

Levobetaxolol hydrochloride: a review of its pharmacology and use in the treatment of chronic open-angle glaucoma and ocular hypertension

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Abstract: Levobetaxolol is a cardioselective β -blocker that has been demonstrated to reduce intraocular pressure in patients affected with primary open-angle glaucoma and ocular hypertension. Levobetaxolol may be an effective neuroprotectant because of its great capacity to block sodium and calcium influx, which might confer a neuroprotective activity. Experimental and clinical studies have demonstrated the effects of levobetaxolol on ocular hemodynamics and visual field, and the pharmacologic differences between β -blockers currently used for the treatment of elevated IOP have become of more than academic interest since a number of studies have shown improvements to various extents. Unlike the initially manufactured 0.5% ophthalmic solution, levobetaxolol is suspended in a different delivery vehicle in levobetaxolol ophthalmic suspension, to increase the ocular tolerance and allow a similarity of effect with a 2-fold reduced concentration (0.25%).

Keywords: levobetaxolol, glaucoma, intraocular pressure, neuroprotection

Introduction

Levobetaxolol hydrochloride was introduced in the early 1980s as the first cardioselective β_1 -adrenergic antagonist for the treatment of elevated intraocular pressure (IOP) (Berrospi and Leibowitz 1982).

Levobetaxolol is a single active isomer of betaxolol, a cardioselective β_1 -adrenergic receptor-blocking agent (betaxolol is a racemic mixture of D- and the active L-isomers).

Since racemic betaxolol and other β -adrenergic antagonists have been shown to reduce IOP by a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry, it is assumed that levobetaxolol has a similar mechanism of action (Reiss and Brubaker 1983). Betaxolol, by having a greater affinity for cardiac (β_1) than pulmonary receptors (β_2), has been demonstrated to offer a reduced potential for pulmonary side effects, particularly in patients with pulmonary diseases (Weinreb et al 1988).

Several clinical studies have demonstrated the IOP lowering effect of the drug, in patients affected with primary open-angle glaucoma (POAG) and ocular hypertension (OHT) (Radius 1983; Caldwell et al 1984; Feghali and Kaufman 1985).

β -blockers can act as a neuroprotectant by reducing sodium influx into cells, and can also protect insulted neurones by reducing influx of calcium. Levobetaxolol may be an effective neuroprotectant because of its great capacity to block sodium and calcium influx, which might confer a neuroprotective activity (Hoste and Sys 1998).

Experimental and clinical studies have demonstrated the effects of levobetaxolol on ocular hemodynamics and visual fields, and the pharmacology differences between β -blockers currently used for the treatment of elevated IOP have become of more than

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academic interest since a number of studies have shown improvements to various extents (Drance 1998, 1999; Turacli et al 1998; Harris et al 1995, 2000).

Unlike the initially manufactured 0.5% ophthalmic solution, levobetaxolol is suspended in a different delivery vehicle in levobetaxolol ophthalmic suspension, to increase the ocular tolerance and allow a similarity of effect with a 2-fold reduced concentration (0.25%). The cationic exchange resin in which levobetaxolol is suspended provides microscopic beads 5 microns in diameter, and residence time in the cul-de-sac is increased with the addition of a poly-acrylic polymer (Weinreb and Jani 1992; Yarangümeli and Kural 2004). It has been demonstrated that levobetaxolol ophthalmic suspension has similar efficacy in reducing the IOP in POAG and OHT patients when compared with betaxolol solution (Weinreb et al 1990).

The present paper provides a brief review of the literature on the pharmacologic and clinical investigations on levobetaxolol.

Levobetaxolol hydrochloride ophthalmic suspension

In comparisons between non-cardioselective β -blockers in reactive airway subjects, levobetaxolol was demonstrated to have less effect on pulmonary function (FEV_1 and forced vital capacity [FVC]) (Schoene et al 1984), by having a greater affinity for cardiac than pulmonary receptors.

The cardiovascular effects of levobetaxolol were compared in double-masked, crossover studies with timolol maleate ophthalmic solution 0.5%. Levobetaxolol was shown during exercise to have significantly less effect on heart rate and systolic blood pressure than timolol maleate (Phan et al 1991; Yamada et al 2001).

