Beta Adrenergic Blocking Agents In the Treatment of Primary Open-Angle Glaucoma

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INTRODUCTION

Perhaps the most widely accepted non-invasive treatment modality for chronic open angle glaucoma is the use of beta adrenergic blocking agents(beta-blockers). Topical beta-blockers have been shown to lower intraocular pressure by decreasing the amount of aqueous produced in the ciliary processes. The exact mechanism is not known, but the effectiveness of these particular agents in controlling intraocular pressure is well documented.

This paper will discuss a few of the proposed theories as to how beta-blockers induce their affect on the autonomic nervous system causing a reduction in the formation of aqueous humor. The profile of three topical beta-blockers approved for ophthalmic use in the United States will be reviewed. Finally the dissipation phenomena (shortterm escape or longterm drift) associated with certain beta adrenergic blocking agents will be examined.

GLAUCOMA

Glaucoma is a condition in which there is a significant increase in the intraocular pressure that if allowed to persists can cause irreversible damage to the axonal fibers of the ganglion and/or retinal vasculature thus leading to loss of vision. The increased intraocular pressure (IOP) may result from a decrease in the rate of outflow of aqueous by the trabecular meshwork located in the anterior chamber angle, or could also be the result of excess aqueous formation by the ciliary processes thus placing too much demand on the outflow channels. Understand that the cause is not always so easily discernible and can be a combination of the above mentioned processes.

Primary open angle glaucoma is the most common form of glaucoma[4]. With this form of glaucoma the anterior chamber angle is anatomically open and upon direct view with a gonio mirror there is no evidence of obstructive debris, such as pigment granules, in the tracbeculum. However, there is still an associated increase in intraocular pressure which cannot be accounted for. Beta adrenergic blocking agents tend to be more efficient, having fewer adverse effects, and is therefore the drug of choice for managing chronic primary open angle glaucoma. In order to understand the pharmacodynamics of beta-blockers and their ability to lower intraocular pressure, we must first understand the physiological process by which aqueous humor is produced.

Note: A detailed description of how aqueous humor is formed would be lengthy and is beyond the scope of this paper.

AQUEOUS HUMOR

Aqueous is formed by epithelial cells in the ciliary processes and appears to be the result of three physiological functions; diffusion, secretion and ultrafiltration. Of these three processes, secretion and ultrafiltration tend to be the primary targets of interest for pharmacological induced effects of aqueous formation. It is a general consensus that beta blockers decrease intraocular pressure by reducing aqueous formation[1]. There are two widely accepted theories as to how this is accomplished. First, is the notion that beta-blockers cause vasoconstriction of the arteriole vasculature supplying the ciliary processes. A decrease in the rate of ultrafiltration is a direct result of the vasoconstriction and therefore the amount of aqueous formed over a period of time is significantly decreased. Second, it is believed that beta-blockers inhibit the active transport and secretion process within the epithelial cells

hence less aqueous is secreted into the posterior chamber of the eye.[1,4]

AUTONOMIC NERVOUS SYSTEM

Specific receptors have been identified in various tissue and organs of the human body which if stimulated by certain endogenous and/or exogenous chemicals will respond accordingly. In the adrenergic system these receptors have been labeled as either alpha or beta. These two classes have been further subdivided into alpha 1, alpha 2 and beta 1, beta 2 respectively. To minimize the risk of any major systemic complications, a basic understanding of the autonomic nervous system and a thorough case history are required prior to the administering of beta blockers and other systemic drugs. For example receptors in pulmonary tissue are primarily beta 2 which if stimulated will cause bronchodilation. Cardiac tissue has been shown to consist almost exclusively of beta 1 receptors; stimulation of these receptors will result in tachycardia and increased conduction time[1]. Therefore pharmacological blockade of beta 2 receptors would be undesirable for a person with chronic obstructive pulmonary disease (COPD) and similarly an individual with a history of cardiac failure and/or severe bradycardia should avoid cardioselective blocking agents[1,2,7]. Like most organs of the body the eye has receptors of both types. However it appears that stimulation of the beta receptors, more specifically beta 2 receptors, are responsible for the formation of aqueous by the ciliary processes[1]. Based on the previous statement one could theorize that if stimulation of beta 2 receptors increases aqueous formation then the converse also holds true.

