A care of essential tremor masked by the topical beta blocker timolol maleate

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Abstract
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A CASE OF ESSENTIAL TREMOR
MASKED BY THE TOPICAL
BETA BLOCKER TIMOLOL MALEATE

By

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A thesis submitted to the faculty of the
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Biographical Information
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Pamela deCalesta received her Bachelor of Science Degree in Professional Microbiology from Montana State University in 1993. She plans on receiving her Doctor of Optometry degree from Pacific University College of Optometry in May of 1998. On July 1, 1998 she will begin a one-year Optometric Residency at the Portland Veterans Hospital in Portland, Oregon. Involvement on a national level while in Optometry school has included: serving as Trustee and Trustee-Elect to the American Optometric Student Association, serving as the National Student Liaison to the Association of Schools and Colleges of Optometry, and serving as a member of the American Optometric Association Centennial Advisory Committee. On a local level she enjoyed serving as a Fourth Year Representative, Treasurer and Equipment Representative for her class and as Student Representative to the Oregon Optometric Association. She received the American Optometric Association Student Leadership Award and the Dean’s Award. She is married to a member of the Pacific University College of Optometry Class of 2000, Daran deCalesta. Future plans following the VA Residency include working in an Optometry & Ophthalmology group practice in the Pacific Northwest and starting a bridal and wedding consulting business. She is very happy to have completed her Optometric Thesis and learned a great deal while writing this case report. However, she still believes that an Optometric Thesis should be optional and not required.
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ABSTRACT:

Side effects inherent to systemic beta-blockers make propranolol contraindicated in patients with certain cardiac and pulmonary conditions. Due to systemic absorption, topical beta-blockers such as timolol maleate, which are used as anti-glaucoma agents, have similar contraindications.

The follow report describes an ocular hypertensive patient who was switched from timolol maleate to latanoprost because of a newly diagnosed possibility of mild COPD. The patient developed a bilateral hand tremor, which was previously blocked by systemic absorption of the topical beta-blocker. Included are classification, differential diagnosis and treatment of essential tremor, as well as a review of the mechanism of action and contraindications of timolol maleate and latanoprost.

KEY WORDS:

Essential tremor, glaucoma, ocular hypertension, timolol maleate, latanoprost
INTRODUCTION:

The introduction of new topical glaucoma medications such as latanoprost, with minimal systemic side effects or contraindications provides an alternative to traditional treatment with topical beta-blockers such as timolol maleate. Because topically applied ocular medications are absorbed systemically, the use of beta-blockers is contraindicated in patients with cardiac or pulmonary conditions. In addition, eyecare professionals must continually evaluate their patients using these medications for systemic side effects because it has been shown that as many as 40% of patients treated with topical timolol maleate develop a decrease in pulmonary function.

Although changing from one medication to another is indicated whenever a patient develops cardiac or respiratory difficulties, this alteration in medication can have surprising results. In this case report, an ocular hypertensive patient with a tentative diagnosis of mild COPD and no symptomology, was switched from timolol maleate to latanoprost. He subsequently developed a bilateral hand tremor. Further exploration determined that the systemic absorption of the topical beta-blocker was masking an underlying essential tremor. Due to the patient's successful non-symptomatic history with topical timolol and the uncertainty of the COPD diagnosis, the beta-blocker was reinstated and the tremor resolved. The classification, differential diagnosis, and treatment of essential tremor is discussed as well as the mechanism of action and relative contraindications of timolol maleate and latanoprost.

CASE REPORT:

A seventy-three year old white male with a history of ocular hypertension presented for a routine six-month intraocular pressure check. IOP measurements before treatment were not known, but intraocular pressures had been well controlled with Timoptic 0.5% bid OU during the four years this patient had been followed. Hypertension, which was well controlled with nifedipine and a diuretic, was the only significant systemic condition. At the time of this visit, no new visual or systemic changes were noted, except the patient reported a new possible diagnosis of mild COPD. It was noted that the patient had no recorded history of lung problems during past eye exams and the medical chart was not available to confirm the diagnosis of COPD.