Betaxolol, a racemic mixture of D and the active L-isomers, is commercially available in two forms: 0.5% ophthalmic solution, and the 0.25% ophthalmic suspension.

IOP reduction

β -adrenergic receptors are present in the ciliary epithelium-process, choroid, retina, iris, and longitudinal and circular ciliary muscles, and at a lower percentage in the lens and cornea (Sharif et al 2001). They are also found in the trabecular meshwork (Yarangümeli and Kural 2004). Aqueous humor production is mediated by the non-pigmented ciliary epithelial cells of the ciliary process (Okisaka et al 1974).

A rise in cAMP causes an increase in aqueous formation mediated by β -agonist activity (Neufeld et al 1972; Townsend and Brubaker 1980; Sears 1984). Aqueous humor outflow

is increased by adrenergic stimulation relaxing (cAMP stimulation) trabecular meshwork (Neufeld et al 1975; Neufeld 1978; Wiederholt 1998).

Epinephrine and isoproterenol enhance aqueous humor outflow, reducing cell area and increasing intercellular space in trabecular meshwork and Schlemm's canal endothelial cells through a β -stimulation (Crider and Sharif 2002).

In non-pigmented ciliary epithelial cells, levobetaxolol was more potent than dextrobetaxolol or racemic betaxolol at inhibiting isoproterenol-stimulated cAMP production (Nathanson 1988; Crider and Sharif 2002).

Experimental data on the inhibition of adenylyl cyclase activity in non-pigmented ciliary epithelial cells and trabecular meshwork cells demonstrate that β_2 -receptors predominate in ciliary body and trabecular meshwork (Nathanson 1981; Coca-Prados and Wax 1986; Wax and Molinoff 1987; Friedman et al 1999; Crider and Sharif 2002).

Levobetaxolol would therefore be expected to be more potent in decreasing aqueous humor production than dextrobetaxolol, which is supported by the fact that levobetaxolol is more potent in decreasing IOP than dextrobetaxolol. Levobetaxolol was 89-fold β_1 -selective relative to its potency at β_2 -receptors in functional assays using isolated animal tissues (guinea pig atria for β_1 -receptors, guinea pig tracheal rings for β_2 -receptors). In this study levobetaxolol demonstrated higher β_1 - and β_2 -receptor affinities and functional potencies, and a higher β_1 -selectivity than dextrobetaxolol. Levobunolol and (l)-timolol, while having high affinities and potencies at β_1 - and β_2 -receptors, exhibited insignificant β -receptor selectivity (2- and 3-fold β_1 -selective) (Sharif et al 2001). Levobetaxolol exhibited a higher affinity at cloned human β_1 -($K_i = 0.76$ nM) than at β_2 -($K_i = 32.6$ nM) receptors, while dextrobetaxolol was much weaker at both receptors (43-fold β_1 -selectivity for levobetaxolol) at recombinant human β_1 - and β_2 -receptors (Sharif et al 2001).

In an animal in vivo model, levobetaxolol was more potent than dextrobetaxolol in reducing IOP by a maximum of $25.9 \pm 3.2\%$, whereas the same dose of dextrobetaxolol reduced IOP by $15.5 \pm 3.6\%$; the efficacy of racemic betaxolol was very similar to that of levobetaxolol (Sharif et al 2001).

Topical treatment with betaxolol has been shown to reduce IOP significantly in normal subjects, and in POAG and OHT patients in placebo-controlled studies (Radius 1983; Caldwell et al 1984; Feghali and Kaufman 1985), as well as in masked comparisons with timolol (Berry et al 1984; Allen et al 1986; Stewart et al 1986), and levobunolol (Long et al 1988). All these drugs have been found comparable with regard to their efficacy in lowering IOP; however, the

decrease of IOP has been found to be significantly smaller with betaxolol compared with timolol or levobunolol in a number of clinical trials (Radius 1983; Caldwell et al 1984; Berry et al 1984; Feghali and Kaufman 1985; Stewart et al 1986; Allen et al 1986; Long et al 1988; Messmer et al 1991; Kaiser et al 1994; Yarangümeli and Kural 2004).

