

Chapter 10

Antiadrenergic Drugs (Adrenergic Receptor Antagonists) and Drugs for Glaucoma

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are competitive antagonists at α or β or both α and β adrenergic receptors, and differ in important ways from the "adrenergic neurone blocking drugs", which act by interfering with storage or release of adrenergic transmitter. These differences are given in Table 10.1.

α ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the α adrenergic receptors without affecting those mediated through β receptors.

GENERAL EFFECTS OF α BLOCKERS

1. Blockade of vasoconstrictor α_1 (also α_2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels $\rightarrow$ venous return and cardiac output are reduced $\rightarrow$ fall in BP. Postural reflex is interfered with $\rightarrow$ marked *hypotension* occurs on standing $\rightarrow$ dizziness and syncope. Hypovolemia accentuates the hypotension. The α blockers abolish the pressor action of Adr (injected i.v. in animals), which then produces only fall in BP due to β_2 mediated vasodilatation (also see p. 143). This was first demonstrated by Sir HH Dale (1913)

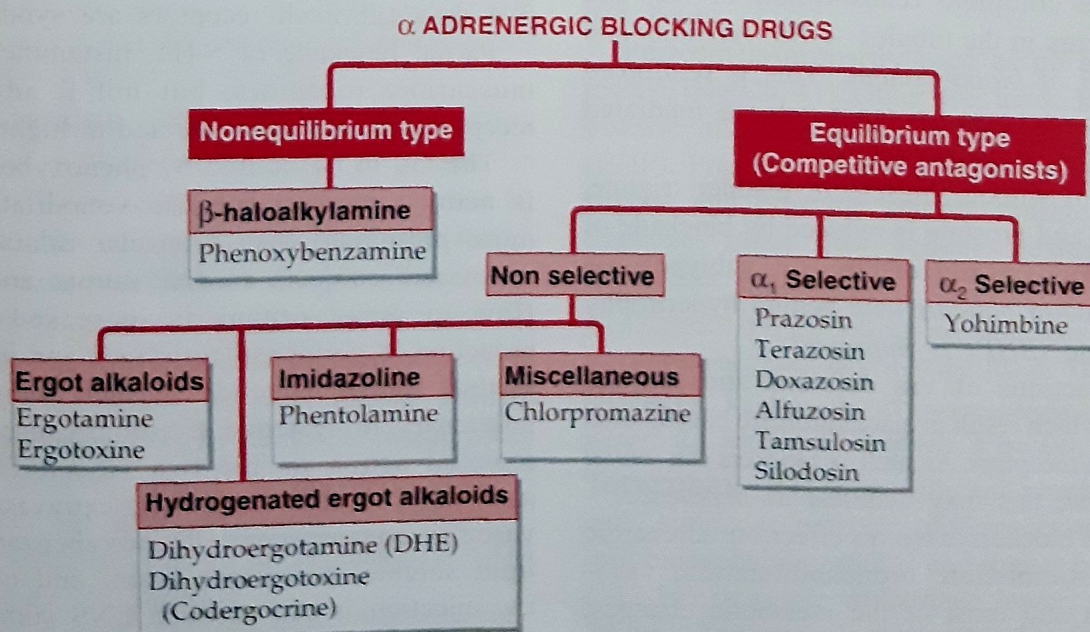


Table 10.1: Differences between antiadrenergic and adrenergic neurone blocking drugs

	Antiadrenergic drugs	Adrenergic neurone blocking drugs
1. Locus of action	Adrenergic receptors on effector cells or neurones	Adrenergic neuronal membrane or contents
2. Effects of adrenergic nerve stimulation	Blocked (less completely)	Blocked (more completely)
3. Effect of injected Adr	Blocked	Not blocked (may be potentiated)
4. Type of effects blocked by a single drug	Either α or β (except Labetalol and its congeners)	Sympathetic function decreased irrespective of the receptor type
5. Examples	α —Phentolamine β —Propranolol	Reserpine, Guanethidine, Bretylium, α -methyl-p-tyrosine

and is called *vasomotor reversal of Dale*. Pressor and other actions of selective α agonists (phenylephrine) are suppressed.

2. Reflex *tachycardia* occurs due to fall in mean arterial pressure and increased release of NA from cardiac sympathetic neurones due to blockade of presynaptic α_2 receptors.

3. *Nasal stuffiness* and *miosis* result from blockade of α receptors in nasal blood vessels and in radial muscles of iris respectively.

4. Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences—loose motion may occur.

5. Hypotension produced by α blockers can reduce renal blood flow $\rightarrow$ g.f.r. is reduced and more complete reabsorption of Na^+ and water occurs in the tubules $\rightarrow$ *Na^+ retention* and *expansion of blood volume*. This is reinforced by reflex increase in renin release mediated through β_1 receptors.

6. Tone of smooth muscle in bladder trigone, sphincter and prostate is reduced by blockade of α_1 receptors (mostly of the α_{1A} subtype) $\rightarrow$ *urine flow in patients with benign hypertrophy of prostate (BHP) is improved*.

7. Contractions of vas deferens and seminal vesicles which result in ejaculation are coordinated through α receptors. As such, α blockers can *inhibit ejaculation*; this may manifest as *impotence*.

The α blockers have no effect on adrenergic cardiac stimulation, bronchodilatation, vasodilatation and most of the metabolic changes, because these are mediated predominantly through β receptors.

Apart from these common effects, most of which manifest as side effects, many α blockers have some additional actions. The pharmacological profile of an α blocker is mainly governed by its central effects and by the relative activity on α_1 and α_2 receptor subtypes. Only the distinctive features of individual α blockers are described below.

