VA Pharmacy Benefits Management Strategic Health Group and Medical Advisory Panel
Drug Class Review
Ophthalmic Beta-Adrenergic Blocking Agents

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OBJECTIVE:

1. To review the safety, efficacy, and administration of the currently available ophthalmic beta-adrenergic blocking agents.

Table 1: Ophthalmic Beta-Blockers Marketed in the U.S.

Generic Name	Trade Name	Generic Available	Manufacturer	Patent Expiration
Timolol maleate solution	Timoptic®	Yes	Merck, various	3/25/1997
Timolol maleate gel-forming solution	Timoptic-XE®	No	Merck	8/29/2006
Timolol hemihydrate	Betimol®	No	Ciba Vision	3/31/1998
Metipranolol HCl	OptiPranolol®	No	Bausch & Lomb	12/29/1994
Carteolol HCl	Ocupress®	No	Otsuka America	1/05/1999
Levobunolol HCl	Betagan ® AKBeta®	Yes Yes	Allergan, various Akorn, various	6/28/1992
Betaxolol HCl suspension	Betoptic S®	No	Alcon	6/30/2000

2. To define selection criteria for formulary addition of these agents to the National Formulary of the Veterans Health Administration.

I. INDICATIONS [1-10]

Ophthalmic beta-adrenergic blocking agents are indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or primary open-angle glaucoma. Timolol maleate is also indicated in the treatment of glaucoma in aphakic eyes. Non-FDA-approved uses include adjunct treatment for angle-closure glaucoma, angle-closure glaucoma during or after iridectomy, secondary open angle glaucoma and treatment of malignant glaucoma.

II. PHARMACOLOGY [1-16]

Receptor Selectivity

Beta-adrenergic antagonists inhibit the binding of catecholamines at the beta-adrenoreceptor. In general, beta-blocking agents are categorized as either selective or non-selective. Non-selective beta-blockers inhibit both the β_1 and the β_2 receptors, while selective agents have a higher affinity for the β_1 receptors. Cardiac tissue contains primarily β_1 receptors and β_2 receptors are primarily in the bronchial and peripheral vascular muscle. The effect of selective beta-blockade is dose dependent. At higher doses, selective beta-blockers will inhibit both types of receptors. Timolol, levobunolol, metipranolol, and carteolol are nonselective beta-adrenergic blocking agents. Betaxolol is a selective β_1-adrenergic blocking agent.

Mechanism of Action

The beta-adrenergic blocking agents reduce intraocular pressure by blockade of β_2-adrenergic receptors in the ciliary epithelium, controlling the secretion of aqueous humor. Additionally, they may reduce the production of aqueous humor, which is controlled by the β_2-adrenergic receptors in the ciliary epithelium.

Intrinsic Sympathomimetic Activity

Partial beta-agonist activity or intrinsic sympathomimetic activity (ISA), is a property of some beta-blockers. These drugs have partial agonist activity similar to isoproterenol. This sympathomimetic effect may minimize the reduction in heart rate and the development of bronchospasm produced by β_2-blockade. The only ocular beta-blocker in the United States with ISA is carteolol.

Local Anesthetic Activity

Beta-blockers may produce a local anesthetic effect due to their lipophilic characteristics, causing the cell membrane to stabilize. In the eye, a topical beta-blocker may stabilize the pain fibers of the cornea and produce corneal anesthesia. Local anesthesia is not a desirable characteristic of ophthalmic medications. Although propranolol may cause an anesthetic response with ophthalmic use, the currently available ophthalmic beta-blockers have not demonstrated a clinically significant anesthetic effect.

III. PHARMACOKINETICS [9-11]

Table 2 lists selected pharmacodynamic and pharmacokinetic properties for the various ocular beta-blockers. The most common dosage studied for all agents is twice daily. The longer half-life of some agents suggests the possibility of less frequent dosing.

