

β -Blocker–Induced Complications and the Patient With Glaucoma

Newer Treatments to Help Reduce Systemic Adverse Events

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Primarily open-angle glaucoma is a condition associated with an elevated intraocular pressure (IOP) that is defined as optic nerve degeneration with a slowly progressive deterioration of the visual field that may lead to blindness.¹ More than 1 million Americans are being treated for glaucoma, and 80 000 are legally blind as a result of the disease.² Glaucoma has its highest prevalence among the elderly population, with an incidence of approximately 1% in those older than 60 years, 3% in those between the ages of 70 and 80 years, and more than 9% in those older than 80 years.³ Treatment is directed at lowering high ocular pressures. The initial treatment, in most cases topical therapy with a β -adrenergic blocking agent, reduces the IOP to help preserve sight. But such topical agents may also have adverse systemic effects on cardiac, pulmonary, central nervous system (CNS), and endocrine functions.

Although treatment of glaucoma originates with the ophthalmologist, it may be the primary care physician who first observes the systemic effects of glaucoma medication. This is, at least in part, because the population of patients with glaucoma is older and is likely to seek medical attention for a variety of other disorders that are treated by the primary care physician or internist. This comanagement by the primary care physician and ophthalmologist, while necessary to effectively treat elderly patients with diseases of diverse origin, may cause several problems. First, elderly patients may be receiving multiple medications, a circumstance that is confusing and difficult to track, even for the most attentive physician. Second, patients may not fully inform their primary care physicians about their glaucoma therapy, unless they are specifically asked about "eye medication." When this is the case, systemic symptoms produced by topical β -blockers, such as wheezing, shortness of breath, arrhythmia, or even depression, may be falsely attributed to coexisting disease, the use of

other systemic medication, or advanced age. As a result, patients may be pharmacologically treated for a disorder without the underlying factor that caused or aggravated the condition being removed.

Fortunately, the ophthalmic community has long recognized the safety concerns involved in the use of β -blockers and new treatment options, with favorable adverse event profiles recently having become available. However, there remains a great need for increased awareness of the potential adverse effects of topical β -blocker therapy. The purpose of this review is to discuss the clinical adverse events associated with topical β -blockers and to provide information regarding newer glaucoma products and their systemic safety profiles.

TOPICAL β -ADRENERGIC ANTAGONISTS

Currently, the most common agents used in treating glaucoma are the topical β -adrenergic antagonists. There are a number of commercially available drugs in this category, all of which reduce aqueous humor formation by means of β -adrenergic blockade.⁴ These drugs differ in struc-

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ture and in their β_1 or β_2 selectivity, which may affect both efficacy and adverse effects. In general, β_1 selectivity is associated with cardiac adverse effects and β_2 selectivity with pulmonary and vascular adverse effects and hypoglycemia, especially in the patient with diabetes.

Topical medication may enter the systemic circulation via the nasolacrimal ducts, where it can be absorbed through the nasal, oropharyngeal, and gastrointestinal mucosa.⁵ Access to the systemic compartment is also possible through the conjunctival vascular system. Although blood levels of topical medication are not as high as those detectable after oral administration, small amounts of systemically absorbed β -blockers can produce significant adverse events in predisposed patients.⁶⁻⁸ Soon after the introduction of topical β -blockers in the late 1970s, their potential for systemic activity was apparent. Topical timolol maleate therapy was suspected of contributing to 32 deaths within 7 years of its initial commercial production. Several more common, although less severe, adverse effects were also reported, including reduced exercise tolerance, CNS symptoms, psychological changes, and altered serum lipid levels.⁹

Cardiovascular Effects

It has long been recognized that potentially serious cardiovascular events may occur from topical β -blockade. β -Blockers have been found to contribute to congestive heart failure and arrhythmia, to adversely alter serum lipids, to reduce exercise tolerance, and to decrease nocturnal blood pressure.

Because β -blockers exert a negative inotropic action on the myocardium, they may compromise patients with congestive heart failure, particularly those with significant systemic hypotension, severe pulmonary or systemic edema, or a recent acute decompensation episode.¹⁰ Initially, these mechanisms allow cardiac function to continue in the face of poor peripheral perfusion and diminished oxygen delivery to the myocardium.^{10,11} Cardiac function deteriorates over the long-term, however,

thus increasing the impetus for further compensatory mechanisms. The use of timolol maleate has been reported to contribute to congestive heart failure, although such cases are rare, as has the use of betaxolol hydrochloride, the β_1 -selective blocker that has less β_1 -binding activity at the cardiac receptors.¹¹⁻¹⁴ To our knowledge, the use of topical β -blockers has not been associated with any reported deaths due to cardiac failure.^{9,15}

Recent data have strengthened the hypothesis that oral β -blocker therapy can have a favorable impact on the course of disease in patients with congestive heart failure. A study by Packer et al¹⁶ found that patients with mild, moderate, or severe congestive heart failure who were treated with carvedilol had a reduced risk of death, as well as fewer hospitalizations for cardiovascular conditions.

