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Veterans'MATES

Therapeutic brief 23

Impact of Glaucoma Medications on Co-morbidities

In 2008 over 31,000 veterans were dispensed medicines for glaucoma.[1] The systemic absorption of glaucoma eye drops can lead to adverse drug events and also impact on co-morbidities.

Inside

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In particular topical beta blockers have well documented systemic effects due to the presence of beta adrenoreceptors in vascular smooth muscle, the heart and bronchial tree.[2,3,4] DVA prescribing data indicates that the use of timolol eye drops is associated with an increase in bronchoconstriction as evidenced by increased use of beta agonists and inhaled steroids, and increased hospitalisation for respiratory conditions.[1] This therapeutic brief aims to: outline the different drugs used in the management of primary open angle glaucoma, highlight how drug selection may impact on coexisting cardiovascular and respiratory disease and suggest how to minimise systemic absorption by optimising eye drop instillation.

A key principle in glaucoma management is optimal communication between the ophthalmologist, who typically initiates and monitors the glaucoma treatment, and the GP to whom the patient may be more likely to present with systemic side effects.

Key points

- Eye drops have systemic effects which can impact on co-morbidities.
- Concurrent use of verapamil and topical beta blockers is contraindicated.
- Avoid topical beta blockers in veterans with bradycardia, decompensated heart failure and heart block.
- Topical beta blockers and pilocarpine can cause bronchoconstriction; enquire about respiratory symptoms and inhaler use.
- Ensure good communication between ophthalmologist, GP and patient.

What is glaucoma?

Glaucoma is an optic neuropathy; retinal ganglion cell death results in progressive optic nerve dysfunction and peripheral visual field loss. If left untreated permanent blindness may result.

Primary open-angle glaucoma (POAG), the subject of this brief, is the most common type of glaucoma accounting for about ⅔ of cases.[5] Development of POAG is strongly associated with elevated intraocular pressure (IOP); the risk for those with IOP›26mmHg is 13 times higher than that for those with lower IOP.[6]

POAG is asymptomatic. Intraocular pressure elevations up to 40 mmHg generally cause no pain or visual symptoms and patients can be unaware of visual field loss even when they have 'tunnel vision' of 10 to 20 degrees.

In a large proportion of patients IOP remains in the normal range (generally accepted as 10–20 mmHg). This normal-tension glaucoma is thought to account for up to 30% of glaucoma cases in Western countries.[5] Similarly IOP may be elevated with no evidence of optic nerve damage (ocular hypertension). The pathophysiology of glaucoma is most likely a result of innate optic nerve vulnerability factors. Other risk factors for POAG include increasing age and family history.

In the general population the prevalence of POAG is approximately 1–4% but this increases with age. Analysis of the DVA database indicates that in 2008 approximately 10.6% of veterans were receiving treatment for glaucoma. This much higher prevalence in the veteran population (average age 80 yrs) correlates with previous studies in over 65 year olds including the Blue Mountains Eye Study which found evidence of definite or probable open angle glaucoma in 8.7% of people 75 to 85 years of age.[7,8,9]

2 Management of primary open angle glaucoma

The aim of glaucoma therapy is to reduce the IOP. This has been shown to reduce the risk of long term visual field loss in those with glaucoma and ocular hypertension.[10] There is no threshold for the initiation of treatment and no standard guidelines for the optimal target IOP. Treatment is adjusted based on close follow up of visual fields and optic disc damage. Target pressures are lowered if there is disease progression despite treatment.

Intraocular pressure can be lowered by topical and systemic medical therapy (see table 1), laser therapy and surgery.

Glaucoma medications lower IOP by reducing the production of aqueous humour or increasing its outflow.

Prostaglandin analogues are considered first line therapy in POAG because of 1) the convenience of once daily dosing 2) their minimal systemic effects 3) their superiority in lowering IOP. A meta-analysis comparing latanoprost and timolol showed a 5% difference in IOP lowering effect in favour of latanoprost.[11] Analysis of the DVA prescribing data shows that prostaglandin analogues are the most commonly prescribed medications to treat glaucoma, with latanoprost accounting for the majority of use.[1]

Beta blockers are second line therapy, with alpha$_2$ agonists and carbonic anhydrase inhibitors both third line medical therapies. Pilocarpine is now used infrequently because of its side effects.