Table 2: Selected Pharmacodynamic and Pharmacokinetic Properties of Ophthalmic Beta-Blockers[a]

Property	Betaxolol	Carteolol	Levobunolol	Metipranolol	Timolol
β-blockade (Propranolol = 1)	4	10	6	2	6
ISA[b]	0	++	0	0	0
β_1 selectivity	++	0	0	0	0
Stinging, burning	+++	±	++	+	++
Heart rate decrease	±	+	++	++	++
Bronchoconstriction	±	+	++	++	++
Dyslipidemia	?[d]	0	?	?	+
Onset (Min)	30	nd[c]	< 60	≤30	30
Maximum effect (hr)	2	nd	2-6	≅ 2	1-2
Duration (hr)	12	12	12-24	12-24	12-24
Elimination half-life(hr)	12-20	3-7	6	3-4	3-5

[a] Table adapted and modified from Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1995:478h and Frishman WF, et al. J Clin Pharmacol 1994;34:795-803.
[b] ISA=Intrinsic Sympathomimetic Activity
[c] nd=no data
[d] ?=unknown

IV. CLINICAL EFFICACY [12,17-29]

In 1977 the Food and Drug Administration approved timolol maleate to treat elevated IOP in patients with glaucoma. Timolol has been used as the basis for comparing the safety and efficacy of all other ophthalmic beta-blockers. **Table 3** provides a summary of comparative ophthalmic beta-blocker studies.

Levobunolol and timolol have been shown equally efficacious for the short and long term management of IOP.[21] Debate has surrounded the optimal dosing of these agents. Levobunolol is marketed with a once or twice daily regimen. No significant difference was seen in IOP lowering between once daily administration of timolol 0.25% or levobunolol 0.25% over a three month period.[23] In contrast, once daily administration of levobunolol 0.5% or 1% was significantly better than timolol 0.5% over a three month period.[22]

The use of betaxolol in IOP has shown mixed results. While betaxolol was shown to decrease IOP from baseline, the results at 6 months of therapy were not as significant as those with timolol or with levobunol over a three month period.[17,18] Two trials have shown an equivalent effect on IOP with betaxolol and timolol.[25,26] While betaxolol may

not demonstrate the same efficacy in lowering IOP as other agents, its circulatory effects are beneficial.Circulatory effects are important for maintaining perfusion of the optic nerve. This results in preservation of visual fields, an important aspect of glaucoma therapy. Selective beta-blockers have been shown to be more efficacious than non-selective agents in this area. Betaxolol may act a calcium channel blocker thereby improving optic nerve perfusion. [27,28]

The use of carteolol 1% and timolol 0.25% showed no difference in IOP lowering over a one month period.[20] Equivalent lowering of IOP was seen with carteolol 1% and 2% with timolol 0.5%.[19] However, levobunolol was shown superior to carteolol in 59 patients over a 3 month period.[30]

Once daily dosing with timolol gel forming solution 0.5% was proven equally efficacious to timolol maleate 0.5% twice daily, in lowering IOP over a 3 month period. [24] Stewart, et al. addressed the issue of once daily dosing with both preparations. Timolol hemihydrate 0.5% and timolol gel-forming solution 0.5% were compared in 43 patients over a 3 month period and were proven equally efficacious in lowering IOP. [31]

In general, all agents studied were effective in lowering IOP. There may be advantages to the use of certain agents in specific patient populations. Differences in efficacy should be considered when selecting an agent for these groups. The impact on visual field preservation should also be considered.

Table 3: Comparative Ophthalmic Beta-Blocker Studies Evaluating Effect on Intraocular Pressure[a]