BETA ADRENERGIC BLOCKING AGENTS

As stated previously it is a general consensus that beta blockers lower intraocular pressure by reducing aqueous formation. What still remains uncertain is the exact mechanism as to how beta blockers accomplish this. Again it has been theorized that blockade of intraocular beta receptors is the underlying mechanism[1]. This would suggest that sympathetic innervation alone is responsible for the formation of aqueous. However, research studies on animals in which sympathetic innervation to the eye was severed and also individuals with Horner's syndrome have nullified this theory[6]. Data from such studies indicate that aqueous formation is not always significantly reduced in the denervated eye. It has also been proposed that beta-blockers exhibit their effect by binding to receptors in the ciliary processes which are primarily beta 2. This still does not explain why certain drugs that are selective for beta 1 receptors can also cause a lowering of intraocular pressure. The most current

explanation of this latter observation is that beta 1 selective agents if administered in high enough concentration will saturate beta 2 receptors.[5,6]

MISCELLANEOUS

- Several oral beta blockers have demonstrated a short-lived stimulatory response of beta receptors prior to their antagonistic effect. This has been referred to as intrinsic sympathomimetic activity (ISA) and does not appear to be a significant occurrence among the topical beta-blockers used for ophthalmic purposes.[6]

- Occasionally individuals may complain of slight stinging and/or burning upon instillation of topical beta-blockers in the eye. This may be related to a transient membrane stabilization causing a local anesthetizing effect of the corneal epithelium. The membrane stabilization is not associated with the receptor blocking attribute of the drug, but rather to its lipophilic property. Of the three U.S. approved beta-blocker agents timolol tends to exhibit this phenomena the greatest.[1,5,6]

- The term tachyphylaxis has been reserved for the rapid near-total loss of drug efficacy within the first few does. This term may not be appropriate for a similar occurrence sometimes observed with beta-blockers in which the agent is maximally effective in the first few days of therapy but after several days the intraocular pressure begins to increase towards baseline pressure. This phenomena is referred to as shortterm escape. Similarly IOP's have been known to increase towards baseline pressure over several months following initial drug therapy and this is known as longterm drift. (See Shortterm Escape/Longterm Drift).[1,3,5]

- Beta-blockers instilled unilaterally have shown a consensual lowering of intraocular pressure in the fellow eye.[6]

There are three topical beta-blocker pharmaceutical agents in the United States that have been approved by the Food and Drug Administration for ophthalmic use; timolol maleate (Timoptic), levobunolol HCl (Betagan) and betaxolol HCl (Betoptic). Each of these drugs are similar in their chemical structure consisting of both an aromatic ring and an alkyl side chain (Fig. 1).[6] It is the side chain component which accounts for the lipophilicity of the drug and enhances penetration of the intact corneal epithelium. Aside from their chemical composition Betagan, Betoptic and Timoptic have a similar mode of action in terms of lowering intraocular pressure via decreasing aqueous formation by the ciliary processes. Betagan and Timoptic have demonstrated intrinsic activity with both beta 1 and beta 2 receptors and for this reason are referred to as nonselective beta-blockers. While Betoptic on the other hand shows a bias for beta 1 receptors and therefore is called cardioselective.

Figure 1

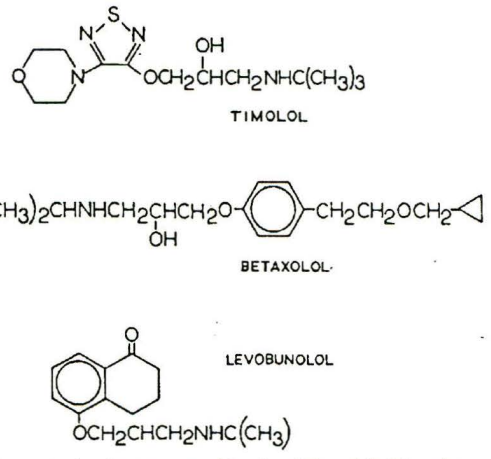

Fig 1—Molecular structure of Food and Drug Administration–approved topical β-blockers.

