye drops and solutions.

The nasopharyngeal mucosa is the primary site of systemic absorption of drugs applied topically to the eye. The extent of absorption depends on several factors including drop size, blink rate, physical capacity of the lacrimal sac and physicochemical properties of the drug. The conjunctival sac has a capacity of only 10 µL and an average eye drop is 25–50 µL, so 60–80% of an eye drop can overflow and enter lacrimal drainage.[1] Peak drug levels typically occur much more rapidly (similar to an intravenous bolus) than with oral administration.[2]

Absorption through the nasopharyngeal mucosa also avoids a first pass through the liver and for some drugs this will increase the proportion of drug reaching the systemic circulation. Timolol, which exhibits extensive first pass metabolism is such a case.

All the adverse effects associated with oral administration of timolol have also been reported with ophthalmic administration. This includes CNS, cardiovascular and respiratory effects so topical timolol has the potential to cause bradycardia and bronchospasm in susceptible people. As glaucoma is more prevalent in the elderly, who are also more likely to have co-morbidities, it is especially relevant to consider the potential effects of topical beta-blockers on any pre-existing conditions.[1]

Generally, the same precautions and contraindications should be observed with topical beta-blockers than those advised with oral administration. Relatively rare idiosyncratic adverse reactions such as hair loss have also been reported with timolol and other beta-blocker eye drops. This indicates that it is also possible for unpredictable (non-dose related) systemic reactions, such as hypersensitivity, to occur following administration of any eye drop preparation. An eye drop preparation should be avoided if it contains a drug which has previously caused a hypersensitivity or 'allergic' reaction in that person.

The systemic absorption of drugs from eye drops can be significantly reduced by simple advice

Digital nasolacrimal occlusion for three minutes or eyelid closure for two minutes immediately after instillation of the drops have both been shown to reduce plasma concentrations significantly. Digital nasolacrimal occlusion involves applying gentle pressure over the tear duct with a clean finger. Either of these methods can be used to reduce the absorption of any drug for which systemic absorption may be problematic such as corticosteroids, beta-blockers and cholinergic agents. They will reduce dose related adverse effects such as bradycardia with a beta-blocker but as they do not block systemic absorption completely and contraindications and precautions should still be observed. In addition, neither of these techniques remove the risk of non-dose related effects such as hypersensitivity.

Management of this case

Firstly it is important to examine the persons technique as people often use more drops than prescribed, 'just to make sure' or because they have difficulty telling how many drops they have instilled. This may lead to an excessive dose of the drug and more being available for absorption. A second person to check technique is useful and especially important to someone new to eye drop administration.

This person's side effects may be dose related so digital nasolacrimal occlusion or eyelid closure could be tried initially to try and stop or reduce them. Betaxolol is an alternative beta-blocker which is available as an eye drop. This is cardioselective (timolol is non-cardioselective) and is less well absorbed from eye drops than timolol. In this case it may be better tolerated than timolol.

Finally, if side effects are still troublesome a non beta-blocker agent, such as a prostaglandin analogue may be preferred.

References

1. Rait JL. Systemic effects of topical ophthalmic ß-adrenoceptor antagonists. Aust NZ J Ophthalmol 1999;27:57–64.
2. Lama PL. Systemic adverse effects of beta-adrenergic blockers: An evidence-based assessment. Am J Ophthalmol 2002;134:749–760.

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