In two controlled clinical studies, in which a total of 356 patients were dosed for 3 months, betaxolol ophthalmic suspension produced clinically relevant reductions in IOP at all follow-up visits. At 8 AM after night-time dosing (trough), IOP was reduced from baseline by approximately 4–5 mmHg (16%–21%). At 10 AM, 2 hours after dosing (peak), IOP was reduced from baseline by approximately 5–6 mmHg (20% to 23%) (Weinreb et al 1990).

Adverse effects

Although betaxolol is pharmacodynamically selective for β_1 -adrenoreceptors, the extent of β_1 -receptor occupancy of topically applied betaxolol in the systemic circulation has been found to be less than that of the three non-selective blockers: timolol, levobunolol, and carteolol (Phan et al 1991; Yamada et al 2001); this indicates a lesser systemic β_1 -blocking activity of betaxolol, associated with negligible systemic β_2 -blockade, which provides a better safety profile for the drug.

Systemic absorption allows topical β -adrenergic blockers to cause adverse effects on pulmonary, cardiac and central nervous system (Van Buskirk 1980; Le Jeunne et al 1990). Non-selective β -blockers commonly used in glaucoma therapy cause bronchopulmonary constriction and depress cardiovascular performance (Le Jeunne et al 1990; Sharif et al 2001) while selective β -blockers such as betaxolol and levobetaxolol do not have this side effect. In the heart β_1 -adrenoceptors predominate, while in the lung and trachea there is a predominance of β_2 -adrenoceptors (Rugg et al 1978; Henry et al 1990; Satoh et al 1993).

Sharif and Xu (2004) determined the relative affinities and selectivities of timolol, levobunolol, levobetaxolol racemic betaxolol, and other β -blockers at the native β_1 - and β_2 -adrenoceptors in guinea pig heart and lung using radioligand binding, demonstrating that racemic betaxolol and levobetaxolol exhibited a higher affinity and greater selectivity for the β -adrenoceptors than the destro enantiomer.

Betaxolol and levobetaxolol possessed a 193- to 233-fold selectivity for β_1 -receptors, and levobunolol a 140-fold selectivity for β_2 -receptors; timolol was essentially non-selective.

Any ocular hypotensive treatment that can reduce blood pressure and heart rate can act as an additional risk factor in

the development and progression of POAG (Quaranta et al 2006). Most of the studies have shown the lack of effects of betaxolol on the cardiovascular system (Berrospi and Leibowitz 1982; Caldwell et al 1984; Feghali and Kaufman 1985; Berry et al 1984; Long et al 1988).

Due to the very low binding affinity to pulmonary β_2 -receptors, betaxolol is generally well tolerated and does not produce significant modification of pulmonary function tests in glaucoma patients with asthma and chronic obstructive pulmonary disease (Weinreb et al 1988; Van Buskirk et al 1986; Goldberg and Goldberg 1995; Schoene et al 1984).

However, it should be remembered that some pulmonary complications have also been reported associated with betaxolol treatment (Harris et al 1986; Roholt 1987).

Effects on ocular blood flow

Betaxolol can improve ocular perfusion, increasing blood velocity in retinal and epipapillary capillaries (Arend et al 1998); can increase end-diastolic velocity and decrease resistance index trough (determined by color Doppler imaging), a vasorelaxant effect in retrobulbar vessels (posterior ciliary arteries, central retinal artery) (Harris et al 1995; Steigerwalt et al 2001); and can increase retinal blood flow as a long-term effect after drug application (Yoshida et al 1998).

Kulkarni and De Santis (2001) demonstrated the vasorelaxant effects of DL-betaxolol, D-betaxolol, and L-betaxolol on bovine retinal vessels. The compounds had the same vasodilatory effect without statistically significant differences.

Levobetaxolol would have the same action on blood ocular vessels as racemic betaxolol (unrelated to stereoselective β -blocking activity), perhaps involving an interaction with calcium channels.