The first topical beta blocker approved in the United States by the Food and Drug Administration for ophthalmic use was timolol maleate in 1978.[1,5,6] Timolol maleate (Timoptic) is a non selective beta adrenergic blocking agent and is the drug of choice for the initial treatment of primary open angle glaucoma.[6] The reason for this is that Timoptic exhibits relatively few side effects including little or no local anesthesia and minimal intrinsic sympathomimetic activity (ISA). Timoptic is manufactured by Merck Sharp and Dohme pharmaceutical and is commercially available in concentrations of 0.25% or 0.5%.[2] It is commonly prescribed to be administered one drop in the affected eye twice daily. By itself Timoptic has been shown to lower intraocular pressure by as much as thirty percent and if combined with other glaucomatous agents a more significant lowering of IOP can be achieved. Timoptic lowers intraocular pressure by decreasing aqueous formation however, it has no effect on outflow.[1,6] The phenomena of shortterm escape has been observed with initial usage of this particular beta blocker and it has been postulated that the reason for this is that the number of beta receptors in the tissues of the ciliary processes increase.[1,3] The increase in the number of beta receptors in turn cause a relative increase in sensitivity of the ocular tissue to sympathetic stimulation. The primary concern when prescribing any pharmaceutical agent is its potential side effect(s). Timoptic is no exception. Aside from a general irritation that might be expected with the chronic use of any topical agent, other ocular complications of Timoptic consist of the following; burning and tearing upon instillation, foreign body sensation, decreased tear film integrity, superficial punctate keratitis and visual or refractive disturbance to name a few.[2]

Systemic side effects are the main concern and those most frequently observed are associated with the central nervous system. These include general fatigue, memory loss, mental depression and dissociative behavior. Other systemic side effects are cardiovascular related namely bradycardia, systemic hypotension and palpitations. Adverse reactions of the respiratory tract include wheezing, dyspnea or labored breathing. Some individuals have experienced nausea, vomiting, diarrhea and abdominal pain.[2]

Although the list of potential ocular and systemic side effects may appear extensive, the actual occurrence of any major complications is relatively minimal and usually occur in patients with pre-existing diseases. Contraindications for Timoptic are history of bronchial asthma, chronic obstructive pulmonary disease, cardiac

failure or hypersensitivity to any component of the drug.

These adverse side effects can be minimized by having the patient keep eyelids closed two to three minutes following drug instillation into the eye and provide digital nasolacrimal duct obstruction. Also the patient's blood pressure and pulse rate should be monitored before and after drug treatment is initiated. Finally, the individual should be thoroughly educated regarding possible signs and symptoms.[1,6]

BETAGAN

A second beta adrenergic blocking agent with attributes similar to that of timoptic is levobunolol (Betagan). Like Timoptic, Betagan is a nonselective beta blocker. Betagan exhibits very little intrinsic sympathomimetic activity and minimal anesthetizing properties. This beta adrenergic blocking agent is manufactured by Allergan and is commercially available at a concentration of 0.5%. The drug is usually administered twice daily however, once a day instillation has proven effective in a number of patients. The theory behind the long term effectiveness of Betagan has been attributed to its major metabolite (dihydrolevobunolol) which is just as effective in plasma as the initial compound itself.[1,2,7]

Side effects with betagan are also similar to those of timoptic and are relatively few. Ocular side effects include transient stinging and burning upon instillation. Also an associated blepharitis has been observed with this drug. Systemic side effects as well as contraindications are the same as for Timpotic.

