THE CLINICAL CHARACTERISTICS

OF TIMOLOL MALEATE IN THE

TREATMENT OF

GLAUCOMA

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One of the newest advancements in the treatment and control of glaucoma is timolol maleate. Timolol maleate is described as a nonselective blocking agent of \( B_1 \) and \( B_2 \) adrenergic receptors. When applied topically to the eye it has the action of reducing elevated as well as normal intraocular pressure. Unlike some \( B \)-adrenergic blocking agents, timolol does not have sympathomimetic effects nor local anesthetic (membrane-stabilizing) activity. Timolol maleate is currently produced and marketed in ophthalmic solution by Merck Sharp & Dohme under the trade name Timoptic*. The purpose of this paper is to discuss the clinical nature, actions, indications and usage, contraindications and precautions, adverse reactions, and dosage and administration.

Timolol maleate is a beta-adrenergic receptor blocking agent. Its chemical name is \((\_\_\_)-1-(\text{tert-butylamino})-3-(4\text{-morpholino}-1,2,5\text{-thiadiazol-3-yl})\text{oxy}-2\text{-propanol maleate} \ (1:1)(\text{salt})\). It has the following structural formula:

![Timolol Structural Formula](https://example.com/timolol_formula.png)

Timolol has shown a \( B \)-adrenergic blocking potency five to ten times greater than propranolol, the only other \( B \)-blocking agent currently marketed in the United States. The onset of reduction
in intraocular pressure following administration of timolol can usually be detected within one half hour after a single dose. This reduction in intraocular pressure will occur in normal as well as glaucomatous eyes. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Observations over a period of one year indicate that the intraocular pressure-lowering effect of timolol is well maintained.

An interesting note is that timolol can have a contralateral hypotensive effect on an untreated eye. That is, with topical application in one eye, a significant reduction in pressure is seen in the contralateral, untreated eye. The contralateral response may suggest that systemic absorption of the drug may be active at the untreated eye.

The precise mechanism of the ocular hypotensive action of timolol is not clearly established at this time. Tonography and fluphotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. Unlike miotics, timolol reduces intraocular pressure with little or no effect on pupil size or visual acuity due to increased accommodation. Therefore, dim or blurred vision and night blindness produced by miotics are not evident. Also, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted is avoided.

Boger and co-workers compared timolol to pilocarpine and
epinephrine in the therapy of open-angle glaucoma using a randomized, double masked protocol over a ten-week period. In patients with untreated intraocular pressures of 22mmHg or greater, timolol 0.25% or 0.5% administered twice daily produced a greater reduction in intraocular pressure than 1, 2, 3, or 4 per cent pilocarpine solution administered four times a day or 0.5, 1, or 2 per cent epinephrine hydrochloride solution administered twice a day.

In controlled multiclinic studies comparing timolol to pilocarpine it was found that 61% of patients treated with timolol had intraocular pressures reduced to less than 22mmHg compared to 32% of patients treated with pilocarpine.

In the multiclinic studies comparing timolol with epinephrine, 69% of patients treated with timolol had intraocular pressures reduced to less than 22mmHg compared to 42% of patients treated with epinephrine.

Other findings through studies found that timolol was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. Timolol was found to be well tolerated by patients wearing PMMA hard contact lenses. Timolol has not been studied in patients wearing lenses made with materials other than PMMA.

Timolol is indicated primarily in chronic open angle glaucoma. It has also been found in clinical trials to reduce intraocular pressure in patients with aphakic glaucoma, ocular hypertension, and some patients with secondary glaucoma. When used in conjunction with timolol, other adrenergic amines, such as norepinephrine and
epinephrine, produce an additional hypotensive response. In some patients, timolol's ocular hypotensive effects are additive to miotics and carbonic anhydrase inhibitors.

Timolol ophthalmic solution is generally well tolerated. Occasionally, signs and symptoms of mild ocular irritation have been reported. A significant slowing of the pulse has been the only significant side effect noted. This appears to be due to systemic absorption of the B-blocking agent. Timolol was not shown to affect blood pressure. Local hypersensitivity reactions have occurred rarely.

The use of timolol should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These conditions would include bronchial asthma; sinus bradycardia and greater than first degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; and concomitant use with adrenergic-augmenting psychotropic drugs.

Patients who are already receiving a beta-adrenergic blocking agent orally and who are given timolol should be observed for a potential additive effect, either on the intraocular pressure or on the known systemic effects of beta blockade.

Timolol has not been studied in human pregnancy or in children. Therefore it has not been recommended for these individuals.

Timolol maleate is currently marketed by Merck Sharp & Dohme. It goes by the trade name Timoptic*. Timoptic Ophthalmic Solution* is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dose strengths: Each ml of Timoptic* 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate).
Each ml of Timoptic\textsuperscript{*} 0.5\% contains 5.0 mg of timolol (6.8 mg timolol maleate). Inactive ingredients include monobasic and dibasic sodium phosphate; sodium hydroxide to adjust the pH; water for injection; benzalkonium chloride 0.01\% as a preservative. Timoptic\textsuperscript{*} is stable at room temperature.

The usual starting dose is one drop of 0.25\% Timoptic\textsuperscript{*} in each eye twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5\% solution in each eye twice a day. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in each eye. Because of diurnal variations in intraocular pressure, satisfactory response to the once a day dose is best determined by measuring the intraocular pressure at different times of the day.

Dosages above one drop of 0.5\% Timoptic\textsuperscript{*} twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patients intraocular pressure is still not at a satisfactory level, concomitant therapy with pilocarpine and other miotics, and/or epinephrine, and/or systemic administered carbonic anhydrase inhibitors such as acetazolamide, can be instituted.

When patients are being transferred from other antiglaucoma agents, on the first day continue with the agent(s) already being used and add one drop of 0.25\% Timoptic\textsuperscript{*} in each eye twice a day. If a higher dosage of Timoptic\textsuperscript{*} is required, substitute one drop of 0.5\% solution in each eye twice a day.
When Timoptic* is to be added to other antiglaucoma therapy, one drop of 0.25% per each eye twice a day is tried first. If a higher dosage is required, substitute one drop of 0.5% Timoptic* in each eye twice a day.
BIBLIOGRAPHY


