Topical ophthalmic medications: what potential for systemic side effects and interactions with other medications?

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All topical ophthalmic agents should be considered potentially potent systemically

Many Australians are prescribed topical ophthalmic medications for chronic conditions such as glaucoma, ocular inflammation, infection and allergy. Despite their overall safety, these agents have the potential to cause significant systemic side effects and to have serious interactions with oral medications. In many cases, these effects may go unreported by the patient or misdiagnosed by the medical community. There is a need for improved prescribing practices in both the ophthalmic and general medical communities, with increased awareness of the full range of therapeutic agents being taken by the patient. With the recent passage of legislation allowing optometrists prescribing rights under the Pharmaceutical Benefits Scheme (PBS) (*National Health Amendment [Pharmaceutical Benefits] Act 2007* [Cwlth]), it is timely to remind all health care practitioners of the potential hazards of topical ophthalmic medications.

Pharmacokinetics make ocular drug delivery more akin to intravenous than to oral administration.[1] Topically administered medications gain access to the highly vascular nasal mucosa and are variably absorbed, avoiding first-pass hepatic metabolism.[2,3] One drop of timolol 0.5% solution in each eye approximates a 10 mg oral dose for treating systemic hypertension or angina.[2] All topical agents should be considered as potentially potent systemically.

A retrospective analysis of de-identified PBS billing data from Medicare Australia revealed that, between 1999 and 2004, 20 000 Australians per year had been exposed to co-supply of topical and systemic β-blockers.[4] This combination has been linked with adverse respiratory and cardiovascular events, as well as reduced topical ocular hypotensive efficacy.[5] The scale of this as a Quality Use of Medicines issue is larger than was anticipated. Multiple factors may be responsible: an assumption that topical therapy is systemically "homoeopathic"; the fact that many patients may not mention eye drops when asked about their drug history; and the fact that patients may not remember their full list of medications.

Topical medications usually constitute first-line therapy for glaucoma. Parasympathomimetics (pilocarpine derivatives) have been in use for 140 years, topical β-blockers for 30 years, and, more recently, carbonic anhydrase inhibitors, α_2-agonists and prostaglandin analogues have emerged. While the overall safety of these agents is recognised, there is a potential for serious side effects in a small proportion of people. As well as their own direct effects systemically, topical agents may have significant additive or interactive effects with systemic medications.

Topical β-blockers may precipitate or aggravate bronchospasm, congestive heart failure, bradyarrhythmias, sinus arrest, a variety of central nervous system effects and dyslipidaemias.[6-8] In this issue of the Journal, Schweitzer and colleagues (*page 406*)[9] describe a case involving two episodes of melancholic depression in a patient who had been prescribed β-blocker antiglaucoma agents. Taking these medications has been rated as the most significant risk factor for falls in glaucoma patients.[10] Parasympathomimetics locally provoke brow ache and/or headache, miosis and myopia, and, with systemic absorption, carry the risk of bradycardia, hypotension, bronchospasm,[7] gastrointestinal symptoms and urinary frequency. Topical α_2-agonists have been associated with central nervous system depression and with profound hypotension in children.[11] Topical carbonic anhydrase inhibitors do not seem to produce the metabolic side effects of their oral counterparts, but may be associated with an idiosyncratic bone marrow suppression and sulphonamide allergy.[6] To date, topical prostaglandin analogues have not been associated with cardiovascular or respiratory side effects, adding support to their use as first-line antiglaucoma agents.[6] However, their use has been associated with headache, flu-like symptoms and myalgias in up to 10% of patients, with case reports of neurological referral and investigation.[11,12]

Co-prescription of systemic and topical β-blockers can reduce heart rate in patients with glaucoma.[5] Simultaneous administration of topical timolol and systemic verapamil has been associated with severe bradycardia.[7] Co-administration of topical α_2-agonists with oral monoamine oxidase inhibitors carries a risk of hypertensive crisis and is contraindicated.[3] Salicylates have been shown to cause accumulation of systemically administered carbonic anhydrase inhibitors; this is also theoretically possible with topical carbonic anhydrase inhibitors.[3]