Reference	Drug and Dosage	No. of Patients	Duration of Treatment (Mo)	IOP[i] (mm HG) Mean Baseline	IOP[i] (mm HG) Overall Mean Reduction (%)	Patients Requiring Adjunctive Therapy (withdrawn: Inadequate control of IOP)
Allen et al. (1986)[17]	Betaxolol 0.25%[b]	20	6	27.2	1.0 (3.68)[c,d]	(8)[d]
	Betaxolol 0.5%[b]	20				
	Timolol 0.25%[b]	18		26.6	4.5 (16.9)[c,d]	(1)[d]
	Timolol 0.5%[b]	18				
Long et al. (1988)[18]	Levobunolol 0.25%[b]	27	3	24.9	6.2(24)[d,e]	1
	Levobunolol 0.5%[b]	30		25.2	6.0 (23.7)[d,e]	1
	Betaxolol 0.5%[b]	28		24.5	3.7 (15.1)[d,e]	1
Stewart et al (1991)[19]	Carteolol 1%[b]	33	3	25.3	6.3(24)[e,f]	1
	Carteolol 2%[b]	29		25.3	5.8(23)[e,f]	2
	Timolol 0.5%[b]	33		24.8	6.5(28)[e,f]	1
Scoville et al. (1988)[20]	Timolol 0.25%[b]	47	1	23.5	3.77(16)[f]	NA[i]
	Carteolol 1%[b]	50		22.8	2.90(12.7)[f]	NA
Cinotti et al. (1985)[21]	Levobunolol 0.5%[b]	52	15	26.7	8.0(30)[e,f]	4
	Levobunolol 1%[b]	54		27.5	8.2(29.8)[e,f]	4
	Timolol 0.5%[b]	56		27.3	8.0(29.3)[e,f]	5
Wandel et al. (1986)[22]	Levobunolol 0.5%[g]	30	3	28.2	7.0(24.8)[d,e]	(4)
	Levobunolol 1%[g]	32		26.9	6.5(24.2)[d,e]	(4)
	Timolol 0.5%[g]	30		26.4	4.5(17)[d,e]	(7)
Silverstone et al (1991)[23]	Levobunolol 0.25%[g]	39	3	24.7	5.3(22)[e,f]	(1)
	Timolol 0.25%[g]	41		25.1	5.4(22)[e,f]	(3)
Roselund (1996)[24]	Timolol gel forming solution 0.5%[g]	112	3	27.9	8.5(30)[e,f]	NA
	Timolol solution 0.5%[b]	111		27.3	8.4(31)[e,f]	NA
Stewart et al (1986)[25]	Betaxolol 0.5%[b]	15	6	29.0	7.6(26)[e,f]	0
	Timolol 0.5%[b]	14		27.6	8.4(29)[e,f]	0
Berry et al. (1984)[26]	Betaxolol 0.5%[b]	20	6.5	29.8	8.6(28.9)[e,f]	13
	Timolol 0.5%[b]	26		29.8	9.9(33.2)[e,f]	14
Mills and Wright (1986)[29]	Metipranolol 0.3%[b]	10	2	21.7	3.2(15)[f]	2[h]
	Timolol 0.25%[b]	10		22.6	2.49(11)[f]	2[h]
Behrens-Baumann et al. (1994)[30]	Levobunolol 0.5%[b]	29	3	26.2	7.3(27.4)[d,e]	NA
	Carteolol 2%[b]	30		25.2	4.1(16.3)[d,e]	NA
Stewart et al. (1998)[31]	Timolol hemihydrate 0.5%	22	3	23.6	5.3(22.4)[f]	NA
	Timolol gel forming solution 0.5%	21		23.7	5.3(22.4)[f]	NA
DuBiner et al. (1996)[32]	Timolol hemihydrate 0.25%[b]	91	3	24.4	4.2(17)[f]	NA
	Timolol hemihydrate 0.5%[b]	91		24.9	7.0(28)[f]	NA
	Timolol maleate 0.25%[b]	91		24.4	4.9(20)[f]	NA
	Timolol maleate 0.5%[b]	92		25	6.8(27)[f]	NA

[a] Adapted and modified from Sorenson SJ, et al. Ann Pharmacother 1996 30 (1):43-54.
[b] 1drop q12h
[c] Median reduction at week 26
[d] Statistically significant difference between the two drugs studied
[e] Statistically significant difference from baseline
[f] No statistically significant difference between the two drugs studied
[g] 1 drop qd
[h] Poor or no response to therapy
[I] IOP = Intraocular pressure; NA = Not available

V. ADVERSE EFFECTS [17-33]

In general, the ophthalmic beta-blockers are safe and effective agents for treating elevated IOP. Topical beta-blockers may be absorbed systemically via the nasolacrimal duct. Because there is no first-pass metabolism of topical beta-blockers, there is high bioavailability of these drugs when absorbed via this route. Obstructing nasolacrimal drainage can greatly reduce the amount of drug absorbed systemically.

Both ocular and systemic adverse effects may occur with the use of these agents. Ocular stinging is typically associated with betaxolol and metipranolol. Transient blurred vision is reported with timolol gel-forming solution. Metipranolol has been associated with granulomatous anterior uveitis and was withdrawn from clinical use in the United Kingdom in 1991. Systemic effects of the ophthalmic beta-blockers include cardiovascular, respiratory and central nervous system reactions. Cardiovascular adverse effects include arrhythmia, syncope, and palpitation. Additionally, changes in lipid profiles have been shown with timolol.[33] The clinical significance of these changes remains to be determined. Respiratory complications reported include bronchospasm, dyspnea, wheezing, decreased pulmonary function and respiratory failure. Central nervous system effects include hallucinations, sleep disturbances, depression, sexual dysfunction and emotional lability.