Table 1: Classes of drugs currently used

Class	Generic names	Brand names
Prostaglandin analogues	Latanoprost Travoprost Bimatoprost	Xalatan 0.005% Travatan 0.004% Lumigan 0.03%
Beta blockers	Timolol (beta$_1$ and beta$_2$ receptor blocker) Betaxolol (beta$_1$ receptor blocker)	Tenopt, Timoptol, Timoptol-XE 0.25% and 0.5% and Nyogel 0.1% Betoptic S 0.25% and Betoptic 0.5%, BetoQuin 0.5%
Alpha$_2$ agonists	Apraclonidine Brimonidine	Iopidine 0.5% Alphagan and Enidin 0.2%
Carbonic anhydrase inhibitors	Brinzolamide Dorzolamide Acetazolamide (oral)	Azopt and BrinzoQuin 1% Trusopt 2% Diamox 250mg
Cholinergics	Pilocarpine	Pilopt, PV Carpine, Isopto Carpine 1%/2%/4%; Pilopt, PV Carpine 6%
Combination Products	Timolol 0.5%/Brimonidine 0.2% Timolol 0.5%/Dorzolamide 2% Timolol 0.5%/Latanoprost 0.005% Timolol 0.5%/Travoprost 0.004% Timolol 0.5%/Bimatoprost 0.03%	Combigan Cosopt Xalacom Duotrav Ganfort

Glaucoma treatment and co-morbidities

Eye drops used in the treatment of glaucoma have significant systemic absorption. After instillation 80% drains through the nasolacrimal duct and enters the systemic circulation through the nasal mucosa avoiding first pass metabolism in the liver.[2] Glaucoma medications may then impact on co-morbidities, particularly cardiovascular and respiratory disease. The incidence of adverse effects in clinical practice depends on the risk profile of the population being treated.

The systemic side effects of topical beta blockers – bradycardia, bronchospasm, hypotension, syncope – are especially relevant to the elderly veteran population (average age 80 yrs with 7 co-morbidities).

Local and systemic adverse effects of glaucoma medications can limit their use (see table 2). However, systemic adverse effects can be reduced by correct installation of eye drops (see page 3).

Table 2: Adverse effects of topical glaucoma medications[12,5]

Medication	Local effect	Systemic effect
Prostaglandin analogues	Ocular irritation and redness, blepharitis, bitter taste, irreversible increase in iris pigmentation, thickening and darkening of eyelashes, keratitis	Headache, asthma, dyspnoea
Beta blockers	Stinging on instillation	Bradycardia, hypotension, syncope, fatigue, bronchospasm
Alpha$_2$ agonists	Ocular irritation and allergic reaction	Dry mouth, taste disturbance, headache, dizziness, drowsiness, hypotension, palpitations **Rare:** syncope
Carbonic anhydrase inhibitors	Ocular irritation, blurred vision	Bitter taste, GI disturbance, headache, dizziness **Rare:** Allergic reactions
Cholinergics	Fluctuating blurred vision, ocular irritation	Frontal headache **Rare:** bronchospasm, bradycardia, hypotension

Rare: incidence less than 0.1%

Cardiovascular disease and glaucoma

Topical beta blockers should be avoided in those with bradycardia, decompensated heart failure and heart block. The co-prescribing of a topical beta blocker and verapamil should be avoided because of the risk of profound bradycardia.[12] Analysis of the DVA prescribing data for 2008 showed 830 veterans were dispensed verapamil and were also receiving treatment for glaucoma. Of these, 38% had been prescribed topical timolol to treat their glaucoma.[1]

Topical and systemic beta blockers are co-prescribed in about 20% of patients with glaucoma.[14] It is important that ophthalmologists are made aware that a patient is taking systemic beta blockers as the IOP lowering efficacy of the topical beta blocker will be reduced and the risk of systemic side effects increased. This is particularly relevant in veterans with chronic heart failure where systemic beta blockers are frequently used. In 2008, 46% of veterans with chronic heart failure and glaucoma were treated with topical beta blockers.