Corrected acuities with habitual lenses were 20/15 O.D. and 20/20-2 O.S. Extraocular muscles were full without restrictions and pupils were equal, round, and reactive to light without an afferent pupillary defect. Slit lamp exam was unremarkable with deep, non-occludable anterior chambers. Goldmann applanation tonometry revealed IOPs of 20 mmHg O.D. and O.S. Humphrey 30-2 visual fields were full O.U. The patient was instructed to continue the Timoptic 0.5% bid O.U. and return to clinic in three weeks for a fundus exam through a dilated pupil and medical chart review to evaluate the questionable history of COPD.
A review of the patient’s medical chart at the next visit confirmed a tentative diagnosis of mild COPD, although the patient had no complaints of shortness of breath. The diagnosis was based on changes seen in serial chest X-rays, which had been ordered to follow an ill-defined opacity in the lungs thought to be secondary to pneumonia. Entrance acuities, EOMs, pupils, and anterior segment were similar to the previous exam. IOPs were 19 and 21 mmHg, O.D. and O.S. respectively. Fundus evaluation through a dilated pupil revealed cup to disc ratios of .3/.3 O.D. and .2/.2 OS with healthy rims. Scattered pinpoint drusen and mild RPE changes were noted near the macular region O.U. The periphery was intact with no retinal holes or tears. Because of the tentative diagnosis of mild COPD, the patient was instructed to discontinue the Timoptic 0.5% bid and begin a two-month trial with latanoprost 0.005% qhs O.U. Lacrimal occlusion and eyelid closure were reviewed with the patient as well as the possible side effects of iris color change due to the use of latanoprost 0.005%.

Five days after the discontinuation of the topical Timolol, the patient presented to the emergency room with a recent onset of bilateral hand tremors. The tremors, which were limited to his hands, were first noted the previous morning as he tried to eat his cereal. Emergency room evaluation revealed intact cranial nerves and normal motor and cerebellar function. The patient noted no headaches or visual changes and was alert and oriented. On testing, the tremors were noted to occur when the hands were outstretched, and not when the hands were at rest. History revealed that the only change within the last week was the discontinuation of the timolol maleate and institution of latanoprost. At this point, the eye clinic was notified and the patient was cooperatively diagnosed with essential tremor, which had previously been masked by the topical beta-blocker. The patient was instructed to discontinue the latanoprost and reinstate the Timoptic 0.5% bid O.U. with lacrimal occlusion and eyelid closure for a trial period. This was done due to the patient’s successful non-symptomatic history with topical timolol, the questionable nature of the COPD diagnosis, and the possible positive systemic side effect of timolol in blocking the essential tremor. The patient was also asked to return to clinic in three days for evaluation and report immediately if shortness of breath developed.

At the three-day follow-up the tremors were almost completely resolved and IOPs were measured at 18 mmHg O.U. with Goldmann applanation tonometry. The patient denied symptoms of shortness of breath. At this time, he also mentioned that his daily blood pressure checks had indicated an increase in BP during the five days he was not using the Timoptic. The patient was instructed to continue with the Timoptic and return to clinic in one month. At the one-month follow-up the ocular and systemic findings were similar. At the request of the patient and in consultation with the primary care physician, it was decided to continue the Timoptic 0.5% but to decrease the dosage to once daily in the morning. The possibility of increased tremors with the lower dosage was discussed with the patient, he was instructed to return to clinic in three months for review and intraocular pressure check, or immediately if ocular changes or shortness of breath were noted.

DISCUSSION:

The goal of glaucoma therapy is to reduce the intraocular pressure, therefore preventing damage to the optic nerve and resultant loss of vision. Timolol maleate (Timoptic, Merck), has accounted for 60-70% of glaucoma prescriptions in the U.S. in past years and continues to be a
treatment of first choice. Its method of action is to reduce the rate of aqueous humor production by non-selectively blocking the beta adrenoreceptors in the ciliary body, hence lowering the intraocular pressure an average of 27%.\textsuperscript{1,2} Local adverse affects have included discomfort upon instillation, increased conjunctival hyperemia, superficial punctate keratopathy, and decreased corneal sensitivity. When first introduced to the market, the only labeled systemic side effect was a slight reduction in resting heart rate. Within two years, reports received by the United States Food and Drug Administration and the National Registry of Drug-Induced Ocular Side Effects had documented cardiac, pulmonary, and central nervous system effects.\textsuperscript{1,3,4}

As a result of the newly reported side effects, studies were done to link the symptoms of systemic beta blockade with topical administration of a beta-blocker such as timolol maleate. The results proved that approximately 80% of a topical eye drop is systemically absorbed directly into the bloodstream via the conjunctival epithelium, nasolacrimal duct, and nasal mucosa. Systemic levels can be quite high with topical administration because topical drops do not undergo first pass metabolism by the liver. In contrast, 40-70% of a dose of oral propranolol will undergo first-pass hepatic metabolism before entering systemic circulation. Plasma levels achieved from topical timolol can cause the same CNS, cardiac, and pulmonary side effects as systemic timolol or propranolol. Detectable blood plasma levels can be found as early as thirty minutes following topical beta blocker instillation.\textsuperscript{4,5,6,7}

