

The Development of β -Adrenergic Blocking Drugs for Management of Primary Open-Angle Glaucoma

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In the last few years, there has been a marked increase in the number of drugs available for the management of open-angle glaucoma. The development of these newer ophthalmic drugs has been prompted by a desire to make available, to the public, products that display maximum efficacy (with respect to the glaucoma) but minimal side effects on the body generally or on the health of the eye or on vision. The major development has been in a set of drugs active on β -adrenergic receptors (the " β -blockers"). While many of these newer drugs are, as yet, available only in Europe or Japan, in 1986, three new ophthalmic β -blockers became available in the English-speaking world.¹ It is our intent in this article to review why there has been this major expansion in the number of drugs available to manage glaucoma or ocular hypertension — an expansion that comes from many years experience with 8 different drugs worldwide.^a With the increasing availability of these glaucoma medications to the optometrist in the USA², it is recognized that the optometrist in Canada will have been exposed to reports of the use of timolol, levobunolol

and betaxolol by colleagues.³ Indeed, the optometric community in the USA is continuing to lobby to make therapeutic drugs available to all optometrists.⁴

Drugs in the beta blocker classification are also widely administered as oral drugs to manage cardiac arrhythmia, (and associated angina or systemic hypertension) and sometimes migraine. Orally administered β -blockers can be expected to exert some action on the eye. For example, small ocular hypotensive effects ($\leq 10\%$ change in IOP) can occur especially shortly after these drugs are taken. Although extensive studies have been conducted on the ocular hypotensive action of systemically administered β -blockers, this mode of administration of β -blockers has not been adopted in general practice as a means to manage glaucoma. These effects will therefore not be discussed further. Our review will concentrate on the use of β -blockers as eyedrops in Canada, the USA, Europe and Japan.

For those not familiar with β -blockers, a few words on terminology seem appropriate. β -blockers have been shown to bind to β -adrenergic receptors but do not activate them; instead these drugs deny the normal neurotransmitter (norepinephrine) access to beta adrenergic receptors.⁵ Drugs in this class may be also referred to as sympatholytic drugs or β -adrenoceptor antagonists. β_1 receptors are located in the heart and in the ciliary body particularly in the walls of blood vessels and some on muscle cells. Stimulating β_1 sites increases heart rate⁶ and indirectly increases aqueous humor production. Blocking β_1 sites results in decreased heart rate and force of cardiac contraction,⁵ and decreased aqueous production while having little effect on

the pulmonary system. β_2 receptors are associated with smooth muscles in the walls of blood vessels and the lungs. Thus, stimulating β_2 receptors causes bronchodilatation, vasodilatation (or vasoconstriction depending on the site in the body) and acts on the ciliary body to increase aqueous production. There are many β_2 sites in the iris and ciliary body,⁷ and in the trabecular meshwork vasculature. Stimulating β_2 sites in the trabecular region appears to facilitate escape of aqueous from the eye. Blocking β_2 sites causes the bronchi to constrict and causes some reduction in aqueous production while having little effect on heart rate.⁵ Thus a β_2 -blocker (or a drug with combined β_1 , β_2 - blocking activity) can exacerbate symptoms in asthmatics (even precipitating an asthmatic attack due to acute broncho-constriction). A β_1 -blocker (or a drug with combined β_1 , β_2 -blocking activity) can precipitate bradycardia (slowing of heart rate below normal levels), exacerbate cardiac arrhythmias in a few patients and lower blood pressure below normal levels. Attention to these vital signs in a patient constitutes one aspect of patient management in the selection of the appropriate ophthalmic β -blocker although the clinical relevance of mean heart rate reductions of 5 to 10 bpm (4% to 8%) is questionable.