However, carvedilol is a unique, nonselective β -receptor antagonist with an atypical pharmacologic profile; in addition to its antagonistic properties, it also blocks α_1 -receptors and exerts antioxidant effects, which may contribute to its actions in heart failure. In their discussion, Packer and colleagues¹⁶ noted that there is not yet sufficient evidence to conclude that other β -blockers would demonstrate similar clinical benefits on morbidity or mortality or alter the natural history of the disorder.

The physiologic activity of β -blockers also creates a potential for possibly causing conduction disturbances, such as arrhythmias. These agents reduce sinus node automaticity; prolong sinoatrial, intra-atrial, and atrioventricular conduction times; and increase atrioventricular nodal refractoriness.¹⁷ Thus, topical β -blockade may cause bradycardia and heart block in patients with underlying conduction system disease. It may also limit cardiac ability to compensate for lost pacemaker function. Case reports in the literature relate the use of topical β -blockers to syncope, bradycardia, systemic hypotension, palpitation, arrhythmia, and heart block.^{11,18,19} When administered with quinidine, timolol maleate has produced bradycardia and syncope.²⁰

As in patients with congestive heart failure, there may be benefit in

some patients from the antiarrhythmic activity of β -blockers, which are all classified as class II agents except for sotalol hydrochloride (class III).^{20,21} If there is a benefit, it may stem from the ability of β -blockers to blunt the effect of excessive sympathetic drive, to prolong the action potential of the cardiac membrane, and to reduce mean sympathetic tone with long-term dosing.^{21,22}

Topical β -blockers may also influence serum lipid levels. Several studies have previously evaluated the effect of topical β -blockers on lipid levels, prompted by reports that oral nonselective β -blockers have been found to affect triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels and total cholesterol-HDL ratios.²³⁻²⁶ Coleman et al²⁷ treated 28 healthy volunteers (age range, 21-60 years; mean age, 35.2 years) with 0.5% timolol maleate for an average of 76 days. Baseline HDL levels decreased by 1.45 ± 0.29 (mean $[\pm SD]$) mmol/L (56.1 ± 11.2 mg/dL), with the largest declines occurring in those with the highest baseline values. The authors found no change in total cholesterol, LDL, or triglyceride levels. A second study, conducted by West and Longstaff,²⁸ involved 17 patients with elevated IOP who were being treated with timolol. No changes in total cholesterol or lipid fractions were found after 15 weeks of monitoring. Freedman et al²⁹ compared the effects of topical 1.0% carteolol hydrochloride and 0.5% timolol maleate in 58 healthy adult men. A crossover design resulted in patients being treated with both drugs. Both drugs produced a decrease in HDL levels, although it was significantly smaller for those taking carteolol (-3.3% , -0.04 mmol/L [-1.5 mg/dL]) than for those taking timolol maleate (-8.0% , -0.10 mmol/L [-3.9 mg/dL]). There were no significant changes in other lipid fractions or total cholesterol levels.

The results of a recent multicenter trial with women aged 60 years or older diagnosed with ocular hypertension or glaucoma found that treatment with topical timolol adversely affected HDL levels ($P < .001$) and total cholesterol-HDL ratios ($P = .001$) from baseline, although there was no significant change from

baseline in total cholesterol, LDL, and total glucose levels. Over 12 weeks of monitoring, patients receiving timolol had a reduction in HDL (6.3%, -0.09 mmol/L [-3.4 mg/dL]). Patients treated with carteolol, however, experienced no adverse effects on plasma lipid levels.³⁰ These findings may be clinically important in patients with preexisting lipid disorders and in patients requiring long-term topical β -blocker therapy.³⁰