The high degree of lipid solubility innate to timolol enables it to more easily penetrate the plasma cerebrospinal fluid barrier and ultimately produce CNS effects such as lethargy, confusion, depression, anxiety, weakness, sleep disturbance, and sexual dysfunction. It is very common for patients to fail to link their symptomology to the use of topical timolol until after discontinuation of the medication. For this reason, the prescribing doctor should probe for the presence of possible CNS side effects during regular patient office visits.\textsuperscript{1,8,9,10}

Less common are the cardiac and pulmonary side effects associated with topical beta blocker-induced systemic beta blockade. Cardiac blockade involves mainly beta-1 adrenoreceptors and causes decreased cardiac rate, decreased myocardial contractility, and prolongation of atrioventricular conduction. This will result in reduced resting and exercise-induced maximum heart rate and a lower blood pressure. Episodes of syncope, bradycardia and dyspnea while using topical timolol, have been documented.\textsuperscript{7} Parasympathetic blockade of beta-2 receptors primarily affects the pulmonary system and can result in impaired lung function that is relatively asymptomatic or bronchospasm and bronchial asthma attacks. Pre-existing bronchospastic disease may have increased risk for bradyarrhythmia, hypotension, syncope, and bronchospasm associated with systemic beta blockade. Patients with a history of asthmatic bronchitis have been found to have a 25% decrease in forced expiratory volume less than fifteen minutes after topical instillation. Lung function tests are recommended before and during treatment with topical ocular timolol in patients at risk.\textsuperscript{11} Topical timolol use is contraindicated in patients with a past history of bronchial asthma, severe chronic pulmonary disease, congestive heart failure, preexisting cardiac disease, sinus bradycardia, and high grade heart block. Patients, especially those at risk, should be closely monitored during the first week of initial treatment because data supports that this is the critical period when most side effects will become manifest.\textsuperscript{1,2,4,8,9,12}
Other documented systemic effects of topical timolol are dermatologic rashes and alopecia. Beta blockade caused by beta-blockers can also mask the diabetic “shakes” that normally serve to warn a patient of an impending hypoglycemic attack. Potential drug side effects associated with concurrent use of topical beta-blockers can be particularly serious with verapamil, diltiazem, amiodarone, and digitalis.\(^\text{12}\)

Eyelid closure and punctal occlusion have been found to both increase ocular exposure time which increases drug efficacy, and decrease systemic absorption through the nasolacrimal system. Although there is documentation of great variation between amount and method of systemic absorption among topical timolol patients, even a small decrease in the absorption could have a great effect on the level of systemic beta-blockade. Systemic absorption of topical medications may be reduced by up to 50% with the practice of punctal occlusion. Gentle eye closure while sitting for three minutes has been shown to reduce systemic absorption of timolol by 66% and may be safer and easier than punctal occlusion. Both punctal occlusion and eyelid closure have been shown to be effective in reducing absorption but significant beta blockade can occur with even relatively low plasma levels.

Comparison of morning versus evening instillation of 0.5% timolol reveals no statistically significant difference in IOP lowering effect. A similar result was found in comparing once daily administration of 0.25% timolol with the same dosage of 0.5% timolol. This indicates that a lower concentration of timolol maleate in a once daily dosage is sufficient for maximum IOP reduction. Potentially, once-daily dosing could increase compliance and decrease the likelihood of systemic blockade-induced side effects.\(^\text{6,9,13,14}\)

In order to reduce the incidence of systemic complications secondary to topical beta-blocker instillation, there are several steps that should be followed. First, a complete patient history to determine the presence of cardiac, pulmonary or drug interaction contraindications should be performed. The patient’s pulse should be evaluated and reconsideration of use of a beta-blocker should occur if the heart rate is irregular or below sixty beats per minute. Instruction regarding dosage amount and time of day, eyelid closure and punctal occlusion, and the possibility of systemic side effects should be given. The family physician should be informed of the start of a topical beta-blocker and questioned about any known contraindications or potential drug interactions. The patient should be monitored carefully during the first week of treatment and educated to return to the clinic immediately if systemic side effects are experienced.\(^\text{11,13}\)