As indicated above, these β -blocking drugs rarely show absolute selectivity between β_1 or β_2 sites. Thus, these β -blockers can act by:

- blocking either β_1 or β_2 receptors. Those which preferentially block β_1 sites are called cardioselective (because they will not affect the pulmonary system at normal clinical doses).

a. Every effort has been made to provide correct information on drug availability, indications and contraindications, limits of use and accumulated reports of side effects. Sources of information include the articles listed below and the following pharmaceutical directories — *Compendium of Pharmaceuticals and Specialties (Canada)*, 1987 Edition; *Physicians Desk Reference — Ophthalmology (USA)*, 1987 Edition; *Rote Liste (West Germany)*, 1987 Edition; *British National Formulary (UK)*, 1987 Edition.

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- blocking both β_1 and β_2 receptors, these are called non-selective blockers.
- from an ocular perspective, two other factors need to be considered since some of these drugs have *membrane stabilizing activity*. Repeated instillation of a drug which has this action can result in corneal anesthesia in some individuals and eventually punctate keratitis or general lid irritation. Some β -blockers have *intrinsic sympathomimetic activity*. They have some ability to stimulate one or more types of adrenergic receptor (i.e. mimic the action of norepinephrine or epinephrine).

These functions are not always rigidly distinct, for example a drug may mostly block β_1 sites but if the dose is sufficient it will also block β_2 sites. At certain doses some β -blockers (depending on their potency) can show membrane stabilizing and/or intrinsic sympathomimetic activity.

A large number of β -blockers have been investigated to see if an eyedrop preparation of the drug will lower intraocular pressure.⁵⁻⁹ (Table 1).

We will review several of these β -blockers in alphabetical order. For all of these drugs, the efficacy (i.e. the magnitude and time-base of the clinical effect) of any one drug (used in the form of eye-drops) has frequently been found to be enhanced by the use of a second topical ocular hypotensive drug (e.g. use of two ophthalmic β -blockers simultaneously or the concurrent use of epinephrine eye-drops or pilocarpine eyedrops). Orally-administered anti-glaucoma drugs (e.g. the carbonic anhydrase inhibitors such as acetazolamide) have also been shown to add to the ocular hypotensive action of a topical ophthalmic β -blocker. However, for the most part, reports of synergistic effects, although of academic interest, will not be commented upon further. In the clinical setting, such combined therapy is generally used only in patients who fail to respond adequately to single drug use or during changeover from one set of eyedrops to another. Two effective "combination" drugs have enjoyed considerable use for many years (epinephrine-pilocarpine combinations in Canada and USA and epinephrine-guanethidine combinations in Europe). Other anti-glaucoma combinations which are available in some countries include, pilocarpine + physostigmine, pilocarpine + neostigmine, pilocarpine + dipivefrin, guanethidine + dipivefrin, pilocarpine + phenylephrine, pilocarpine

TABLE 1
Beta adrenoreceptor blocking agents

	Division I non-cardioselective	Division II cardioselective
Group 1 have MSA and ISA	alprenolol bunolol carteolol oxprenolol pindolol ^b	acebutolol
Group 2 have MSA but no ISA	bupranolol labetalol ^a levobunolol ^b metipranolol ^b propranolol	
Group 3 have ISA but no MSA		practolol ^c
Group 4 have no MSA and no ISA	befunolol nadolol sotalol timolol ^d	atenolol ^c betaxolol ^d metoprolol ^d tolamolol ^d

MSA = membrane stabilizing activity, a quinidine-like effect, local anesthesia, eventually punctate keratitis

ISA = intrinsic sympathomimetic activity, may be desirable, hastens drug action

a - also blocks α_1 adrenoreceptor sites

b - has been said to have no MSA

c - has some ability to block β_2 sites as well

d - may have some MSA

+ metipranolol and pilocarpine + 3',4'-dihydroxy-2 methylaminoacetophenon.