The use of β_1 selective agents may be beneficial to patients with pulmonary conditions. Betaxolol has been proven safe and effective in glaucoma patients with pulmonary disease. However, anecdotal reports of adverse pulmonary and cardiac events with betaxolol use exist. Alterations in serum lipid levels with carteolol have been shown to be minimal to none. This lipid neutral effect makes carteolol an alternate choice in patients most at risk from adverse lipid changes.

VI. DRUG INTERACTIONS [9, 34]

The use of beta-blockers during immunotherapy, skin end-point titration or actual immunotherapy, makes it extremely difficult to treat an anaphylactic reaction related to the therapy. Current recommendations state that ophthalmic and systemic beta-blockers be stopped during immunotherapy. [34]

Additional drug interactions are found in **Table 5**.

Table 5: Ophthalmic Beta-Blocker Drug Interactions[a]

Ophthalmic Beta-	Interacting Drug	Description

Blocker		
All	Oral beta-blockers	Potential additive effects on systemic beta-blockade.
All	Ophthalmic epinephrine	One case of systemic hypertension reported with the combination, possibly from unopposed α-adrenergic stimulation. The combination has been used successfully in lowering IOP.
All	Quinidine	One case of sinus bradycardia reported with the coadministration of timolol.
All	Verapamil	Bradycardia and asystole reported with the coadministration of oral verapamil.

[a]Table adapted and modified from Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1995:478j.

VII. DOSING AND ADMINISTRATION[1-10]

Table 6: Ophthalmic Beta-Blocker Dosing

Beta-blocker	Dose
Timolol maleate 0.25%, 0.5%	1 drop in the affected eye(s) twice daily.
Timolol gel-forming solution 0.25%, 0.5%	1 drop in the affected eye(s) daily.
Timolol hemihydrate 0.25%, 0.5%	1 drop in the affected eye(s) twice daily.
Metipranolol HCl 0.3%	1 drop in the affected eye(s) twice daily.
Carteolol HCl 1%	1 drop in affected eye(s) twice daily.
Levobunolol HCl 0.25%, 0.5%	1 drop in the affected eye(s) once or twice a day.
Betaxolol HCl Susp. 0.25%	1-2 drops in affected eye(s) twice daily.

VIII. COST [35-42]

When considering the cost of the ophthalmic beta-blockers, a drop-by-drop comparison is necessary because of potential drop size, flow restrictor valves and total volume differences among the various agents. **Table 7** is a summary of the ophthalmic beta-blocker drop studies.

Medication wastage could also be a factor when determining cost. This is difficult to assess in drop studies, which have been done in controlled laboratory settings without patients. More wastage may have been documented with patient administration due to technique. In practice, patients may have more drops miss the eye, larger drop volume and inability to use the entire vial contents.

Table 7: Ophthalmic Beta-Blocker Drop Studies

			5 ml				10 ml			
Reference	Drug	Manufacturer	Avg. No. of Drops	Avg. Total Volume (mL)	Drop Size (µL)	Days of Therapy[a]	Avg. No. of Drops	Avg. Total Volume (mL)	Drop Size (µL)	Days of Therapy[a]
Ball and Schneider (1992)[35]	Levobunolol	Allergan	104.5	5.43	52.5	28.5				57
	Betaxolol susp.	Alcon	159	5.41	34	39.8				
	Metipranolol	Bausch & Lomb	156	5.64	37	38.5				77
	Timolol maleate	Merck	169	5.58	33	42.5				85
	Betaxolol soln.	Alcon	164	5.15	31	41.0				82
Belanger and Winstead (1992)[36]	Timolol maleate	Merck	206	5.77	28	51	379	10.61	28	94
	Levobunolol	Allergan	117	5.38	46	29	222	10.21	46	55
	Betaxolol soln	Alcon	177	5.31	30	44	332	9.96	30	83
Schwartz et al (1989)[37]	Timolol maleate	Merck					391	11.1	28	98
	Levobunolol	Allergan					220	10.1	46	55
Sorenson and Abel (1994)[38]	Carteolol	Otsuka	147.6	5.13	34.8	36.92				
Koe (1995)[39]	Timolol maleate	Merck					568	11.1	19.5	142
	Timolol hemihydrate	Ciba Vision					323	10.5	32.5	81
Weiss and Hendrickson (1994)[40]	Timolol maleate gel	Merck	135	5.0[b]	37.0	67.5				
	Metipranolol	Bausch & Lomb	175	5.0[b]	28.6	43.75				
Stewart (1997)[41]	Levobunolol	Allergan					240	10.10	42	32.3
	Levobunolol	Alcorn					217	9.79	45	33.6
	Carteolol	Otsuka					318	9.88	31	58.0
	Timolol maleate gel	Merck	113	5.57	49	35.3				
	Timolol maleate	Merck					334	10.71	32	55.6
	Levobunolol	Alcon					239	9.83	41	39.7
	Betaxolol	Schein					245	9.81	40	28.0
	Levobunolol	Alcon					223	9.85	44	30.6
	Metipranolol	Bausch & Lomb					249	9.99	40	40.3
	Timolol hemihydrate	Ciba Vision					298	10.44	35	45.3
Fiscella (1998)[42]	Betaxolol	Alcon					323	10.5	32	80.8
	Betaxolol	Alcon	124.5	4.9	39	31				
	Timolol maleate	Merck	204.7	5.4	26	51				
	Timolol gel	Merck	133.3	5.9	44	67				
	Levobunolol	Allergan	106	5.2	49	27				
	Levobunolol	Schein	109	5.4	50	27				
	Metipranolol	Bausch & Lomb	146	5.2	36	37				
	Carteolol	Otsuka	140.9	5.2	37	35				

