

Debate

Series editors:
Susan Lightman &
Peter McCluskey

CONTROVERSIES IN OPHTHALMOLOGY

Should β blockers be abandoned as initial monotherapy in chronic open angle glaucoma? The controversy

I Goldberg

β Blockers lower intraocular pressure (IOP) by reducing the rate of aqueous inflow.¹ Shortly after the commercial release of topical timolol maleate in 1978 it became the most widely used ocular hypotensive agent. Its potency, combined with its twice daily frequency of instillation and lack of induction of miosis or accommodative spasm, was seen as a major advantage.² Timolol was considered a revolutionary advance in the medical management of glaucoma.

In Australia, only laevobunolol later provided an alternative to timolol as a non-selective β blocker, and in 1995 betaxolol hydrochloride offered the choice of a relatively selective β blocker. Betaxolol has been demonstrated to have a wider safety margin than the non-selective agents, particularly for the cardiovascular and respiratory systems.³ It is less likely than timolol to provoke bradyarrhythmias, heart block, and bronchoconstriction. It is also somewhat less effective as an ocular hypotensive agent.⁴ In the laboratory, betaxolol has been found to have calcium channel blocking effects independent of its β blocking properties,⁵ and this has led to speculation that it may be useful not only in IOP reduction, but also as an inhibitor of episodic vasoconstriction in the optic nerve head region (one of the postulated mechanisms of glaucomatous damage),⁶ and as an agent that may offer a

modicum of neuroprotection by inhibiting the calcium influx that is an inherent part of apoptosis.⁷ To date, optic nerve head concentrations of topically applied betaxolol necessary to produce these additional benefits have not been demonstrated, and there has been no clear, adequately controlled, and robust clinical evidence to support these speculations.

Particularly in Europe, other β blockers, such as carteolol, have been available. Possible advantages for some of these molecules include differences in membrane stabilisation properties and partial agonist activity. In Germany, for example, up to 22 different β blockers have been marketed. Despite many claims over the years, no clearcut advantages have been demonstrated for any one molecule, and timolol has retained its clear market lead over all others internationally. Because of its relative selectivity, only betaxolol has been a significant challenger.

Before 1978, our antiglaucoma medical options included, cholinergics such as pilocarpine and carbachol, adrenergic agonists such as dipivefrin, and oral carbonic anhydrase inhibitors. Significant problems attended the use of all the non- β blocker options. By eliminating the topical side effects (miosis, dimmed vision, accommodative spasm, and brow ache) and by reducing the required frequency of instillation of the miotics (four times to once or twice daily), by being far

Table 1 Local and systemic side effects of available antiglaucoma medications in 1978 before availability of β blockers

Agents	Physiological effects	Resulting symptoms	
Cholinergics	Miosis	Dimmed vision Slow adjustment to poor illumination Rigid pupil for cataract surgery	
	Accommodative spasm	Fluctuating myopia and blurred vision Brow ache	
	Parasympathetic stimulation	Salivation/lacrimation Bowel/bladder hyperactivity Bronchoconstriction	
Adrenergics	Reactive hyperaemia	Red eyes	
	Pigment accumulation	Conjunctival adrenochrome deposits	
	Induced allergic reaction	Allergic blepharoconjunctivitis	
	Adrenergic stimulation:	Tachyarrhythmias Systemic hypertension	
Systemic carbonic anhydrase inhibitors	Increased renal bicarbonate excretion resulting in metabolic acidosis	Altered taste	
		Paraesthesia	
		Renal calculi	
		Anergy/lethargy	
		Anorexia/weight loss	
		Aplastic anaemias	
		Systemic allergic reactions	
		Stevens-Johnson syndrome	
		Resemblance to sulphonamides	

Correspondence to:
Ivan Goldberg;
igoldberg@bigpond.net.au

I Goldberg
Lead clinician
Eye Associates, Level 4,
187 Macquarie Street,
Sydney NSW 2000,
Australia

Accepted for publication
21 February 2002

Debate

more potent than dipivefrin and less likely to provoke surface discomfort or allergic blepharoconjunctivitis, and by avoiding the systemic toxicity of oral carbonic anhydrase inhibitors (anergy, paraesthesiae, altered taste, renal calculi, sulphonamide-type reactions), timolol rapidly became the most popular first choice for medical therapy (see Table 1).