Calcium-sodium channel blocking activity and neuroprotection

β_1 -blockers can act as neuroprotectants by reducing sodium influx into cells acting as; they can also protect insulted neurones by reducing calcium influx. Levobetaxolol may be an effective neuroprotectant because of its great capacity to block sodium and calcium influx (Melena et al 1999; Chidlow et al 2000; Osborne et al 2004).

An ischemic-like insult to the optic nerve causes a decline of ATP and failure of the Na^+/K^+ -ATPase, which leads to an accumulation of intra-axonal sodium. This rise in intracellular sodium leads to reversal of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, which imports damaging quantities of calcium into the intracellular compartment. Elevated

extracellular concentrations of glutamate cause excitotoxic injury, leading to an excessive stimulation of ganglion cell glutamate receptors and an entry of Ca^{2+} and Na^{+} ions. This rise in ion concentration will activate the opening of voltage-gated channels and cause a greater elevation of Na^{+} and Ca^{2+} concentration, a trigger for a cascade of events that lead to cell death.

Glutamate receptor antagonist or the use of sodium or calcium channel blockers can protect the ganglion cell bodies from excitotoxic injury. Glutamate antagonists would not be effective at the axonal level, so to protect the entire ganglion cell in glaucoma, the ideal way would be that of using a glutamate receptor antagonist together with a sodium-channel blocker or a substance that prevents the reversal of sodium/calcium exchanger (Osborne et al 2004).

Betaxolol can inhibit Na^{+} influx modulating the gating mechanism of the Na^{+} channel, not interfering with ion conductance directly. Betaxolol inhibited veratridine-stimulated (lipophilic toxin that causes a persistent activation of the Na^{+} channel) Na^{+} influx into rat cortical synaptosomes without statistically significant differences between the effects of levobetaxolol and that of racemic betaxolol, so that it is possible to conclude that stereoselectivity is not relevant to the affinity of betaxolol for the neurotoxin site 2 of the Na^{+} channel. Atenolol, timolol, levobunolol, and catechol were significantly less active than betaxolol (Chidlow et al 2000).

It has been demonstrated that betaxolol has an affinity for the L-type voltage-gated calcium channel and is able to counteract the N-methyl-D-aspartate-induced influx of radioactive calcium into the retina (Melena et al 2001).

Osborne et al (2004), using an ischemia/reperfusion model recording flash electroretinograms after a reperfusion period in ischemic rat retinas, showed that levobetaxolol is more effective than timolol as a neuroprotectant.

Levobetaxolol demonstrates a higher affinity than dextrobetaxolol against L-type Ca^{2+} channels, but no significant affinity at N-type Ca^{2+} channels. Levobetaxolol is able to counteract the NMDA-induced influx of radioactive calcium into rat retinas (Sharif et al 2001; Melena et al 2001). This L-type Ca^{2+} channel blocking activity is clinically relevant because an increase in optic nerve head blood flow and beneficial effects on visual fields in glaucoma patients are associated with various Ca^{2+} -antagonists (Cellini et al 1997; Koseki et al 1999).

Levobetaxolol could act as a neuroprotectant both for the axon (in which voltage-sensitive sodium channels are responsible for generation and propagation of action potentials)

(Chidlow et al 2000), and for the cell body and dendrites, reducing the toxic influx of calcium glutamate-mediated (Osborne et al 2004) blocking of both calcium and sodium channels.

Furthermore, it has been shown that systemic dosed levobetaxolol exerts a neuroprotective action in photic-induced retinal damage. This molecule can upregulate endogenous b-fibroblast growth factor and ciliary neurotrophic factor-mRNA (two growth factors implicated in the protection of photoreceptor cells). Levobetaxolol was able to protect the retinal function (tested with an electroretinogram), and to prevent changes in retinal morphology after photic-induced retinopathy (Agarwal et al 2002).

Conclusions

Betaxolol is a well-documented drug in glaucoma therapy, and its efficacy in lowering the IOP is comparable with that of the non-selective β -blockers.

Betaxolol offers a superior safety profile, especially in patients with cardio-pulmonary diseases. Due to the calcium channel-blocker activity, betaxolol has all the characteristics for improving ocular perfusion and protecting retinal ganglion cells from loss related to glaucoma.