Atenolol

Atenolol is a cardioselective β_1 -blocker which may be employed to treat high blood pressure. It is not currently used in glaucoma therapy in Canada or USA although it underwent extensive trials in the late 1970s in a variety of topical formulations. It has no membrane stabilizing activity and almost no intrinsic sympathomimetic activity.⁹ Topical atenolol 4% was found to have only small effects on blood pressure and heart rate.^{10,11} Atenolol eyedrops (1% to 4%) produced a dose-dependent fall in IOP of 1 to 4 mmHg¹⁰ or 4.9 to 6.3 mmHg^{11,12} with a single instillation. Single drops of atenolol 4% were reported to lower IOP by

an average of 5.6 mmHg (range 3.2 to 13.2 mm)¹³ and two drops lowered IOP by 8 to 10 mmHg.¹⁴ Similar results were also observed over one week with instillation twice a day for patients with initial pressures ≤ 30 mmHg¹⁰. However, atenolol 4% eyedrops, twice a day, appear to be unable to hold pressures down for more than a week or two especially if starting pressures are ≥ 30 mmHg.^{15,16} A subsequent trial of atenolol 4% eyedrops (single drops) on normal healthy subjects indicated that the hypotensive effects of atenolol would only be observed in ocular hypertensive and/or glaucomatous eyes since the trial showed only 1 to 1.5 mm reduction in IOP¹⁷ in normal individuals. The pressure reduction from a single drop was reported to persist for not over 6 hours.¹¹ Atenolol is considered less lipid soluble and more water soluble

than many β -blockers so does not penetrate the cornea readily. While no effects on corneal sensitivity were reported following short term use of atenolol eyedrops,¹⁰ dry eyes and conjunctivitis¹⁸ might follow longer use.

Befunolol

Befunolol, a non-selective β -blocker, was developed in Japan and is available in Germany and Japan as 0.20% (or 0.25%) and 0.5% solutions for instillation into the eye. Befunolol eyedrops have been reported to produce modest reductions in systolic blood pressure (≈ 10 mmHg) when used over several weeks.¹⁹ They decreased the ability of the heart to respond to exercise²⁰ but had only a small effect on pulmonary function. Befunolol decreases aqueous production. Befunolol is reported to be particularly effective in eyes with various forms of secondary glaucoma.²¹⁻²³ Single drops of befunolol 0.5% promptly reduced IOP in primary glaucomatous or ocular hypertensive eyes (initial IOP ≤ 30 mm Hg) by 5 to 15 mm Hg while the 0.25% concentration produced a slightly smaller effect.¹⁹ Both effects were maintained with either drug on a twice-daily basis.¹⁹ Similar effects have been reported by others.^{24,25} In a detailed study on patients with secondary glaucoma, slightly smaller, but long term effects, were produced²² — again, with only slight effects on blood pressure. Its recommended clinical use would be twice-daily with the availability of two concentrations to allow titration. Befunolol is said to be comparable to pilocarpine for controlling the IOP.²¹ The pressure lowering effect of befunolol can be enhanced by concurrent use of pilocarpine or acetazolamide.²³ Few unwanted systemic effects occur.²⁶ Overall, befunolol has been found to have only small effects on blood pressure or heart rate^{19,22,24} has not so far been found to affect corneal sensitivity, outflow resistance, pupil size, nor refraction.^{19,24} Other potential unwanted effects include headache, general ocular irritation and blepharitis.²⁶

Betaxolol

Betaxolol is now widely available as an ophthalmic product (Canada, USA, Europe) as a 0.5% solution. This cardio-selective β_1 blocker, when instilled into the eye can slow the heart (about 2 beats/

