CHAPTER 3

DRUG PROFILE-TIMOLOL
3.1. Drug Profile-Timolol maleate

Timolol maleate is a non selective beta adrenergic receptor antagonist. In 1979, Timolol maleate was approved for ophthalmic use. Timolol maleate, a β-adrenergic receptor antagonist, provides an average IOP reduction of 20–35%. Food and Drug Administration’s (FDA) ‘gold standard’ drug for IOP reduction.

![Structure of Timolol maleate](image)

**Figure 1.** Structure of Timolol maleate.

3.2. Physicochemical properties

Chemically Timolol maleate is (−)-(S)-1-(tert-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt); (S)-1-[(1,1-dimethylethyl)amino]-3-[(4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl)oxy]-2-propanol (Z)-2-butenedioate (1:1) (salt); CAS Reg. No. 26921-17-5. Its structure is given in Figure 1. Its empirical formula is C_{13}H_{24}N_{4}O_{3}S,C_{4}H_{4}O_{4} and its molecular weight is 432.5. Timolol maleate is a white or almost white powder; odourless or almost odourless. It is soluble in water, methanol, ethanol and practically insoluble in ether. It is moderately lipophilic drug with an octanol-water coefficient of 1.16 at pH 7.4 at 37°C. It should be kept in a well-closed container, protected from light. A solution of 0.2 g of Timolol maleate in 10 ml of water is clear and colourless.

3.3. Pharmacology

3.3.1. Therapeutic use

Treatment of hypertension, alone or in combination with other agents; reduction of risk of reinfarction post-myocardial infarction; migraine prophylaxis; treatment of elevated IOP in chronic open-angle glaucoma, ocular hypertension, aphakic glaucoma patients, patients with
secondary glaucoma, and in patients with elevated IOP who need ocular pressure lowering. Hypersensitivity to β-blockers; greater than first-degree heart block; congestive heart failure (CHF) unless secondary to tachyarrhythmia treatable with β-blockers; overt cardiac failure; sinus bradycardia; cardiogenic shock; bronchial asthma or bronchospasm.

3.3.2. Dosage and Administration
Timolol maleate is available in the form of ophthalmic drops of 0.25% to 0.5% solution which are to be instilled 1-2 drops in affected eyes twice daily. In the same concentration its gel formulation is also available which is administered 1-2 drops one or two times daily. Orally 10 mg of Timolol maleate tablet can be administered twice a day. Or 20mg tablet once a day

3.3.3. Mechanism of Action
Timolol maleate is a β1 and β2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilizing) activity. It acts on the beta receptors present on the ciliary body and reduces the aqueous secretion by ciliary body (figure 2.1).
Mechanism of action of timolol maleate

β-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, β-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

β-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous. Timolol maleate (0.25% and 0.5%) eye drops have found to be effective in lowering intraocular pressure in patients with glaucoma by about 26-38% and is more effective than adrenaline and pilocarpine. They act by both improving drainage and reducing production of aqueous humor. In some patients there is increase in IOP in spite of continuing treatment but in majority, response is maintained.
3.3.4. Pharmacokinetics

Timolol is rapidly and about 90% absorbed following oral administration. Its $T_{\text{max}}$ is approximately 1 to 2 h. It shows a bioavailability of 60%. It is not extensively bound to plasma proteins. It undergoes approximately 80% first-pass metabolism and its $t_\frac{1}{2}$ is approximately 2.5-5 hrs (approx 4 hrs).

On topical ocular application of single dose of 0.6% eye drop of Timolol in the rabbits, the highest concentrations of 45.56 µg were observed in the cornea; followed by 3.62 µg in the iris, 2.80 µg in the aqueous humor, 0.2 µg in lens and 0.033 µg in vitreous humor (Francoeur et al 1985).

In a study involving healthy human subjects were given a single 20-mg oral dose of Timolol (two tablets of 10 mg). The mean plasma Timolol levels were near 3.2 ng/ml. The terminal half-life of Timolol was $2.62 \pm 0.38$ hr, and peak plasma levels of 82.5 ng/ml (Fourtillan et al 1980) occurred at 1.55 hr after drug administration.

In another study involving topical administration of multiple doses of Timolol aqueous solution in rabbit eyes. The aqueous humor concentration $C_{\text{max}}$ of 30.7 µg is observed at $T_{\text{max}}$ of 0.42 hr (Huang et al 1983).

3.3.5. Drug Interactions and toxicity

Timolol may enhance or reverse antihypertensive effect of clonidine and a potentially life-threatening situations may occur, especially on withdrawal. Together with epinephrine initial hypertensive episode may occur followed by bradycardia. With ergot derivatives peripheral ischemia, manifested by cold extremities and possible gangrene, may occur. Along with insulin it causes prolonged hypoglycaemia may occur. Some non steroidal anti inflammatory agents may impair antihypertensive effect of Timolol.

The adverse reactions associated with Timolol may lead to hypotension; heart palpitations; bradycardia; heart failure, oedema. Dizziness; depression; lethargy; headache; insomnia; anxiety; tremor; paresthesia. Blurred vision, light sensitivity (topical use). Impotence; sexual dysfunction; decreased libido; dysuria; urinary retention. Alteration of glucose metabolism; masking of hypoglycaemia; increased triglycerides, uric acid, potassium. Wheezing; cough; breathing
difficulties, especially in asthmatics. It is excreted in breast milk. Oral and ophthalmic forms may precipitate bronchospasm in susceptible patients. Administer drug with caution to patients with CHF controlled by digitalis and diuretics. Notify health care provider at first sign or symptom of CHF or of unexplained respiratory symptoms in any patient. Drug may potentiate insulin-induced hypoglycaemia. Drug may precipitate or aggravate symptoms of arterial insufficiency. Drug may mask clinical signs (eg, tachycardia) of developing or continuing hyperthyroidism. Abrupt withdrawal may exacerbate symptoms of hyperthyroidism, including thyroid storm.
[BIBLIOGRAPHY]