References

- Agarwal N, Martin E, Krishnamoorthy RR, et al. 2002. Levobetaxolol-induced Up-regulation of retinal bFGF and CNTF mRNAs and preservation of retinal function against a photic-induced retinopathy. *Exp Eye Res*, 74:445–53.
- Allen RC, Hertzmark E, Walzer AM, et al. 1986. A double-masked comparison of betaxolol versus timolol in the treatment of open-angle glaucoma. *Am J Ophthalmol*, 101:535–41.
- Arend O, Harris A, Arend S, et al. 1998. The acute effect of topical beta-adrenoreceptor blocking agents on retinal and optic nerve head circulation. *Acta Ophthalmol Scand*, 76:43–9.
- Berrosi AR, Leibowitz HM. 1982. Betaxolol. A new beta-adrenergic blocking agent for treatment of glaucoma. *Arch Ophthalmol*, 100:943–6.
- Berry DP, Van Buskirk EM, Shields MB. 1984. Betaxolol and timolol. A comparison of efficacy and side effects. *Arch Ophthalmol*, 102:42–5.
- Caldwell DR, Salisbury CR, Guzek JP. 1984. Effects of topical betaxolol in ocular hypertensive patients. *Arch Ophthalmol*, 102:539–40.
- Cellini M, Possati GL, Caramazza N et al. 1997. The use of flunarizine in the management of low-tension glaucoma: a color Doppler study. *Acta Ophthalmol Scand*, 224(Suppl):57–8.
- Chidlow G, Melena J, Osborne NN. 2000. Betaxolol, a beta(1)-adrenoceptor antagonist, reduces Na^{+} influx into cortical synaptosomes by direct interaction with Na^{+} channels: comparison with other beta-adrenoceptor antagonists. *Br J Pharmacol*, 130:759–66.
- Coca-Prados M, Wax MB. 1986. Transformation of human ciliary epithelial cells by simian virus 40: induction of cell proliferation and retention of beta 2-adrenergic receptors. *Proc Natl Acad Sci USA*, 83:8754–8.
- Crider JY, Sharif NA. 2002. Adenylyl cyclase activity mediated by beta-adrenoceptors in immortalized human trabecular meshwork and non-pigmented ciliary epithelial cells. *J Ocul Pharmacol Ther*, 18:221–30.
- Drance SM. 1988. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. *J Glaucoma*, 7:247–52.