However, since then, we have seen the introduction of topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide), α_2 adrenergic agonists (apraclonidine and brimonidine), a docosanoid (unoprostone), potent prostaglandin analogues (latanoprost and travoprost), and a prostamide (bimatoprost). Even though the use of these newer agents has expanded rapidly in many countries, worldwide timolol remains the most common first agent prescribed.

Should this be the case? Do the benefits the β blockers offer and the potential problems they pose continue to justify their first line use? Or do the newer agents offer a benefit to risk and cost ratio, which recommends them ahead of the β blockers? Should β blockers be abandoned as our first line medical defence against glaucoma?

FINANCIAL DISCLOSURE

Dr Goldberg has received honoraria, study support and/or travel reimbursements from Alcon, Allergan, Merck, and Pharmacia, chairs advisory boards for Alcon, Allergan, and Pharmacia, and is on an editorial board for Merck.

REFERENCES

- 1 **Yablonski ME**, Zimmerman TJ, Waltman SR, *et al*. A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. *Exp Eye Res* 1978;**27**:135–42.
- 2 **Zimmerman TJ**, Kaufman HE. Timolol. A beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977;**95**:601–4.
- 3 **Goldberg I**, Goldberg H. Betaxolol eye drops—a clinical trial of efficacy and safety. *Aust NZ J Ophthalmol* 1995;**23**:17–24.
- 4 **Stewart RH**, Kimbrough RL, Ward RL. Betaxolol vs timolol: a six-month double-blind comparison. *Arch Ophthalmol* 1986;**104**:46–8.
- 5 **Yu DY**, Su EN, Cringle SJ, *et al*. Systemic and ocular vascular roles of the antiglaucoma agents beta-adrenergic antagonists and Ca²⁺ entry blockers. *Surv Ophthalmol* 1999;**43**(Suppl 1):S214–22.
- 6 **O'Brien C**. Vasospasm and glaucoma. *Br J Ophthalmol* 1998;**88**:855–6.
- 7 **Osborne NN**, Wood JP, Chidlow G, *et al*. Ganglion cell death in glaucoma: what do we really know? *Br J Ophthalmol* 1999;**83**:980–6.

Br J Ophthalmol 2002;**86**:692–693

Should β blockers be abandoned as initial monotherapy in chronic open angle glaucoma? View 1

A Anton

As a result of our use of β blockers as initial therapy for glaucoma for several decades, we have acquired extensive knowledge about their advantages and limitations. β Blockers lower intraocular pressure (IOP) efficaciously—from 18% to 35%,¹ provoke fewer ocular adverse events, and have an easier dose regimen compared with pre-existing topical antiglaucoma medications—miotics and sympathomimetics. Although initial reports described timolol as highly safe, clinical experience and long term studies have exposed its potential systemic and topical side effects and limitations. Such knowledge has allowed adequate selection of who should or should not be treated with β blockers.²

Are there reasons to change the first line treatment used for decades now that we know β blockers so well? Yes, because there are now available newer medications with useful properties, and without the potential adverse effects and long term drift that characterised β blockers. When we, as ophthalmologists, choose a drug to treat patients with glaucoma we look for a medication that lowers IOP below target pressure and has minimal potential to cause harm to their eyes, their general health, and their quality of life. While the ideal hypotensive drug (very powerful,

easy to use, and with no side effects) is still to be discovered, today there are better choices than β blockers as initial treatment for most cases.

What are these options? α_2 Agonists, prostaglandin analogues and related drugs, and topical carbonic anhydrase inhibitors should be considered in order to prescribe the optimal treatment for each individual.

How do these new agents compare with the β blockers as hypotensive agents? Some of them offer similar or better hypotensive efficacy than β blockers. Brimonidine lowers IOP 20–27% and is as effective as timolol at peak³ but, at least with short term use, may not be at trough, and is more effective than is betaxolol suspension. Significantly more effective than any β blockers, latanoprost reduces IOP by 25–30% for most patients, and this effect is maintained throughout the day.⁴

Are the new agents easy to use? Yes. Dose regimen is once daily for latanoprost, bimatoprost, and travoprost, and twice to three times a day for brimonidine and topical carbonic anhydrase inhibitors.