min²⁷) and lower the blood pressure (by 7 mmHg).²⁷ Betaxolol eyedrops lowered the IOP 3.8 to 11 mmHg^{1,27-29} or 17% to 27%.³⁰⁻³⁴ By itself betaxolol was not as effective as timolol in lowering the IOP when the pressure was 26 mmHg or more.³⁴ However other studies found equal pressure reduction by these two beta blockers.^{27,35} Betaxolol is usually instilled twice a day, one drop each eye. Decisions as to the use of betaxolol are based on a variety of factors. Like the other ophthalmic β -blockers, betaxolol stings a little when first instilled.^{27,29,36,37} Such irritation has been found in 22% to 70% of patients in controlled trials but betaxolol is said to produce fewer side effects than timolol.³⁸ When betaxolol 0.5% eyedrops are instilled bid over many weeks, the maximum reduction of IOP can be expected within 1 week and the IOP remains relatively constant thereafter.^{27,33,35} in at least 50% of patients placed on betaxolol as their sole glaucoma medication. Betaxolol penetrates the cornea more readily than timolol does,^{27,39} and like timolol decreases aqueous production,^{1,28} but is not necessarily as effective as timolol for treating open-angle glaucoma.³⁴ Betaxolol is racemic mixture whereas timolol consists of only the 1-isomer.³⁷ If the dose is large enough betaxolol shows some ability to block β_2 sites and therefore causes unwanted pulmonary effects in a few patients.⁴⁰ Betaxolol has been reported to have less effect on lung function³⁸ and exercise-induced tachycardia than timolol does.⁴¹ In one year there were 56 reports of adverse reactions apparently associated with use of topical betaxolol on the eye. Of the nine patients with severe reactions, seven were hospitalized, six for asthma, and one each for asthma with cardiac arrhythmia, respiratory distress, and bradycardia with syncope.⁴² Cardiac beta blockade has been reported.³⁹ Insomnia and depression have occurred. Betaxolol can also decrease corneal sensitivity and cause photophobia, increased tearing and conjunctival hyperemia⁴²; the so-far reported incidence of these problems appears to be small however.

Bupranolol

Bupranolol blocks β_1 and β_2 sites and has significant membrane stabilizing activity. It is administered orally for control of cardiac arrhythmia and is not available

in North America as an ophthalmic product. However this potent β_1 , β_2 blocker is available in Germany (and Japan?) for ophthalmic use in concentrations of 0.05%, 0.1%, 0.25% and 0.5%.⁴³ Single drops of bupranolol 0.05% (in castor oil) reduced IOP by ≈ 5 mmHg in open angle glaucoma patients.⁴⁴ Topical bupranolol 0.5% drops (in castor oil) produced substantial (often > 10 mmHg) hypotensive effect.^{43,45-47} Topical bupranolol 1% (vehicle not stated) provided a similar effect in a glaucomatous eye⁴⁶ and simultaneously lowered the IOP in the untreated eye by 70% as much as in the treated eye.⁴⁶ Bupranolol decreases aqueous production^{46,47} without significant effect on aqueous outflow.⁴⁵⁻⁴⁷ The higher concentrations of bupranolol (0.5% and 1%) have been found to be comparable to pilocarpine 2% or 4% eyedrops in ocular hypertensive patients⁴⁸ but without the unwanted ciliary spasm, miosis and tearing associated with topical pilocarpine. Bupranolol 0.5% has been tested over a period of several weeks and found to maintain its clinical efficacy.⁴⁹ Bupranolol drops can however produce significant ocular irritation and blepharitis.⁴⁹ In some patients a modest corneal anesthesia has been reported.^{43,45,47} Only slight effects on tear film production have been reported.⁴⁵

Carteolol

Carteolol is available as an ophthalmic drug in Japan, England, Italy, France and Germany at 1% or 2% concentrations. It blocks both β_1 and β_2 sites and has some membrane stabilizing action and some intrinsic sympathomimetic activity.⁵⁰ It lowers the IOP by reducing aqueous secretion.⁵¹ In a concentration of 1% or 2% instilled three times a day, carteolol lowered the IOP by about 9 mmHg or by 34%.⁵⁰ Carteolol was reported to maintain the IOP of 84% of primary open-angle glaucoma patients below a pressure of 24 mmHg.⁵² Carteolol 2% eyedrops slowed the heart an average of 6 bpm.⁵³ Carteolol can however cause superficial keratitis⁵³ to an extent that the product is marketed with the warning that it should not be used in dry eye patients as it can aggravate or precipitate this condition.