Topical β -blockers have at least 2 other potential cardiovascular side effects: diminished exercise tolerance and nocturnal hypotension. β -Adrenergic blockers may reduce maximum tachycardia and cardiac output as well as limit peripheral vasodilation.^{31,32} These effects are directly counter to the physiologic changes produced by exercise and can lead to reduced oxygen uptake and decreased exercise tolerance. Limitations of peripheral vasodilation may affect sweating and core temperature regulation, increasing the risk for dehydration and hyperthermia. In fact, topical timolol therapy has demonstrated some of these effects in 3 studies involving healthy individuals. Doyle et al³³ found a reduction in maximum heart rate and time to exhaustion after topical timolol therapy. The patients of Leier et al³⁴ demonstrated decreased maximum heart rate in both the short-term and the long-term after timolol administration. Atkins³⁵ also found that patients' heart rates were significantly reduced from baseline with timolol therapy. The β_1 -selective activity of betaxolol has not been associated with these effects.³⁶

Not only is exercise generally beneficial for health, but it can also reduce IOP, at least temporarily. Even regular walking has been shown to produce such reductions in patients with glaucoma.³⁶ Thus, it may be that topical β -blockers with less influence on exercise tolerance will be preferred in the future.

The significance of nocturnal hypotension, which has been noted in some patients taking oral β -blockers for systemic hypertension, is not clearly understood at this point. Certain agents cause reduced nocturnal pressure (metipranolol, sotalol) and

others do not (atenolol, pindolol, and labetalol).^{37,38} In terms of patients with glaucoma, the results of several studies suggest that nocturnal hypotension may play a role in the progression of chronic open-angle glaucoma.³⁹⁻⁴¹ However, to our knowledge, no clear association exists as yet, and further study is required to characterize this effect.

Pulmonary Effects

One of the most serious potential adverse effects of β -blockade is an exacerbation of reactive airway disease, possibly leading to respiratory arrest. β -Blockers act on β_2 receptors that are in the lung.⁴² However, β -blocker therapy does not produce bronchoconstriction in normal individuals.⁴³ Thus, the activity at the receptor site may not be a complete explanation for how these drugs affect the pulmonary system. The precise mechanism is not known.

Studies with topical agents have shown that timolol maleate, carteolol, and, to a much lesser extent, betaxolol can produce pulmonary effects. Topical therapy, most often with a nonselective β -blocker such as timolol maleate, has been associated with worsening of reactive airway disease and bronchitis, as indicated by symptoms such as wheezing, dyspnea, cough, and bronchial spasm.^{44,45} In one study, the use of timolol maleate increased the need for bronchodilator therapy in 47% of patients with asthma.^{46,47} Respiratory arrest occurred in 1 patient with asthma within 20 minutes of receiving a first drop of timolol maleate, and 12 respiratory deaths were recorded in the first 8 years of the commercial production of timolol.^{48,49}

Paradoxically, in another study, 12 patients treated with betaxolol exhibited increased respiratory symptoms without any actual worsening of airway function.⁵⁰ But the safety of betaxolol therapy is not definitively established in this regard. It may exacerbate asthma sufficiently to lead to hospitalization.^{51,52}

Three studies suggest the possibility that betaxolol can adversely affect the pulmonary system. Hugues⁴⁶ found no change in vital ca-

capacity or forced expiratory volume in 1 second (FEV₁) in 9 of 10 patients with asthma treated with betaxolol, but 1 patient had a reduction of FEV₁ by more than 15%. In a 2-year follow-up of 101 patients with reactive airway disease conducted by Weinreb et al,⁵³ 9 patients were withdrawn because of worsening pulmonary status, and, overall, the mean FEV₁-forced vital capacity ratio decreased from 66% to 54%. A third betaxolol study in patients with asthma found that one third had increased asthmatic symptoms, such as wheezing, coughing, and dyspnea, and half had a 15% decrease in FEV₁.⁵⁴ In addition, agents administered systemically with intrinsic sympathomimetic activity may not confer greater protection against respiratory effects. Topical carteolol, which has intrinsic sympathomimetic activity, has demonstrated a detrimental effect on lung function that was greater than that of betaxolol, and oral pindolol has blocked recovery from an asthma attack after terbutaline treatment.^{46,55,56}

CNS and Endocrine Effects

Among the most common adverse effects seen with topical β -blocker use are those associated with the CNS, including depression, fatigue, weakness, confusion, memory loss, headaches, and anxiety.⁴⁵ Approximately 10% of patients report CNS effects, and 5% have to discontinue taking the medication.¹¹ These drugs can cross the blood-brain barrier and inhibit central β -receptors. They also block serotonin receptors and exert other nonspecific and peripherally mediated CNS effects.⁵⁷ Such effects seem to be influenced by the selectivity of the agent. For example, Lynch et al⁵⁸ found that betaxolol produced fewer CNS effects than timolol maleate. Likewise, lipophilic characteristics of β -blockers could influence penetration across the blood-brain barrier and CNS effects. However, to our knowledge, the influence of lipophilic characteristics of β -blockers has not been studied clinically with ophthalmic β -blocker preparations.