Apraclonidine should be used with caution in those with cardiovascular disease, coronary insufficiency and recent MI as it can rarely cause hypotension and chest pain.[12] Brimonidine can also cause hypotension and should similarly be used with caution in those with severe cardiovascular disease and postural hypotension.[15] For both drugs there is a potential additive effect with antihypertensives.

Prostaglandin analogues do not appear to have significant cardiovascular adverse effects and are suitable for use in veterans with stable co-morbid cardiovascular disease.

Respiratory disease and glaucoma

Studies indicate that topical beta blockers used in the treatment of glaucoma and ocular hypertension can cause bronchospasm in those predisposed (including those with no previous diagnosis of asthma).[3,4] They should be used with caution in veterans with asthma or COPD. Analyses performed on the DVA prescribing data indicate use of timolol is associated with increased bronchoconstriction as evidenced by increased use of beta agonists and inhaled corticosteroids and hospitalisation for respiratory conditions.[1] Beta$_1$ selective beta blockers (such as betaxolol) have a higher affinity for beta$_1$ receptors in the heart with less effect on beta$_2$ receptors in bronchi and peripheral vasculature, however this effect is dose-dependent and diminishes at higher doses.[12,2]

Pilocarpine can cause bronchoconstriction due to its cholinergic effects and should also be used with caution in veterans with asthma or COPD.

Large doses of prostaglandins can cause bronchoconstriction and cases of asthma and dyspnoea have uncommonly been reported with prostaglandin analogue eye drops.[16,17] Analysis of the DVA prescribing data indicates latanoprost was associated with increased use of inhaled beta agonists.[1] In view of this, exercise caution when prescribing prostaglandin analogues for veteran patients with reactive airways disease and, at follow up appointments, enquire specifically about shortness of breath or increased use of inhaled beta agonists.

Corticosteroids and glaucoma

Corticosteroids may raise intraocular pressure when administered in any form, including inhaled steroids used in the management of asthma and COPD, and nasal sprays. However topical corticosteroid eye drops are the most potent cause of raised intraocular pressure. All corticosteroids should be used with caution in those with POAG.

The amount of systemic absorption can be reduced by up to two thirds by correct instillation of eye drops.

The 'double **DOT**' technique – **D**on't **O**pen eyes **T**echnique and **D**igital **O**cclusion of the **T**ear duct[13]

- Administer the eye drop then close the eye and apply digital pressure over the lacrimal sac for 2 to 3 minutes
- If 2 or more drops are being administered wait at least 5 minutes between drops

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Optimising glaucoma management

Optimal treatment of glaucoma requires a high level of adherence to therapy; for a condition which is frequently asymptomatic this can be difficult to achieve. Non adherence rates in glaucoma have been reported to vary from 24 to 59%[18]. Patient adherence can be improved by:

- Educating the patient about glaucoma and the importance of ongoing effective treatment.
- Simplifying the treatment regimen as much as possible.
- Observing the patient or carer instilling eye drops.
- Providing written instructions to the patient or carer including technique for correct instillation of eye drops.
- Enquiring about changes to health, new medications and possible side effects.

Consider a medicines review by an accredited pharmacist which may reveal potential drug interactions, systemic side effects or difficulties with administration of eye drops.

It is essential to optimise communication between all healthcare providers:

- in particular that the ophthalmologist is made aware of the patient's current medication regime and co-morbidities and
- the GP is aware of all treatments prescribed by the ophthalmologist.

This is especially relevant when the initial referral was made by an optometrist not the GP.

Further reading

Australian Medicines Handbook 2010[12]

Terminology and Guidelines for Glaucoma, 3rd Edition. European Glaucoma Society 2008. **www.eugs.org**[6]

Soon to be released Guidelines for Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma. **www.nhmrc.gov.au**

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