Labetalol

Although generally classified as a non-selective β_2 -blocker labetalol is consi-

dered by some to also block β_1 receptors to some extent.⁴⁶ Labetalol has some membrane stabilizing activity. It is not currently available as an ophthalmic product but is taken orally to treat acute high blood pressure crises. Labetalol eyedrops (1%, 1 drop) were found to produce small and very variable reductions in IOP (3 to 6 mmHg) within 4 hours while a similar pressure reduction was observed in the contralateral eye.⁵⁴ As with most of the β -blockers, small reductions in systolic blood pressure and pulse rate have also been reported.⁵⁴ Side effects reported¹⁸ were dry eyes and conjunctivitis.

Levobunolol

Levobunolol is a non-selective β -blocker. Orally administered levobunolol has been used to treat systemic hypertension, cardiac arrhythmia and angina. Levobunolol 0.5% is now widely available for ophthalmic use. When instilled, one drop each eye (twice a day) levobunolol 0.5% eyedrops have been found to lower IOP 2.3 to 9.6 mmHg,⁵⁵⁻⁶² or by 9% to 36%,^{58,63,64} especially in patients with IOPs 30 mmHg. Some contralateral effect on IOP is also observed. The plasma level of levobunolol one hour after topical instillation of 1% was 0.3 to 0.6 ng/ml.⁶³ Levobunolol has a rapid onset of action and the IOP has not been found to drift higher after months of treatment. Levobunolol, instilled twice a day, is considered equivalent to timolol for treating glaucoma,^{55,57,58} and like timolol decreases aqueous production.⁶⁴ Levobunolol controlled glaucoma successfully in over 70% of one group of patients.⁶¹ When compared to other ophthalmic β -blockers levobunolol has a long duration of action⁵⁷ so there was hope that once a day administration would prove to be sufficient for controlling glaucoma in some patients⁶¹ but other investigators consider this unlikely.⁶⁵ Levobunolol can be administered concurrently with other anti-glaucoma medications. Levobunolol slowed the heart^{55,57,59} 4 to 10 beats/min^{55,57,59,60} and lowered blood pressure 3 to 6 mmHg (systolic and diastolic).^{33,56,60,66} Others have reported a decrease in systolic pressure of 12 to 14 mmHg and in diastolic pressure of 4 to 6 mmHg.⁵⁷ Topically instilled levobunolol can also decrease pulmonary function by as much as 25%²⁰ and thus, as with timolol, contraindications include: bronchial asthma, chronic pulmonary

disorders, heart block, sinus bradycardia and cardiac valvular disorders. Levobunolol can irritate the eyes and stinging was reported in 22% to 56% of drug-treated patients in controlled trials with 0.5% and 1%^{56,66}; and has caused blepharitis,⁵⁷ or blepharoconjunctivitis in a small number of patients receiving it. Side effects occur in 1% to 4% of users of levobunolol eyedrops and include headache and insomnia. Unwanted effects are apparently more frequent in patients receiving timolol.⁵⁵

Metipranolol

Metipranolol, a non-selective β -blocker,²⁰ is available in the United Kingdom, Germany and France for ophthalmic use in three concentrations: 0.1%, 0.3% and 0.6%. The 0.1% concentration is also available in Germany in combination with pilocarpine 2%. The drug was developed in Germany. FDA approval for metipranolol is currently being sought in the USA especially as the efficacy of the 0.6% concentration has been reported to be same as levobunolol 0.5%.⁶⁶ Metipranolol 0.5% or 0.3% produces a modest (5 to 7 mmHg, 15% to 30%) but sustained reduction in IOP of eyes with open-angle glaucoma.^{67,68} The efficacy of metipranolol 0.25% was reported to equal that of timolol 0.25% drops in open-angle glaucoma.⁶⁹ The 0.3% or 0.6% concentration slowed the heart ≤ 4 beats/min,^{66,68} and lowered diastolic pressure by 3 mmHg, while reducing IOP by about 3 mmHg⁶⁶ or about 5 mmHg.⁶⁶ Topical metipranolol significantly suppressed the ability of the heart to respond to exercise.²⁰ Topical metipranolol, like levobunolol, was found to reduce pulmonary function by 24%.²⁰ Because metipranolol is available in three concentrations it may permit closer control of a patient's IOP without the administration of enough drug to cause unwanted effects.¹ Metipranolol 0.25% in clinical use has not been reported to produce any more corneal anesthesia than timolol 0.25%.⁷⁰ In two studies, glaucoma or ocular hypertensive patients preferred levobunolol 0.5% to metipranolol 0.6% eyedrops when they were asked to compare how much stinging the drops produced on instillation.^{66,71} In the short term, metipranolol 0.6% has been reported to produce about the same effect on tear film stability (reducing TBUT) as that produced by timolol 0.5%.⁷²