Topical steroid drops are key to the management of ocular allergy and inflammatory disease. While they are well tolerated systemically, their ocular side effects are potentially blinding: potentiation of infection, cataract and glaucoma. Commonly perceived as a "safe" alternative, fluorometholone has been associated with all these ocular side effects, albeit less frequently.[13]

Topical chloramphenicol is commonly prescribed to treat infective conjunctivitis, and is used perioperatively with ocular surgery. Although bacteriostatic rather than bactericidal in action, its broad spectrum of activity and lack of systemic use make it an ideal first-line ocular topical agent. Its potential to induce life-threatening aplastic anaemia remains controversial: the risk has been estimated to be about 1 in 150 000, at worst,[14] but it is likely to be much lower.[15] Whether the rare occurrence of this condition is by a dose-dependent or a dose-independent (idiosyncratic) mechanism,[14,15] prescribers need to be cautious when prescribing for patients with a personal or family history of blood abnormalities. Concern about this risk has been enough to marginalise the use of chloramphenicol in the United States. Additionally, chloramphenicol should only be prescribed when conjunctivitis is likely to be bacterial in origin and for clinically appropriate time periods.[16]

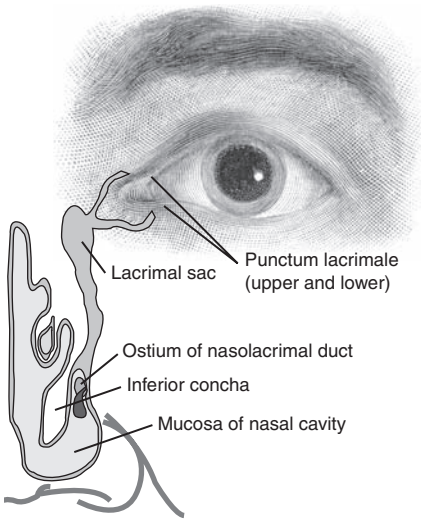
We believe prescribing practice can be improved with simple steps: (i) take a full drug history, and specifically ask about eye drops; (ii) physicians must remember to ask whether the patient's optometrist has prescribed any medication, and should be aware of the newer combination preparations (Combigan [Allergan], Cosopt [Merck, Sharp and Dohme], DuoTrav [Alcon], Xalacom

[Pfizer]), all of which contain the β-blocker timolol; (iii) ophthalmologists (and now optometrists) should be aware of a patient's concurrent systemic health and medication status before commencing any topical agents, particularly β-blockers. The eye is not an isolated organ but may be influenced by systemic diseases and therapies. Further, recent publications[1,4,8] highlight the converse — topical therapies for the eye may have significant systemic effects and/or interactions with systemic medications.

It is important to be alert to possible systemic side effects and interactions between systemic and topical agents and to investigate and modify treatment regimens appropriately. Limit the use of topical steroids, and use them only with adequate supervision. Remind all patients using topical medications to follow the "double DOT" procedure (Don't Open eyes Technique and Digital Occlusion of the Tear duct), which involves closing the eyes and applying digital pressure over the lacrimal sac for 1–2 minutes after drop administration (Box 1, Box 2). This reduces systemic absorption by two-thirds, thereby significantly widening the safety margin of all agents.[17,18]

Recent legislative changes across Australia allow practitioners who are not medically trained to prescribe topical medications, although, at present, legislation varies from state to state. These changes underline the importance of general practitioners and physicians recognising the potential systemic effects of these topical ophthalmic medications and being alert to interactions with other medications. Improved communication between all health care practitioners and ophthalmologists will be vital for patient safety.

1 Lacrimal drainage system



2 The "double DOT" procedure* for reducing systemic absorption of topical ophthalmic medications

* Don't Open eyes Technique and Digital Occlusion of the Tear duct. ◆

Competing interests

Ivan Goldberg has received educational grants from Alcon, Allergan, and Pfizer; honoraria from Alcon, Allergan, Pfizer, Merck and Ellex; and research support from Alcon, Allergan, Pfizer and Novartis.

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(Received 22 Apr 2008, accepted 9 Jul 2008) ❑