Are the new drugs safer for the patient than β blockers? Several studies as well as clinical experience indicate that this is the case. The most important drawback with β blockers is their

A Anton, Instituto de Oftalmobiología Aplicada (IOBA), Universidad de Valladolid, C/Ramón y Cajal 7, 47005 Valladolid, Spain

potential for systemic problems: bradycardia, arrhythmias, congestive heart failure, heart block, and syncope. By blocking the β_2 receptors in the bronchioles, timolol may provoke bronchospasm and worsen chronic obstructive airways disease or asthma. But many other important side effects have been described: depression, increasing low density cholesterol levels (less with carteolol),⁵ hair loss, sexual impotence, fatigue, confusion, and disorientation.⁶ For example, between 1978 and 1985, there were 450 case reports of serious respiratory and cardiovascular events, and the United States Food and Drug Administration and the National Registry of Drug-Induced Ocular Side Effects received reports of 32 cases of death attributed to ophthalmic timolol. In addition, there is masking of hypoglycaemic symptoms in patients with insulin dependent diabetes, and decreased efficacy in patients on systemic β blockers.⁷

Even though experience with the newer medications is necessarily shorter and their more extensive and longer term use will probably enlarge the list of adverse effects, all the new drugs have been used for some years, and all demonstrate a better systemic profile.

Finally, although β blockers have a reasonably good topical adverse effect profile, they may cause dry eye syndrome, conjunctival hyperaemia and burning, stinging, or superficial punctate keratopathy. The topical profile of the newer drugs is similar or only slightly worse, and although the instillation of prostaglandin analogues and related drugs causes iris darkening, there is no evidence that these iris changes have any other consequences.

Do the new drugs maintain their effect over time? While a long term loss of the initial hypotensive effect has been well described with β blockers, typically appearing after 12 months' use,^{8,9} no such effect has been described for latanoprost.

It seems reasonable, therefore, to use β blockers only as second or even third line treatment when other drugs are not tolerated, are unable to lower IOP in a particular patient, or are contraindicated. Why should we use β blockers first if there are medications available that are at least as effective, at least as easy to use, cause significantly fewer systemic side effects, and have similar or only slightly worse local side effects?

FINANCIAL DISCLOSURE

Dr Anton has received honoraria, study support, and/or travel reimbursement from Alcon, Allergan, Merck, and Pharmacia.

REFERENCES

- 1 Zimmerman TJ, Kaufman HE. Timolol, dose response and duration of action. *Arch Ophthalmol* 1977;**95**:605-7.
- 2 Wilson RP, Kanal N, Spaeth GL. Timolol: its effectiveness in different types of glaucoma. *Ophthalmology* 1979;**86**:43-50.
- 3 Schuman JS, for the Brimonidine Study Groups 1 and 2. Effects of systemic β -blocker therapy on the efficacy and safety of topical brimonidine and timolol. *Ophthalmology* 2000;**107**:1171-7.
- 4 Camras CB, Alm A, Watson P, et al for the Latanoprost Study Groups. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. *Ophthalmology* 1996;**103**:1916-24.
- 5 Freedman SF, Freedman NJ, Shields MB, et al. Effects of ocular carteolol and timolol on plasma high-density lipoprotein cholesterol level. *Am J Ophthalmol* 1993;**116**:600-11.
- 6 Nelson WL, Fraunfelder FT, Sills JM, et al. Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985. *Am J Ophthalmol* 1986;**102**:606-11.
- 7 Van Buskirk EM. Adverse reactions from timolol administration. *Ophthalmology* 1980;**87**:447-50.
- 8 Lin LL, Galin MA, Ostbaum SA, et al. Long term timolol therapy. *Surv Ophthalmol* 1979;**23**:377-80.
- 9 Steinert RF, Thomas JV, Boger WP III. Long term drift and continued efficacy after multiyear timolol therapy. *Arch Ophthalmol* 1981;**99**:100-3.

Br J Ophthalmol 2002;**86**:693-694

Should β blockers be abandoned as initial monotherapy in chronic open angle glaucoma? View 2

G L Skuta

Even with the availability of these newer agents, we believe that β blockers, which have been a mainstay of medical glaucoma management for over 20 years for many very good reasons, still play a leading and vital part in our initial management of glaucoma.