Metoprolol

Metoprolol, another cardioselective β_1 blocker, is widely used to treat high blood pressure and is not currently available as an ophthalmic drug. Metoprolol has no intrinsic sympathetic activity and almost no membrane stabilizing activity.⁹ Metoprolol 1% eye drops were found to reduce IOP by 4 to 6 mmHg⁷³ while the 3% concentration lowered IOP about 6 mmHg or about 26%.⁷⁴ It kept the pressure down for 2 to 4 hours.^{74,75} Metoprolol 0.5% eyedrops have small to modest effects on heart rate with reductions of 4 bpm⁷⁶ on a bid regimen but 12 bpm on a qid regimen.⁷⁴ Metoprolol lowered systolic blood pressure by 5 mmHg⁵⁸ but produced no change in diastolic pressure. Common side effects included a burning, itching sensation in the eye⁷³ which resulted in increased tear production.⁷⁴ Tear breakup time has also been reported to be significantly reduced.⁷²

Nadolol

Nadolol blocks β_1 sites and to some degree β_2 sites as well. By blocking β_1 sites nadolol is useful to treat cardiac arrhythmias and associated high blood pressure. It is not available as an ophthalmic product. In a recent study, nadolol 2% eyedrops instilled in the eye produced only a small and brief reduction of the IOP — an effect attributed to their low lipid solubility and thus poor corneal penetration.⁷⁷ However, earlier studies using single drops of nadolol 2% reported an average ocular hypotensive effect of at least 10 mmHg within 2 hrs and that reduction lasted for at least 4 hrs.^{54,78} This effect was confirmed in a subsequent study which evaluated these eyedrops over a period of 4 weeks⁷⁹, using a twice-a-day regimen. When prepared in the form of the prodrug acetyl nadolol 0.5%, it was found to penetrate the cornea more readily and lowered the IOP about 7 mmHg.⁷⁷ Like the other β -blockers nadolol eyedrops can also slow the heart and lower blood pressure⁷⁹ but without effects on the pupil. Serious side effects of dry eyes and periorbital dermatitis have been reported however.⁷⁷

Oxprenolol

Also called oxyprenolol this non-selective β -blocker has membrane stabilizing and

intrinsic sympathomimetic activity.⁷ Oxprenolol is used to treat high blood pressure but is not currently available as an ophthalmic product. One study reported that instillation of oxprenolol drops 0.5% lowered⁸⁰ IOP about 3 mmHg (i.e. about 15%). Another trial showed single drops of 0.5% or 1% reduced IOP by an average of 6 mmHg within 2 to 3 hours. The ocular hypotensive effect was maintained for at least 3 months when oxprenolol was instilled three times a day. Oxprenolol 1.0% (1 drop) when instilled in the eye produced a slight fall in diastolic pressure and in pulse rate (by 3 to 4 beats/min)⁸⁰ and kept the IOP down for 2 to 3 hours but tolerance tended to develop. Potential unwanted effects however include dry eyes, conjunctivitis and even corneal ulceration.¹⁴