- Drance SM. 1999. Introductory comments on potential differences between β -blockers in the treatment of open-angle glaucoma. *Surv Ophthalmol*, 43(Suppl 1):S173–S5.
- Feghali JG, Kaufman PL. 1985. Decreased intraocular pressure in the hypertensive human eye with betaxolol, a beta 1-adrenergic antagonist. *Am J Ophthalmol*, 100:777–82.
- Friedman Z, Bloom E, Polansky JR. 1999. Adrenergic drug effects on cyclic AMP in cultured human trabecular meshwork cells. *Ophthalmic Res*, 31:53–8.
- Goldberg I, Goldberg H. 1995. Betaxolol eye drops. A clinical trial of safety and efficacy. *Aust NZ J Ophthalmol*, 23:17–24.
- Harris A, Arend O, Chung HS, et al. 2000. A comparative study of betaxolol and dorzolamide effect on ocular circulation in normal-tension glaucoma patients. *Ophthalmology*, 107:430–4.
- Harris IS, Greenstein SH, Bloom AF. 1986. Respiratory difficulties with betaxolol. *Am J Ophthalmol*, 102:274–5.
- Harris A, Spaeth GL, Sergott RC, et al. 1995. Retrobulbar arterial hemodynamic effects of betaxolol and timolol in normal-tension glaucoma. *Am J Ophthalmol*, 120:168–75.
- Henry PJ, Rigby PJ, Goldie RG. 1990. Distribution of beta 1- and beta 2-adrenoceptors in mouse trachea and lung: a quantitative autoradiographic study. *Br J Pharmacol*, 99:136–44.
- Hoste AM, Sys SU. 1998. Ca^{2+} channel-blocking activity of propranolol and betaxolol in isolated bovine retinal microartery. *J Cardiovasc Pharmacol*, 32:390–6.
- Kaiser HJ, Flammer J, Stumpfig D, et al. 1994. Longterm visual field follow-up of glaucoma patients treated with beta-blockers. *Surv Ophthalmol*, 38(Suppl):S156–S9.
- Koseki N, Araie M, Yamagami J, et al. 1999. Effects of oral brovincamine on visual field damage in patients with normal-tension glaucoma with low-normal intraocular pressure. *J Glaucoma*, 8:117–23.
- Kulkarni PS, DeSantis L. 2001. Vasorelaxant effects of racemic betaxolol and its R- and S-isomers on bovine retinal vessels. *J Glaucoma*, 10:423–6.
- Le Jeune C, Munera Y, Hugues FC. 1990. Systemic effects of three beta-blocker eyedrops: comparison in healthy volunteers of beta 1- and beta 2-adrenoceptor inhibition. *Clin Pharmacol Ther*, 47:578–83.
- Long DA, Johns GE, Mullen RS, et al. 1988. Levobunolol and betaxolol. A double-masked controlled comparison of efficacy and safety in patients with elevated intraocular pressure. *Ophthalmology*, 95:735–41.
- Melena J, Stanton D, Osborne NN. 2001. Comparative effects of antiglaucoma drugs on voltage-dependent calcium channels. *Graefes Arch Clin Exp Ophthalmol*, 239:522–30.
- Melena J, Wood JP, Osborne NN. 1999. Betaxolol, a beta1-adrenoceptor antagonist, has an affinity for L-type Ca^{2+} channels. *Eur J Pharmacol*, 378:317–22.
- Messmer C, Flammer J, Stumpfig D. 1991. Influence of betaxolol and timolol on the visual fields of patients with glaucoma. *Am J Ophthalmol*, 112:678–81.
- Nathanson JA. 1981. Human ciliary process adrenergic receptor: pharmacological characterization. *Invest Ophthalmol Vis Sci*, 21:798–804.
- Nathanson JA. 1988. Stereospecificity of beta adrenergic antagonists: R-enantiomers show increased selectivity for beta-2 receptors in ciliary process. *J Pharmacol Exp Ther*, 245:94–101.
- Neufeld AH. 1978. Influences of cyclic nucleotides on outflow facility in the vervet monkey. *Exp Eye Res*, 27:387–97.
- Neufeld AH, Dueker DK, Vegge T, et al. 1975. Adenosine 3',5'-monophosphate increases the outflow of aqueous humor from the rabbit eye. *Invest Ophthalmol Vis Sci*, 14: 40–2.
- Neufeld AH, Jampol LM, Sears ML. 1972. Cyclic-AMP in the aqueous humor: the effects of adrenergic agents. *Exp Eye Res*, 14:242–50.
- Okisaka S, Kuwabara T. 1974. Selective destruction of the pigmented epithelium in the ciliary body of the eye. *Science*, 184:1298–9.
- Osborne NN, Wood JP, Chidlow G, et al. 2004. Effectiveness of levobetaxolol and timolol at blunting retinal ischaemia is related to their calcium and sodium blocking activities: relevance to glaucoma. *Brain Res Bull*, 62:525–8.