Because of the contraindication of pulmonary problems for timolol maleate, we switched our patient to latanoprost. Latanoprost 0.005% solution (Xalatan, Pharmacia & Upjohn) is a member of a new class of ocular hypotensive agents known as prostaglandin analogs. Prostaglandins are a group of naturally occurring fatty acids that are found in nearly every tissue in the body. The mechanism of action to reduce IOP appears to result from enhancement of uveoscleral outflow. Latanoprost is highly lipophilic and easily permeates into the cornea where it is hydrolyzed into a hydrophilic free acid, which diffuses into the aqueous. The most commonly reported ocular side effects include: blurred vision, burning and stinging, conjunctival hyperemia, foreign-body sensation, punctate epithelial keratopathy, and increased iris pigmentation. Latanoprost appears to increase the number of melanosomes within the
melanocytes which gradually produces an iris color change from lighter to dark. This is especially common in patients with mixed color irides. Although it may take months to years to become noticeable, the color change in most cases is permanent and therefore, patients should be forewarned. Studies of systemic absorption indicate that it is quickly metabolized and excreted upon entering the circulation. Latanoprost has no cardiopulmonary contraindications, does not have statistically significant effects on heart rate or blood pressure, and is well tolerated in asthmatic patients. Therefore, Latanoprost is indicated for patients with open-angle glaucoma and ocular hypertension with previous intolerance or poor response to other IOP-reducing medications.

Once-daily dosing of latanoprost reduces IOP 27% to 35%, and maintains uniform diurnal and circadian IOP reduction. Evening administration is the most effective. When compared to twice-daily administration of timolol maleate 0.5%, latanoprost 0.005% has been shown to be as effective in lowering IOP in patients with primary open angle glaucoma and ocular hypertension. Latanoprost has been shown to maintain efficacy for up to twelve months and can be used in conjunction with other antiglaucoma agents to further lower IOP. Study results show that once-daily latanoprost in the evening can be safely substituted for timolol maleate 0.5% bid with some enhancement of IOP lowering effect.

Tremor is an involuntary repetitive movement of the extremities or head that is produced by alternating contraction of opposing muscles. Classification of tremor is by area of the body affected, frequency of oscillation, amplitude, and most importantly, the body position that maximizes the tremor. Postural, or action tremor occurs while the body part is maintaining itself against the force of gravity, such as extending one’s arms out in front of the body or lifting an eating utensil. A tremor that occurs while the affected body part is at rest is termed a resting tremor. Tremor with goal-directed movements is referred to as a kinetic or intentional tremor. Both resting tremor, found in Parkinson’s disease, and intentional tremor are characteristic of central nervous system disorders of the cerebellar or extrapyramidal systems. Action tremors have multiple causes including: normal physiologic tremor which is exacerbated by fatigue and anxiety; metabolic tremor associated with drug withdrawal, liver disease, and metal poisoning; orthostatic tremor that occurs only when standing; and drug-induced tremor secondary to amphetamines, steroids, caffeine, antipsychotics and lithium. Benign essential tremor, as diagnosed in this case, is another category of action tremor.

Essential tremor (ET) is the most common of the movement disorders. Although sometimes it can be misdiagnosed as Parkinson’s disease, it is considered “benign”. ET does not affect the lifespan but can cause severe disability and social embarrassment as patients with ET often have difficulty dressing themselves, writing, or handling utensils. United States epidemiological studies have estimated that there are over five million cases of ET with no predilection to gender or race noted. Peak incidence occurs at both the second and sixth decades and once started will last throughout life. Essential tremor most commonly affects the hands and fingers initially. Progression to other body parts and an increase in severity can occur, with head involvement eventually developing in 60% and voice tremor in 24% of these patients. Progression is typically slow and may develop over one to two decades before the patient seeks medical intervention. Anxiety, fatigue, and temperature changes can exacerbate the tremor, which disappears completely with sleep. A fine, low amplitude tremor is the only
symptom in essential tremor. Post mortem examination is rare due to the benign status of the disorder, but the six reported exams have resulted in no obvious pathology in the cerebellar or extrapyramidal systems. There was also no abnormal muscle spindle feedback or change in sensitivity of the peripheral beta receptors. Studies with positron emission tomography have shown increased cerebral blood flow in subjects with ET, indicating a potential central mechanism. Another theory suggests essential tremor may be an exaggeration of normal physiologic tremor, although this evidence has been challenged. Both central and peripheral etiologies have been studied but currently the exact pathophysiology of essential tremor remains unknown.

There is no standard classification system for essential tremor within the current literature but classification by age and history is commonly used. Individuals with essential tremor have a 50-75% chance of a positive family history for the disorder and the condition is believed to be inherited as an autosomal dominant trait with variable penetrance. Familial essential tremor is used for patients with a positive family history and senile essential tremor is used in individuals over the age of 65 with no family history. A “sporadic” form also occurs before the age of 65 with no family history.