A final controversial side effect of β -blockers involves alteration of the endocrine system in patients with diabetes. There is little

information on such topical effects in the ophthalmic literature, but oral administration may reduce the awareness of a hypoglycemic crisis and produce a deterioration in glucose tolerance.^{59,60}

NEW AGENTS WITH POTENTIALLY REDUCED SYSTEMIC EFFECTS

The range of potentially serious adverse effects associated with topical β -blockers can pose considerable challenges to the physician in clinical practice. Recognition and management of systemic sequelae, patient intolerance to adverse events, and the impact of these factors on compliance with therapy and quality of life have previously been discussed and reviewed in the literature.⁶¹⁻⁶³

Several new glaucoma agents with demonstrated efficacy in reducing IOP have been shown to have systemic adverse effect profiles that appear to be more favorable than those found with traditional therapies, including timolol maleate. These new drugs offer alternatives to the ophthalmologist that also may portend advantages in patient management for both the ophthalmologist and the primary care physician.

Latanoprost

Latanoprost is a prostaglandin analog that lowers IOP by increasing uveoscleral outflow.⁶⁴⁻⁶⁶ (It has been recently approved by the Food and Drug Administration under the trade name Xalatan.) Prostaglandins are mediators of inflammation, and were investigated for the treatment of glaucoma because reduced IOP is often associated with ocular inflammation.⁶⁷ Latanoprost represents a new class of glaucoma medications that have the potential to become first-line agents.⁶⁸ Recently, 4 large randomized trials proved once-daily dosing of latanoprost to be equal or superior to treatment with timolol maleate.⁶⁹⁻⁷² The absence of serious systemic adverse effects with latanoprost therapy was noteworthy.

At the end of 6 months of treatment, Watson et al⁶⁹ found that treatment with timolol produced a slight but significant reduction in heart rate

from a baseline value of 73.8 ± 11.6 (mean $[\pm SD]$) beats per minute to 71.8 ± 10.9 beats per minute, with no effect from treatment with latanoprost. Although neither timolol nor latanoprost had a consistent effect on blood pressure, there was a general tendency toward a slight decrease with the use of both agents. Approximately 6.9% of patients receiving timolol maleate reported respiratory or cardiovascular effects, in contrast to 2.0% in the latanoprost group (patients contraindicated to treatment with timolol were excluded from the trial). Thus, there were more patients with shortness of breath, bronchitis, and arterial hypotension in the timolol group.

Alm et al⁷⁰ found a reduction in heart rate with timolol maleate and negligible systemic adverse effects with latanoprost. Camras et al⁷¹ reported relatively few systemic adverse effects with either latanoprost or timolol maleate; however, heart rate was significantly reduced at 6 months with timolol maleate, and there was no change in heart rate with latanoprost. In addition, 13.8% of patients in the timolol maleate group reported headache or lassitude, compared with 6.7% in the latanoprost group.

Finally, in a study comparing the efficacy of 0.005% latanoprost administered once daily with that of 0.5% timolol maleate administered twice daily, Mishima et al⁷² found that latanoprost was more efficacious than timolol maleate in reducing IOP in patients with open-angle glaucoma and ocular hypertension; the main systemic effect was a slight but statistically significant reduction in mean heart rate in the patients in the timolol group at 4, 8, and 12 weeks ($P < .01$); of the 83 patients in the timolol group, 2 exhibited bradycardia and 1 had cardiac arrhythmia.

Increased pigmentation of the iris has been noted in 5% to 15% of patients using latanoprost, occurring in patients with multicolored irises, ie, blue-brown, gray-brown, green-brown, and yellow-brown.⁶⁹⁻⁷² Although the safety of this eye-color change is under investigation, it appears to lack clinical significance; histologically, it has been shown that the change does not al-

ter melanocytes, but an increase in melanin has been observed. In follow-up, patients who developed a darkening of the iris have not revealed any adverse effects on the eye or vision.