Despite the potential and well understood systemic side effects of topical β blockers (see above), the balance of the risks and benefits of using β blockers at all, is more complex than we may realise. For example, even though they enhance

some risks, systemic β blockers reduce the risk of death after myocardial infarction, and have become attractive in the treatment of selected patients with known cardiac disease.¹

Over the past 23 years, we have become comfortable with β blockers and have a sense of familiarity with both their efficacy and side effects. Known side effects of brimonidine include dry nose and mouth, drowsiness, and ocular allergy. Latanoprost may produce hyperaemia and increased iris pigmentation and has been linked

Debate

G L Skuta, Dean A McGee Eye Institute, Department of Ophthalmology, University of Oklahoma College of Medicine, Oklahoma City, Oklahoma, USA

Debate

with uveitis, herpetic keratitis, and cystoid macular oedema. Even after extensive clinical evaluation, the side effect profiles of these newer agents are still being delineated and over time have revealed previously unrecognised side effects such as hypertrichosis with prostaglandins and related agents.² Other side effects could become evident in the future.

Timolol is a highly effective drug—regarded as the “gold standard” with which other new agents must be compared to evaluate their clinical efficacy. How do timolol and latanoprost compare? In the initial studies of latanoprost, this agent and timolol produced a similar IOP lowering effect, which has favoured latanoprost slightly.⁷

With respect to side effects, β blockers produce less conjunctival hyperaemia than does latanoprost, and no iris colour changes. Along with hypertrichosis, these are of concern for some patients, particularly for those requiring unilateral treatment, and in Chinese eyes where trichiasis is not uncommon, the hypertrichosis may not be a benign cosmetic effect. In glaucoma patients who require cataract surgery, β blockers do not need to be stopped preoperatively because of concerns about the potential for inflammatory and cystoid macular oedema complications.^{4,5}

In comparing β blockers with brimonidine as initial monotherapy, both have similar peak IOP effects. However, the trough IOP effect is less with brimonidine than with timolol. Once daily administration appears to be highly effective for many non-selective β blockers, even the non-gel forming preparations. In contrast, brimonidine must be used at least twice daily and, based on these initial studies, appears to be most effective if used on a thrice daily basis.

Brimonidine has a much higher ocular allergy rate, in the 9–13% range after 1 year, rising to 30% after 4 years versus less than 1% for agents such as timolol.⁶ This not infrequent development of ocular allergy and follicular conjunctival reaction plus the need for more frequent administration in comparison with latanoprost and non-selective β blockers may limit to some extent brimonidine's attractiveness as first line therapy.

As a highly lipophilic drug, brimonidine may cross the blood-brain barrier to produce apnoea in infants and somnolence in children, and drowsiness and fatigue in adults. In most young children, β blockers represent a more attractive option than brimonidine when drug treatment is necessary.

In patients for whom the preservative benzalkonium chloride is a concern, β blocker preparations are commercially available either with a different preservative (benzododecinium bromide in Timoptic XE) or no preservative (Timoptic Ocu-dose).

What about cost issues? In recent papers^{7,8} many, but not all, β blockers appeared to be more cost effective than the newer agents. If a β blocker solution (compared with a gel forming preparation) such as timolol is used once daily, the savings may be even more impressive.

What about possibly deleterious effects of chronic medical management on the outcome of subsequent glaucoma drainage surgery? It is the condition of the conjunctiva at the time of glaucoma filtering surgery that seems to be

important. Precise effects of latanoprost and brimonidine on postoperative subconjunctival inflammation and fibrosis are still being defined. One recent paper suggested that these agents increase the number of positively labelled proliferating subconjunctival fibroblasts in a rabbit model.⁹ In another study, β blockers alone appeared to be relatively benign with respect to any negative effect on the outcome of glaucoma filtering surgery, whereas the use of cholinergic and sympathomimetic drugs demonstrated a detrimental effect on surgical outcome.¹⁰

Are our options for the medical management of glaucoma better than they were 5 years ago? Absolutely. Have the newer agents positively impacted our ability to manage glaucoma? They have. Do we now have more attractive alternatives for initial medical treatment of glaucoma in patients who cannot or should not use β blockers? We do. However, β blockers are highly effective ocular hypotensives with well known side effects. Generally, they are well tolerated, have a very low rate of ocular allergy, may be used in children when necessary, and are more cost effective than many other newer alternatives.

Should β blockers be abandoned as initial monotherapy for glaucoma? My answer is no.

FINANCIAL DISCLOSURE

Dr Skuta has received honoraria, study support, and/or travel reimbursement from Allergan, Merck, and Pharmacia, and serves as a consultant to Merck and Pharmacia.