- Phan TM, Nguyen KP, Giacomini JC, et al. 1991. Ophthalmic beta-blockers: determination of plasma and aqueous humor levels by a radioreceptor assay following multiple doses. *J Ocul Pharmacol*, 7:243–52.
- Quaranta L, Gandolfo F, Turano R, et al. 2006. Effects of topical hypotensive drugs on circadian IOP, blood pressure, and calculated diastolic ocular perfusion pressure inpatients with glaucoma. *Invest Ophthalmol Vis Sci*, 47:2917–23.
- Radius RL. 1983. Use of betaxolol in the reduction of elevated intraocular pressure. *Arch Ophthalmol*, 101:898–900.
- Reiss GR, Brubaker RF. 1983. The mechanism of action of betaxolol, a new ocular hypotensive agent. *Ophthalmology*, 90:1369–72.
- Roholt PC. 1987. Betaxolol and restrictive airway disease. Case report. *Arch Ophthalmol*, 105:1172.
- Rugg EL, Barnett DB, Nahorski SR. 1978. Coexistence of beta1 and beta2 adrenoceptors in mammalian lung: evidence from direct binding studies. *Mol Pharmacol*, 14:996–1005.
- Satoh E, Narimatsu A, Hosohata Y, et al. 1993. The affinity of betaxolol, a beta 1-adrenoceptor-selective blocking agent, for beta-adrenoceptors in the bovine trachea and heart. *Br J Pharmacol*, 108:484–9.
- Schoene RB, Abuan T, Ward RL, et al. 1984. Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol*, 97:86–92.
- Sears M. 1984. Pharmacology of the eye. New York: Springer.
- Sharif NA, Xu SX. 2004. Binding affinities of ocular hypotensive beta-blockers levobetaxolol, levobunolol, and timolol at endogenous guinea pig beta-adrenoceptors. *J Ocul Pharmacol Ther*, 20:93–9.
- Sharif NA, Xu SX, Crider JY, et al. 2001. Levobetaxolol (Betaxon) and other beta-adrenergic antagonists: preclinical pharmacology, IOP-lowering activity and sites of action in human eyes. *J Ocul Pharmacol Ther*, 17:305–17.
- Steigerwalt RD Jr, Laurora G, Belcaro GV, et al. 2001. Ocular and retrobulbar blood flow in ocular hypertensives treated with topical timolol, betaxolol and carteolol. *J Ocul Pharmacol Ther*, 17:537–44.
- Stewart RH, Kimbrough RL, Ward RI. 1986. Betaxolol versus timolol. A six-month double-blind comparison. *Arch Ophthalmol*, 104:46–8.
- Townsend DJ, Brubaker RF. 1980. Immediate effect of epinephrine on aqueous formation in the normal human eye as measured by fluorophotometry. *Invest Ophthalmol Vis Sci*, 19:256–66.
- Turacli ME, Ozden RG, Gurses MA. 1988. The effect of betaxolol on ocular blood flow and visual fields in patients with normotension glaucoma. *Eur J Ophthalmol*, 8:62–6.
- Van Buskirk EM. 1980. Adverse reactions from timolol administration. *Ophthalmology*, 87:447–50.
- Van Buskirk EM, Weinreb RN, Berry DP et al. 1986. Betaxolol in patients with glaucoma and asthma. *Am J Ophthalmol*, 101:531–4.
- Wax MB, Molinoff PB. 1987. Distribution and properties of beta-adrenergic receptors in human iris-ciliary body. *Invest Ophthalmol Vis Sci*, 28:420–30.
- Weinreb RN, Caldwell DR, Goode SM et al. 1990. A double-masked three-month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution. *Am J Ophthalmol*, 110:189–92.
- Weinreb RN, Jani R. 1992. A novel formulation of an ophthalmic beta-adrenoreceptor antagonist. *J Parenter Sci Technol*, 46:51–3.
- Weinreb RN, Van Buskirk EM, Cherniack K et al. 1988. Long-term betaxolol therapy in glaucoma patients with pulmonary disease. *Am J Ophthalmol*, 106:162–7.
- Wiederholt M. 1998. Direct involvement of trabecular meshwork in the regulation of aqueous humor outflow. *Curr Opin Ophthalmol*, 9:46–9.
- Yamada Y, Takayanagi R, Tsuchiya K et al. 2001. Assessment of systemic adverse reactions induced by ophthalmic beta-adrenergic receptor antagonists. *J Ocul Pharmacol Ther*, 17:235–48.
- Yarangümelı A, Kural G. 2004. Are there any benefits of Betoptic S (betaxolol HCl ophthalmic suspension) over other beta-blockers in the treatment of glaucoma? *Expert Opin Pharmacother*, 5:1071–81.
- Yoshida A, Ogasawara H, Fujio N et al. 1998. Comparison of short- and long-term effects of betaxolol and timolol on human retinal circulation. *Eye*, 12:848–53.

