Systemic effects of ophthalmic beta blockers

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Treating glaucoma with topical ophthalmic beta blockers can result in life-threatening systemic side effects. These medications should be avoided in some patients.

The role of beta blockers

Beta-adrenergic receptor antagonists, or beta blockers, are a class of drugs that interfere with the transmission of sympathetic nerve impulses by binding to beta-adrenergic receptors. By inhibiting sympathetic stimulation of a target organ, beta blockers compete with neurotransmitters for beta-1 or beta-2 adrenergic receptor sites.

Discovery of ophthalmic benefits

Although beta blockers had been used experimentally since 1958,[1] it was not until 1967 that researchers observed that patients treated for cardiovascular disorders using propranolol (Deralin, Inderal) also had reduced intraocular pressures.[2] This observation led to trials of the direct application of beta blockers to the eye for the treatment of ocular hypertension and glaucoma.

While propranolol became the prototype systemically administered beta blocker, other beta blockers, including timolol (Nyogel, Tenopt, Timoptol), betaxolol (Betoptic, Betoquin) and levobunolol (Betagan), have been developed specifically for ophthalmic application. Fixed combinations of beta antagonists with other agents have also become available, including timolol plus dorzolamide (Cosopt Eye Drops) and timolol plus brimonidine (Combigan). More recently, timolol combined with prostaglandin analogues have become available and these include latanoprost plus timolol (Xalacom Eye Drops) and travoprost plus timolol (DuoTrav).

Beta blockers lower intraocular pressure by antagonising beta-2 receptors on the surface of the ciliary body, which inhibits aqueous production. Timolol and levobunolol are both nonselective beta blockers, whereas betaxolol is more beta-1 receptor selective.

Potential risks identified

It was soon realised that beta receptor blockade posed potential risks. Although serious cardiac depression was uncommon in early trials, heart failure did occur in patients with existing heart disease and in those taking cardiac drugs such as digoxin (Lanoxin, Sigmaxin). In addition, the introduction of propranolol showed that blockade of beta receptors could increase airway resistance, especially in patients with pre-existing asthma. Less often, researchers also observed a range of CNS effects associated with beta blockers, including hallucinations, nightmares, depression and sexual dysfunction.[3-7]

Before the recent advent of topical prostaglandin analogues, which act by increasing aqueous outflow, aqueous suppressants such as timolol were generally accepted as the first choice for glaucoma management due to their reasonable efficacy and acceptable safety and tolerability profiles. However, as their use increased, systemic side effects associated with beta blockers became more apparent. Indeed, all of the side effects associated with systemic beta blockers have now also been reported with topical ophthalmic beta blockers. As a result, the initial enthusiasm about the advantages of beta blockers over drugs such as pilocarpine (Isopto Carpine, Minims Pilocarpine Nitrate, Pilopt, P.V. Carpine) for lowering introcular pressure have since been tempered by concerns over potential life threatening complications. As a result, prostaglandin analogues are now widely preferred as first-line glaucoma therapy.[8]

Systemic side effects of topical beta blockers

Cardiovascular and pulmonary effects

Reversible airways disease is particularly common in the elderly, and its incidence may be increasing.[9] Patients with glaucoma may be unaware that they have mild signs of pulmonary disease.[10] A similar profile exists with respect to the decline in cardiac function with age, so care must be exercised when prescribing any agent that could compromise either of these vital functions.[11] Furthermore, the coprescribing of beta adrenergic antagonists to patients receiving bronchodilators for asthma was found in one study to be among the most common drug-disease interactions identified.[12]

Even in the absence of a clear medical history of any impairment, serious and often life threatening respiratory complications have been documented following the ocular administration of topical timolol.[13-16] In addition, healthy individuals who undergo long term topical application of nonselective beta blockers can develop a subclinical increase in bronchial reactivity that may not be completely reversible on withdrawal of the drug.[17]

Studies with oral or IV formulations of both cardioselective and nonselective beta blockers have demonstrated a propensity to induce marked cardiac slowing and a reduction in pulmonary function.

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However, results indicate that oral, IV and ophthalmic beta blockers have markedly different profiles. Studies involving oral doses of betaxolol suggest they may result in a more marked cardiac slowing than sustained release oral formulations of propranolol or timolol.[18] In addition, blockade of beta-2 receptors arising from nonselective beta blockade may induce a more significant effect on pulmonary parameters, such as FEV_1 and FVC, than that from some cardioselective beta blockers, such as betaxolol.