Brimonidine

Another new agent, brimonidine tartrate (Alphagan), is a relatively selective α_2 -agonist that lowers IOP by reducing aqueous humor production and, probably, by increasing uveoscleral outflow as a secondary effect.⁷³ It is a highly lipophilic drug that can pass the blood-brain barrier and therefore has some potential for causing CNS adverse events. To date, fatigue and dry mouth appear to be the most significant systemic side effects noted, occurring mostly at doses higher in concentration than those available commercially. In a study designed to evaluate the cardiovascular and respiratory effects of brimonidine, Nordlund et al⁷⁴ showed that this drug was associated with a mild, statistically significant, decrease in systolic blood pressure at rest and also during exercise recovery. Unlike timolol maleate, however, it has not been shown to limit exercise tolerance.

Dorzolamide

A third new agent, dorzolamide (introduced under the trade name Trusopt), is the first commercially available topical carbonic anhydrase inhibitor (eg, Diamox). It has been found to lower IOP 18% to 20% throughout the day (mean pressure, 4.5-6.1 mm Hg) from baseline, by suppressing aqueous humor production.^{75,76} The oral carbonic anhydrase inhibitors have traditionally been reserved as last-resort treatment, because adverse systemic effects occur in as many as 50% of patients. Such effects include general malaise, fatigue, depression, loss of libido, paresthesias, tinnitus, nausea, anorexia, gastrointestinal disturbances, blood dyscrasias, and metabolic and respiratory acidosis.^{77,78} No such effects have been reported thus far (to our knowledge) with dorzolamide. There have been no reports of bone marrow depression or aplastic anemia, both of which are rare oc-

currences with oral carbonic anhydrase inhibitors, although red blood cell carbonic anhydrase activity was shown to be reduced by 21% in one study.⁷⁷ In a large, multicenter trial comparing dorzolamide with betaxolol and timolol maleate, a frequently reported side effect in the dorzolamide group was bad taste, which occurred in 27% of patients.⁷⁹ Dorzolamide produced fewer headaches than betaxolol and more gastrointestinal disturbances than either of the other 2 drugs. Patients receiving betaxolol had significantly more cardiovascular adverse events, including angina, hypertension, and bradycardia, than did those in the dorzolamide group. Fatigue and rashes have been reported infrequently. Because dorzolamide is a sulfonamide, it is prudent to remain vigilant in watching for the adverse reactions that are sometimes seen with systemic administration, particularly hypersensitivity.⁸⁰

Apraclonidine

Research has also shown that a new drug, apraclonidine, is an effective adjunct to treatment with timolol maleate in reducing IOP, with few nonocular adverse effects. Similar to brimonidine, apraclonidine is an α_2 -adrenergic agonist. In a study by Stewart et al,⁸¹ 0.5% apraclonidine administered adjunctively with 0.5% timolol maleate produced IOP reductions from baseline that were as significant as those produced with 1.0% apraclonidine treatment and 0.5% timolol maleate. However, sensitivity to apraclonidine treatment at 1.0% was greater than at 0.5% (13.8% vs 20.3%), and treatment was discontinued owing to ocular or nonocular adverse effects in 21.5% of patients receiving 0.5% apraclonidine, which is available commercially, and in 25% of patients receiving 1.0% apraclonidine.

As primary therapy, apraclonidine lowers the IOP approximately 20% 12 hours after dosing, but the percentage is statistically lower than with timolol.⁸² Unfortunately, ocular intolerance has been a problem with apraclonidine in 13% to 36% of cases. The patients present with asymptomatic or mild ocular pruritis. However, they subsequently are

found to have conjunctival erythema and potential periorbital infection. The intolerance subsides quickly on discontinuation of the therapy.⁸³

CONCLUSIONS

New topical agents for the treatment of glaucoma offer significant promise, both in terms of efficacy and in the absence of systemic events. Nevertheless, topical β -blockers are currently the most commonly used therapy for glaucoma. Therefore, increased communication within the medical community is warranted. Careful attention on the part of the primary care physician to the systemic effects of topical β -blockade is paramount for several reasons. These medications must be remembered and ordered correctly on inpatient orders. Many hospitalized patients are treated for glaucoma, yet a small retrospective survey found that as many as 37% do not receive the correct medicine or amount.⁸⁴ Recognizing the importance of these medications can help to ensure that their use is not indiscriminately discontinued without communication with the prescribing ophthalmologist. And, finally, these topical medications may partly or wholly explain an alteration in a patient's systemic condition. Conversely, ophthalmologists can benefit from consultation with the primary care physician to refine the choice of agents for certain patients. Ultimately, more studies and new agents may provide clear-cut guidelines for patient prescription; in the meantime, however, it is critical that ophthalmologists and primary care physicians communicate about the safest, most efficacious usage of such medicine.

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