REFERENCES

- 1 **Gottlieb SS**, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;**339**:489–97.
- 2 **Johnstone MA**. Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. *Am J Ophthalmol* 1997;**124**:544–7.
- 3 **Camras CB**, Alm A, Watson P, *et al* for the Latanoprost Study Group. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. *Ophthalmology* 1996;**103**:1916–24.
- 4 **Moroi SE**, Gottfredsdottir MS, Scheingart MT, *et al*. Cystoid macular edema associated with latanoprost therapy in a case series of patients with glaucoma and ocular hypertension. *Ophthalmology* 1999;**106**:1024–9.
- 5 **Fechtner RD**, Khouri AS, Zimmerman TJ, *et al*. Anterior uveitis associated with latanoprost. *Am J Ophthalmol* 1998;**126**:37–41.
- 6 **Schuman JS**, Horwitz B, Choplin NT, *et al*. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. *Arch Ophthalmol* 1997;**115**:847–52.
- 7 **Vold SD**, Wiggins DA, Jackimiec J. Cost analysis of glaucoma medications. *J Glaucoma* 2000;**9**:150–3.
- 8 **Fiscella RG**, Geller JL, Gryz LL, *et al*. Cost considerations of medical therapy for glaucoma. *Am J Ophthalmol* 1999;**128**:426–33.
- 9 **Lark KK**, Pasha AS, Yan X, *et al*. The effect of latanoprost and brimonidine on rabbit subconjunctival fibroblasts. *J Glaucoma* 1999;**8**:72–6.
- 10 **Broadway DC**, Grierson I, O'Brien C, *et al*. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. *Arch Ophthalmol* 1994;**112**:1446–54.

Should β blockers be abandoned as initial monotherapy in chronic open angle glaucoma? Conclusion

Debate

I Goldberg

he cases for and against the proposition have been made. For the majority of patients, table 2 summarises the likely strengths and weaknesses for each of four groups of antiglaucoma agents, which are available for first line therapy. Consider your verdict.

Even though there is no right or wrong answer, the message seems simple—know your medical

weapons, their advantages and potential side effects, and the needs and challenges facing the individual patient sitting before you in your consulting room. Make your choice with as much professional wisdom as you can muster. Perhaps this article will have focused some of the more important issues for you.

Table 2 Relative advantages and disadvantages of four families of antiglaucoma agents as first line monotherapies

	β Blockers	Brimonidine	Latanoprost	Topical CAls
Efficacy, cost, convenience, and tolerability:				
IOP reduction efficacy for most	+++ 20–25%	++ – +++ 20–25%	++++ 25–30%	+ – ++ 15–20%
Cost	+	+++	+++	++
Instillation frequency	1–2 times daily	2–3 times daily	1 times daily	2–3 times daily
Topical tolerability	+++	++	++	+ – +++
Topical/local effects:				
Topical allergies	+/-	++	+/-	+/-
Preservative free preparations available	Yes	No	No	No
Conjunctival hyperaemia	+/-	+ to ++	+ to +++	+/-
Hypertrichosis	–	–	+ to ++++	–
Iris darkening	–	–	0 to +++	–
Systemic effects:				
Bradycardias/hypotension	+++	–	–	–
Bronchoconstriction	+++	–	–	–
Elevated serum lipids	++	–	–	–
Increased falls in the elderly	++	–	–	–
Apnoea in infants	+/-	+++	–	–
Drowsiness/anergy/fatigue	+	+ to +++	–	+/-
Dry mouth	–	+ to +++	–	–
Uveitis/CMO	–	–	0 to ++	–
Enhancement of herpetic keratopathy	–	–	0 to ++	–
Corneal oedema	–	–	–	0 to ++

CAls = carbonic anhydrase inhibitors

Correspondence to:
Ivan Goldberg;
igoldberg@bigpond.net.au

I Goldberg
Lead clinician
Eye Associates, Level 4,
187 Macquarie Street,
Sydney NSW 2000

Accepted for publication
21 February 2002



Should β blockers be abandoned as initial monotherapy in chronic open angle glaucoma? The controversy

I Goldberg

Br J Ophthalmol 2002 86: 691-695
doi: 10.1136/bjo.86.6.691

Updated information and services can be found at:
<http://bjo.bmj.com/content/86/6/691.full.html>

These include:

References

This article cites 24 articles, 7 of which can be accessed free at:
<http://bjo.bmj.com/content/86/6/691.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Angle](#) (788 articles)
[Glaucoma](#) (776 articles)
[Intraocular pressure](#) (786 articles)
[Neurology](#) (1036 articles)
[Pupil](#) (38 articles)
[Conjunctiva](#) (170 articles)
[Ocular surface](#) (452 articles)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>