In epidemiological studies, however, few differences have been observed between the various topical beta blockers, with beta-1 selective agents also appearing to carry an excess risk of airway obstruction. Thus, selective agents should be subject to the same prescribing caveats as nonselective beta antagonists.[19] There may, however, be some evidence for improved systemic safety using lower concentrations of topically administered timolol, such as is possible with timolol 0.1% when administered as the hydrogel compound Nyogel.[20]

Plasma lipid level effects

Exacerbation of peripheral vascular disease and disturbances of serum lipoproteins, similar to those seen with oral beta blockers, might also be expected with topical applications.[21] Orally administered nonselective beta blockers are known to decrease plasma high-density lipoprotein cholesterol (HDL) levels and could theoretically increase the risk of myocardial infarction.[22] HDL cholesterol levels show a strong inverse correlation with the incidence of coronary heart disease in patients with all levels of total cholesterol.[23-25] Indeed, HDL might be one of the best lipid variables to use as a predictor of coronary heart disease incidence.[23-25] The impact of selective oral beta blockers on lipid profiles appears to be less marked, while oral beta blockers demonstrating a marked intrinsic sympathomimetic (partial agonist) activity do not appear to have a negative effect on HDL cholesterol levels.[26]

Several studies have investigated the effects of ophthalmic betaxolol and timolol on lipid levels. One study of topical ocular betaxolol 0.5% in 75 adult men with recently diagnosed ocular hypertension or primary open angle glaucoma revealed no significant variations in plasma lipid or glucose levels after six months' treatment.[27]

Two small studies investigating the adverse metabolic effects of ocular timolol 0.5% on HDL cholesterol and triglyceride levels in volunteers produced conflicting results.[28,29] Another study compared the effects of ocular timolol and carteolol (a topical ophthalmic beta antagonist with partial agonist activity not currently available in Australia) on plasma HDL cholesterol in a double masked crossover study in 61 normolipidaemic men.[29] The two medications had equivalent effects on intraocular pressure and resting heart rates, but decreases in HDL cholesterol levels were 3.3% for carteolol and 8.0% for timolol. The two beta blockers also differed in their effects on the mean ratio of total cholesterol to HDL cholesterol levels.

The authors estimated that long term use of timolol could correspond to a 17% increase in the risk of myocardial infarction, and calculated that the negative effect of ophthalmic timolol on HDL cholesterol levels was comparable to that of cigarette smoking, moderate obesity or physical inactivity. (The equivalent estimated incremental increase in risk for carteolol was 6.6%.) Although these theoretically increased risks may be small for an individual patient, they could correspond to a substantial increment in the number of myocardial infarctions given the large numbers of patients treated with ophthalmic beta blockers worldwide. The authors concluded that ocular nonselective beta blockers administered without nasolacrimal occlusion can induce a plasma HDL cholesterol decrease of a magnitude that appears to be clinically meaningful.

CNS effects

CNS effects (including neuropsychiatric disturbances) have been reported with the use of a topical beta blocker. These include fatigue, dizziness, headache, confusion, decreased libido and impotence. Other related side effects reported include sleep disturbance, psychosis, depression and hallucination.[3] Although most reports are of a commentary nature, the number of reports made to the US based National Registry of Drug Induced Ocular Side Effects has made topical beta blocker-related CNS events the largest category not related to the eye.[30-34]

Investigators have compared the CNS effects of timolol and betaxolol in patients with a history of decreased libido, impotence, depression and/or sleep disturbance.[35] In an open label component of the study, 16 of 18 patients taking timolol who had one or more of these adverse events noted an improvement when switched to betaxolol. The remaining two patients reported no improvement in their symptoms.

Seven of the patients entered the double-masked, crossover phase of this study. CNS symptoms resolved in two of the these patients and substantially improved in another three patients while on betaxolol. Depression symptoms deteriorated in one patient while on betaxolol. One patient developed wheezing while on timolol and withdrew.