BETOPTIC

Of the three beta blockers that have been approved in the U.S. for ophthalmic use, betaxolol (Betoptic) is the only one which is cardioselective. For this reason Betoptic becomes the drug of choice for treating glaucoma patients with a history of chronic obstructive pulmonary disease and other respiratory disorders. An interesting point to make here is that although Betoptic has a high selectively for beta 1 receptors , it also has only one tenth the beta 1 receptor binding affinity of Timoptic. This is why Timoptic, which is nonselective for beta 1 receptors, will cause greater cardiac beta blockade than Betoptic. Betoptic is available in 0.5% concentration and normal drug dosage regiment is twice daily.

The most frequent side effect encountered with Betoptic is a moderate burning or stinging sensation. However, there appears to be no effect on pupil size, corneal sensitivity or tear production. Although very minimal there are some noticeable systemic effects which include severe depression, disorientation, vertigo, rhinitis, dysuria and prolonged prothrombin time. Once more the contraindications are the same as for Timoptic however, because of its preferential bias for beta 1 receptors it is more safely administered to patients with obstructive pulmonary disease.[2]

SHORTTERM ESCAPE/LONGTERM DRIFT

The descriptive terms shortterm escape and longterm drift have been arbitrarily selected to describe the dissipation phenomena in which timolol's efficacy decreases after several days or several months respectively following initial drug administration. These terms are preferred over more formal pharmacologic terms because they more accurately describe the reduced efficacy observed without implying more than is known about the basic physiology of the drug. For example tachyphylaxis is used to describe a rapid and substantial loss of efficacy during the first few doses of a drug. This does not justify longterm drift which occurs months after therapy and even with shortterm escape there still exist a significant decrease in IOP compared to initial pressure values. Drug tolerance refers to a class of medications in which increasing amounts of a drug are required to obtain the same therapeutic effect with continued administration. Increasing the concentration of timolol does not appear to have any affect on the escape phenomena observed with this drug.[3]

Another idiosyncrasy of timolol is its varied effect when administered by itself or as a supplemental agent to a preexisting drug regimen. the dissipation phenomena is more frequent and more pronounced when timolol is added to maximal drug therapy as in the case of chronic glaucoma compared to when it is the only agent being administered in early glaucoma therapy.

Several theories have been developed to help explain why timolol's marked ocular hypotensive effect diminishes with continued administration. One research group proposed an adaptation mechanism by which the body "reequilibrates" itself with continued adrenergic stimulation or continued adrenergic blockade.[3] It used to be accepted that the number of receptors on cell membranes was constant however, more recent studies support

the fact that the density of beta adrenergic receptors is altered with chronic use of beta adrenergic blocking agents; the number of beta receptors tend to decrease with continued beta adrenergic stimulation and increase with beta adrenergic blockade. It has been demonstrated with timolol that the number of beta receptors in ocular tissues increase within a few days of initial drug administration and this supports the model described above as well as the shortterm escape phenomena.[1,3]

SUMMARY

Although the exact mechanism still remains uncertain, beta adrenergic blocking agents have proven to be effective in lowering intraocular pressure. Having relatively minimal systemic side effects beta-blockers have become the drug of choice for the initial management of primary open angle glaucoma.

Currently there are three topical beta-blockers that have been approved in the U.S. for ophthalmic purposes; timolol maleate (Timoptic), levobunolol (Betagan) and betaxolol (Betoptic).

Timolol and levobunolol are non-selective beta-blockers having an affinity for both beta 1 and beta 2 adrenergic receptors. These two beta-blockers are contraindicated in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular disorders. Betaxolol has a bias for beta 1 adrenergic receptors and for this reason is referred to as cardioselective. Because of its cardioselectivity, betaxolol is safer to use in individuals with pulmonary disorders.

A dissipation phenomena has been observed primarily with timolol in which the initial marked ocular hypotensive effect of the drug decreases with continued administration. If this dissipation phenomena occurs within a period of several days it is referred to as shortterm escape and similarly if it occurs over several months it is know as longterm drift.

To minimize systemic side effects, a thorough case history is required prior to prescribing beta-adrenergic blocking agents.

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