Pindolol

Pindolol is a non-selective β -blocker with some intrinsic sympathomimetic activity,⁷ and very little membrane stabilizing activity. It is used to manage high blood pressure. In West Germany (and France?, Italy?) pindolol is available for ophthalmic use in the 0.5% and 1% concentrations. Trials with pindolol eyedrops have produced variable results. When pindolol 0.5% or 1% was instilled in the eye it was reported to lower IOP by 3 mmHg⁸¹ while in another trial the 0.25% concentration was found to lower IOP by 4 to 6 mmHg or about 18%.⁸² Pindolol 1% eyedrops (single instillation) by 10 mmHg.⁸³ Similarly large reductions in IOP were reported in open angle glaucoma patients in a trial using pindolol 0.5% three times a day⁸⁴ with no change in corneal sensitivity, pupil or visual acuity in most patients. Pindolol 0.5% eyedrops, produced only small reductions in IOP (3 mmHg) and had insignificant effects on heart rate.⁸⁵ However a proportion (reported as 13% in one study⁸⁶) of patients suffered from dry eyes, conjunctivitis, or lid reactions. These necessitated marketing the drug with a firm warning of these effects when used for a long term. This last study reported that pindolol 1% tid was effective in eyes with initial pressures of > 40 mmHg. A recent study⁸⁷ reported that pindolol 1% twice daily produced a sustained reduction of IOP of about 6 mmHg — giving it the same clinical efficacy as the commoner β -blockers such as timolol.

Practolol

Practolol blocks β_1 sites and has some ability to block β_2 sites. This drug has intrinsic sympathomimetic activity.⁹ Practolol has been used to treat high blood pressure but is not now available as an ophthalmic product. Single drops of practolol 10% were found to lower IOP by 4 or 5 mmHg.⁸⁸ Practolol eyedrops however caused an intense immunological reaction (the oculomucocutaneous syndrome) with dry eyes, keratoconjunctivitis, corneal ulcers and in a few cases blindness.⁸⁹ Practolol was subsequently shown to be excessively toxic to the corneal epithelium and to the lacrimal glands. The reason for these effects remains unknown, although an autoimmune response to practolol has been suggested.⁸⁹

Propranolol

Propranolol was the first oral β -blocker and has long been used to treat high blood pressure, angina, arrhythmia and migraine. It is a non-selective β -blocker with some membrane stabilizing activity.⁹ Following initial investigations of the action of systemic propranolol (oral or i.v.) on IOP⁹⁰ propranolol 1% eyedrops were reported to produce substantial reduction in the IOP of glaucomatous eyes,⁹¹ but the same extent of ocular hypotensive effect was not found in other studies.⁹² One investigation using propranolol 0.5% reported a modest ocular hypotensive action.⁹³ Propranolol kept the IOP down for 4 to 6 hours but its ability to control the IOP diminished in about 2 months. It is of interest that a special study found that intranasal administration of propranolol produced a serum level equal to that achieved by intravenous administration.⁹⁴ Unwanted effects include: dry eyes, ocular discomfort and corneal anesthesia although such effects are concentration dependent.⁹³

Timolol

Timolol is a non-selective β -blocker⁵ which was developed to treat high blood pressure and serendipitously found to be an effective "anti-glaucoma" drug. Within the past seven years timolol has become a popular drug for treating open-angle glaucoma. It has become the highest volume sales prescription drug for ophthalmic use.¹ Timolol has very little

membrane stabilizing activity and almost no intrinsic sympathomimetic activity. Timolol is available for ophthalmic use worldwide (Europe, Japan, Australia, USA and Canada). Timolol has now become the standard with which other beta blockers intended for ophthalmic use are compared. Timolol decreases aqueous production⁸ by about 30%. In concentrations of 0.25% or 0.5% instilled twice a day timolol produced clinically useful reductions in IOP (2 to 10 mmHg, 18 to 30%).^{27,28,35,55,57,58,61,76,77,82} The pressure was kept down for at least 6 hours and in some eyes for at least 12 hours.⁹ Clinicians almost always advise twice a day instillation of timolol. Timolol appears to be absorbed more slowly and eliminated more rapidly than other β -blockers which is an unexpected finding in view of its long-lasting ocular hypotensive effect.⁹⁵ With prolonged use of timolol eyedrops, the IOP in some patients shows short term escape and (when timolol is used for 12 months or more) long term drift in the direction of higher pressure. As a result a change in medications becomes necessary. Timolol drops instilled twice a day generally produce more reduction in IOP than topical ocular epinephrine 1% twice a day. If a patient on timolol is also given epinephrine the IOP goes down 5% to 10% more. However if a patient is receiving epinephrine and is then given timolol an even greater hypotensive effect is achieved.⁹⁶ (Epinephrine itself improves aqueous outflow probably by its agonist action on β_2 adrenergic receptors.) When the goal was to keep the IOP below 21 mmHg timolol was considered satisfactory in 64% to 93.7%,^{9,61} pilocarpine was considered satisfactory in 76.2%,⁹ and epinephrine was satisfactory in 69.9%,⁵ of patients. (Acetazolamide given orally every 6 hours will decrease aqueous production by about 40% and lower IOP 6 mmHg.³³) Despite the proven effectiveness of timolol it should be recognized that timolol has cardiovascular effects, slows the heart 1 to 10 beats/min^{27,55,57,59,60,68,76} and lowers blood pressure 2 to 10 mmHg.^{27,29,55,57,60,68,76} Topically applied timolol may decrease the heart's ability to respond to exercise.²⁰ Timolol is contraindicated in patients with bradycardia, asthma,²⁸ or any kind of heart block.