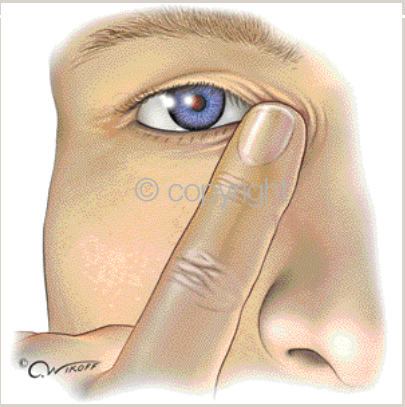
The authors noted evidence that beta blockers may antagonise serotonin or 5-hydroxytryptamine receptors. Betaxolol is a beta-1 selective antagonist and may have less effect on serotonin receptors than a nonselective agent.[36]

Risk of falls

Falls are a major threat to the health and independence of the elderly.[37] The Framingham Study showed that, compared with subjects with no visual impairment, those with moderately impaired visual acuity had a 50% increased risk of hip fracture, and those with poor visual acuity

Administering topical ophthalmic beta blockers using nasolacrimal occlusion: a technique to minimise systemic absorption

- Pull down the lower eyelid to form a pocket and instil the eye drop.
- Tell the patient to close his or her eye and tilt head back to allow the eye drop to be absorbed.
- With the eye still closed, directly apply finger pressure to the medial commissure (the site of union for the upper and lower eyelids) for approximately 2 to 3 minutes. This action blocks the nasolacrimal duct, preventing the eye drop solution entering the lacrimal duct and being absorbed systemically through the nasal cavity.
- Blot excess eye drop solution from around the eye to further reduce the likelihood of systemic absorption.
- Repeat the steps for all beta blocker or beta blocker combination eye drops administered.
- Encourage the patient to wait 2 to 3 minutes before instilling different types of eye drops.
- Encourage the patient to develop a routine for administering his or her own eye drops that incorporates nasolacrimal occlusion.



had a 120% increase in risk.[38]

Researchers have examined the causes of serious falls among 489 ambulatory persons aged 65 years or older who received a comprehensive examination at a glaucoma practice. After excluding any fall that was the result of a major intrinsic event, such as stroke, syncope, or hazardous behaviour, they still found that over one year, 9.6% of patients had at least one fall requiring medical attention or restricted activity.[39]

The greatest single risk factor for these falls appeared to be the use of nonmiotic topical eye medications. Ninety percent of those using nonmiotic topical eye medications in the study were using topical beta blockers.

Overall, 10.5% of participants using topical beta blockers had an injurious fall during the study period, compared with 3.3% of patients taking no eye drops. The risk was further increased for women and patients taking cardiac medication or sedatives.

Even after allowing for the limitations of the study, it appears that we should be alert to this risk when our patients are using these topical medications, particularly in combination with systemic drugs.

Prescribing considerations

Glaucoma is more prevalent in the elderly and the importance of balancing the benefits and risks of prescribing topical beta blockers is especially relevant for this group. Thus potential age-related functional decline, especially reduced cardiac and or pulmonary capacity, as well as the impact of other pharmacological treatment on these functions must be considered before ophthalmic beta blockers are prescribed.[10]

The likelihood of untoward systemic consequences varies depending on several factors, which may be drug related, or due to individual patient sensitivity. Drug-related effects include:

- systemic absorption
- different receptor dynamics (including selectivity)
- the rate of elimination of drugs from the circulation.

To limit the systemic absorption of topical ophthalmic beta blockers, nasolacrimal duct occlusion is recommended during administration (see the box on this page).

Conclusion

Topical beta blockers used in the treatment of glaucoma, especially nonselective beta blockers such as timolol, are known to have significant systemic side effects associated with beta blockade. Although such agents are absorbed in relatively small amounts from the conjunctiva, lacrimal drainage system and nasopharynx, some patients are at risk of potentially life threatening cardiac depression and bronchospasm.[40, 22]

Topical ophthalmic beta blockers should not be used in patients with:

- poorly controlled cardiac insufficiency
- severe atrioventricular heart block
- advanced peripheral vascular disease.

All topical beta blockers appear to carry an excess risk of airway obstruction and cardioselective agents, such as betaxolol, should be used carefully in patients with a history of reversible airway disease.

Neuropsychiatric disturbances, exacerbations of peripheral vascular disease and significant disturbances of serum lipoproteins similar to those seen with oral beta blockers have also been observed.[41]

Careful questioning of all patients after initiation of topical beta adrenergic antagonists is always required to ensure that even in the absence of a clear medical history of any impairment, subtle side effects do not lead to a reduction in the quality of life of patients with glaucoma. MT

A list of references is available on request to the editorial office.

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