A different classification system divides ET into four subtypes. Type I is a form of benign exaggerated physiologic tremor that has a frequency of 6-12 Hz. Benign pathological essential tremor, which has a frequency of 5-7 Hz, is the second type. It contains the familial and senile forms of the disorder. The tremor in this subtype can be minimized through treatment with beta blockers and alcohol. Severe pathologic essential tremor, which is Type III, is very disabling and can include the head and legs. It is not decreased with alcohol or beta-blockers. Type IV, known as symptomatic essential tremor, includes tremors associated with other neurological conditions.

The standard treatment for benign essential tremor is the use of propranolol, a systemic non-selective beta-blocker, which can reduce the tremor to tolerable levels. Results are inconsistent and dosages range from 60-320 mg/day as necessary and as tolerated. Comparative studies have shown that blockade of peripheral beta-2 receptors is the most likely mechanism of reducing the tremor, although central beta-1 effects have not been excluded. The site of action is not fully understood as propranolol is highly lipid soluble and easily penetrates the CNS, therefore blocking both beta-1 and beta-2 adrenoreceptors. As with topical beta-blockers, the presence of chronic obstructive pulmonary disease, asthma, or congestive heart failure contraindicates the use of propranolol. The cardioselective (B1) beta-blocker Metoprolol has been used as an alternative in patients suffering from bronchospasm.

Less common treatments have also been used in cases of essential tremor. Alcohol has been found to reduce an action tremor but is not a treatment of choice for long term use. Primidone, an anticonvulsant, was recently found to be at least as equally effective as propranolol but causes serious acute side effects of vertigo, nausea, ataxia and confusion in 30% of the patients. The effects do typically subside after one to four days of use and the patient is encouraged to “wait it out.” The benzodiazepines Clonazepam and Alprazolam have shown promise in some studies but also induce sedation. A new treatment using Botox A reduced tremor in 70% of patients in recent studies and warrants further investigation. Surgery, which
involves a stereotaxic thalamotomy of the ventral intermediate nucleus, is an option in severe cases or in patients with poor response to medicinal therapies, and is considered effective and long term. New techniques involve surgical implantation of a device connected to a pulse generator that chronically stimulates the ventral intermediate thalamic nucleus. This procedure is considered to be superior to thalamotomy and results show improvement in 90% of patients with complete relief in some cases. In cases when the tremor is not disabling to the patient, the treatment is simply reassurance that the disorder is not serious or life threatening.\textsuperscript{16,19}

Differential diagnosis of benign essential tremor from other types and causes of tremor is usually by history, age, and associated signs and symptoms. Parkinson’s Disease, a common misdiagnosis for sufferers of ET, is characterized by a coarse, resting tremor of 4-8 Hz. The tremor disappears with movement and sleep. A Parkinson’s patient is usually older and has associated signs of cogwheel rigidity, bradykinesia, and micrographia. Handwriting is considered a good differential between the two disorders, as an essential tremor patient’s handwriting is usually large and tremulous.\textsuperscript{16,17,19}

Intentional tremor, caused by a cerebellar disorder, can be elicited with a heel-to-shin test in which the patient will develop the tremor during these intentional movements. Cerebellar disorders will also have accompanying signs of speech disorders, dysmetria or inability to judge movement, and asynergy or lack of coordination. Hepatolenticular degeneration, also known as Wilson’s disease, has a characteristic rapidly violent flapping of the hands and arms and will also display associated ocular and physical signs. A fine, rapid tremor of the face, tongue, and hands is possible in the dementia paralytica caused by neurosyphilis. This tremor is secondary to damage of the frontal lobe connection to the brainstem. Tremor caused by multiple sclerosis occurs with the movement of the limbs, disappears at rest, and will also have associated symptoms. Hyperthyroidism causes a fine, regular and rapid tremor that is usually only in the fingers with accompanying ocular and physical signs. Toxic causes of tremor include alcoholism, drug poisoning, and cocaine or morphine use and will be evidenced by history. Psychologically, tremor can be caused by chronic or acute anxiety and has a variable presentation.\textsuperscript{17}

Conclusion:

Topical beta-blockers are certainly contraindicated in patients with certain cardiac or pulmonary conditions. New diagnosis of these conditions may cause an eyecare practitioner to switch their patient from a beta-blocker to a topical medication with less systemic side effects like latanoprost. Even though this is indicated, it can have surprising results such as the unmasking of this patient’s essential tremor.
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