[a]Calculated on the basis of 1 drop in each eye twice daily except timolol gel which was given as 1 drop in each eye once daily.
[b]Actual total volume measured was not reported in the study.

IX. CONCLUSIONS

- Comparative, multicenter, randomized, double-blind trials have demonstrated that all of the currently available ophthalmic beta-blockers are effective in lowering IOP. Timolol maleate has been in clinical use since 1977 and has continued to be a safe and effective agent in treating glaucoma.
- Preservation of visual fields and optic nerve perfusion is also key in glaucoma therapy. Selective beta-blockers appear more efficacious than non- selective agents.
- There are some differences among the agents in terms of safety. Betaxolol has the advantage of causing minimal systemic effects due to its β_1 selectivity. However, adverse pulmonary and cardiac effects have been reported with its use. Timolol maleate gel-forming solution may have fewer systemic adverse effects than timolol maleate solution, but has the disadvantage of transient blurred vision after application. Carteolol may be a lipid neutral agent with advantages for patients with cardiac comorbidity. Both timolol hemihydrate and levobunolol have similar safety profiles when compared to timolol maleate solution.
- Timolol maleate gel-forming solution is dosed once daily. The once daily regimen may increase patient compliance.
- Drug interactions are similar among the agents.
- Drop studies are useful in determining actual drug cost because drop sizes and container volumes vary from product to product. Timolol maleate solution and gel-forming solution consistently yielded the greatest number of days of therapy per bottle.

X. CRITERIA FOR FORMULARY SELECTION

- Clinical efficacy must be demonstrated in comparative, randomized, multicenter, double-blind trials.
- Acceptable safety and drug interaction profiles must be demonstrated.
- The agent should have demonstrated cost effectiveness as determined by drop studies.
- A once-daily regimen may be desirable to enhance compliance.

XI. RECOMMENDATIONS

- Despite the introduction of newer ophthalmic beta blocking agents and different formulations, timolol maleate solution has maintained its niche in the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma. It has a proven safety record and has been available since 1977. It is available generically and has been the most cost-effective agent per drop in drop studies. Although the gel-forming solution is dosed once daily, it appears more costly than the solution. Levobunolol is as effective in lowering IOP as timolol maleate solution. **Therefore,**

timolol maleate solution or levobunolol should be considered as the ophthalmic beta-blocking agent on the national formulary.

- Betaxolol and carteolol have some advantages over the other ophthalmic beta blocking agents in terms of their systemic side effect profile. Betaxolol may be useful in patients with pulmonary disease, however caution must be exercised when using any of the beta-blockers in these patients. There may be ocular burning and stinging with this agent, which may be less with the suspension formulation. Carteolol may be an alternative agent for patients who experience adverse lipid changes with timolol or levobunolol. **Betaxolol should be added to the national formulary as the ophthalmic beta-blocker for pulmonary patients. Carteolol should be available, with non-formulary use criteria, for patients with special considerations.**
- There are limited comparative data with timolol hemihydrate and timolol maleate so consideration for formulary addition is difficult.

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