Lowering the blood pressure may counteract some of the hoped-for good results of lowering the IOP since perfusion pressure in the retinal capillaries is important in preserving the health and

function of the retinal ganglion cells. The instillation of timolol (or most other β -blockers) into one eye also lowers the IOP of the contralateral, untreated eye. This is clear evidence that systemic absorption of the drug is a factor to be taken into account. Timolol has CNS effects on 10% of users and has mild pulmonary effects (reduced forced expiratory volume) on many, and as such it aggravates asthma.³⁸ Timolol causes fatigue, dizziness and headache in some patients and about 10% of timolol-treated patients develop depression. The external ocular effects can include dry eyes,³⁴ conjunctivitis and mild corneal anesthesia in a few patients³⁸ as well as eliciting a stinging sensation on instillation in about 20% of patients.^{27,64,69}

The usual initial oral dose of timolol for treating high blood pressure is 10 mg twice a day. When one drop of timolol 0.5% is instilled in each eye the dose administered is 0.3 to 0.5 mg, twice a day. Probably at least 80% of a topically instilled eyedrop enters the vascular system more or less directly.⁹⁷ If all of the timolol 0.5% eyedrops were systemically absorbed the expected plasma concentration in a 70 kg patient would be 1.5 ng/ml. Studies have shown that the plasma concentration one hour after topical instillation of one drop of timolol 0.5% each eye was 1.3 ng/ml⁹⁷ in adults. Other studies have shown more beta blockade by timolol than by betaxolol.⁹⁸ A plasma concentration of 0.21 to 0.60 ng/ml levobunolol was reported in a similar study using levobunolol 0.5% eyedrops.⁶²

Hopefully the above review will serve both as a summary and also a basis for comparison of the beta-blockers. From this comparison, it is apparent why only some of the drugs have been approved for ophthalmic use: the others show either limited efficacy (compared to timolol) or precipitate unwanted side effects at too high a frequency to be tolerated in regular use.

It can be anticipated that the proliferation of β -blockers for treating glaucoma will result in lowered costs to the patient. Possibly one of these drugs (or others being developed) will prove to be more selective, more effective, safer and even longer lasting so that once a day instillation will be sufficient as is advocated for a special pilocarpine gel (Pilopine HS) which contains pilocarpine 4%. As yet none of the β -blockers achieves all of these goals.

At this time, several other β -blockers are being tested for possible use as topical ocular hypotensive drugs. Such drugs include arotinol, bunolol, falintolol and soquinolol. As is evident from the bibliography in this article, β -blockers are studied and developed often on a regional basis. It is unknown at this time if any of the currently marketed or investigational β -blockers will achieve the worldwide acceptance that timolol maleate ophthalmic solution has in less than 10 years of clinical use. That such a goal is present in the minds of some is however evident from the enormous effort currently being expended in trials of ophthalmic β -blockers. An extensive listing of these clinical trials is provided in a recently published article.⁹⁹

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