Phenoxybenzamine It is a halogenated alkylamine that cyclizes spontaneously in the body giving rise to a highly reactive ethyleniminium intermediate which reacts with α adrenoceptors and other biomolecules by forming strong covalent bonds. The α blockade is of nonequilibrium (irreversible) type and develops gradually (even after i.v. injection) and lasts for 3–4 days till fresh receptors are synthesized.

Partial blockade of 5-HT, histaminergic and muscarinic receptors, but not β adrenergic receptors, can be demonstrated at higher doses.

The fall in BP caused by phenoxybenzamine is mainly postural because venodilatation is more prominent than arteriolar dilatation. In recumbent subjects cardiac output and blood flow to many organs is increased due to reduction in peripheral resistance and increased venous return. It tends to shift blood from pulmonary to systemic circuit because of differential action on the two vascular beds. It also tends to shift fluid from extravascular to vascular compartment. Phenoxybenzamine is lipid soluble, penetrates brain, and on rapid i.v. injection it can produce CNS stimulation, nausea and vomiting. However, oral doses produce depression, tiredness and lethargy.

Major side effects are postural hypotension, palpitation, nasal blockage, miosis, inhibition of ejaculation.

Pharmacokinetics Oral absorption of phenoxybenzamine is erratic and incomplete; i.m. and s.c. injections are very painful—should not be given. Though most of the dose administered i.v. is excreted in urine in 24 hours, small amounts that have covalently reacted remain in tissues for long periods. Chronic administration leads to accumulation in adipose tissue.

Dose: 20–60 mg/day oral; 1 mg/kg by slow i.v. infusion over 1 hour.

Phenoxybenzamine is used primarily in pheochromocytoma, occasionally in peripheral vascular disease.

FENOXENE 10 mg cap, 50 mg/ml inj. **BIOPHENOX** 50 mg in 1 ml inj.

Natural and hydrogenated ergot alkaloids (see Ch. 12 and Ch. 21) Ergot alkaloids are the adrenergic antagonists with which Dale demonstrated the vasomotor reversal phenomenon. The amino acid alkaloids *ergotamine* and *ergotoxine* are partial agonist and antagonist at α adrenergic, serotonergic and dopaminergic receptors.

The amine alkaloid *ergometrine* has no α blocking activity.

The natural ergot alkaloids produce long lasting vasoconstriction which predominates over their α blocking action—peripheral vascular insufficiency and gangrene of toes and fingers occurs in ergotism. Ergotoxine is a more potent α blocker and less potent vasoconstrictor than ergotamine. Hydrogenation reduces vasoconstrictor and increases α blocking activity.

The α blockade produced by ergot alkaloids is low grade and clinically not useful. Their principal use is in migraine (see Ch. 12). Dihydroergotoxine has been used as a cognition enhancer (see Ch. 35).

Phentolamine This is a rapidly acting α blocker with short duration of action (in minutes). Because of nonselective α_1 and α_2 blockade, NA release is increased and tachycardia occurs. Venodilatation predominates over arteriolar dilatation. Phentolamine is used for diagnosis and intraoperative management of pheochromocytoma, as well as for control of hypertension due to clonidine withdrawal, cheese reaction, etc. It is the most suitable α blocker for local infiltration to counteract vasoconstriction due to extravasated NA/DA during their i.v. infusion.

Dose: 5 mg i.v. repeated as required;

REGITINE, FENTANOR 10 mg/ml inj.

Prazosin It is first of the highly selective α_1 blockers having $\alpha_1 : \alpha_2$ selectivity ratio 1000:1. All subtypes of α_1 receptor (α_{1A} , α_{1B} , α_{1D}) are blocked equally. It blocks sympathetically mediated vasoconstriction and produces fall in BP which is attended by only mild tachycardia, because NA release is not increased due to absence of α_2 blockade.

Prazosin dilates arterioles more than veins. Postural hypotension is less marked, but may occur in the beginning, causing dizziness and fainting as 'first dose effect'. This can be minimized by starting with a low dose and taking it at bedtime. Subsequently tolerance develops to this side effect due to haemodynamic adjustments. Other α blocking side effects (miosis, nasal stuffiness, inhibition of ejaculation) are also milder. For the above reasons, prazosin (also other α_1 blockers) has largely replaced phenoxybenzamine. Prazosin, in addition, inhibits phosphodiesterase which degrades cAMP. Increase in smooth muscle cAMP could contribute to its vasodilator action.

Prazosin is effective orally (bioavailability ~60%), highly bound to plasma proteins (mainly to α_1 acid glycoprotein), metabolized in liver and excreted primarily in bile. Its plasma $t_{1/2}$ is 2–3 hours; effect of a single dose lasts for 6–8 hours.

Prazosin is primarily used as an antihypertensive (see Ch. 41). Other uses are in Raynaud's disease and benign hypertrophy of prostate (BHP). Prazosin blocks α_1 receptors in bladder trigone and prostatic smooth muscle, thereby improves urine flow, reduces residual urine in bladder.

PAZOPRES 0.5, 1.0 and 2.0 mg tabs. Start with 0.5–1 mg at bedtime; usual dose 1–4 mg BD or TDS.

MINIPRESS XL: Prazosin GITS (gastrointestinal therapeutic system) 2.5 mg and 5 mg tablets; 1 tab OD.

Terazosin It is chemically and pharmacologically similar to prazosin; differences are higher oral bioavailability (90%) and longer plasma $t_{1/2}$ (~12 hr); a single daily dose lowers BP over 24 hrs. Terazosin is more popular for use in BHP due to single daily dose and a probable

apoptosis promoting effect on prostate. This effect is unrelated to α_1 receptor blockade, but may retard the progression of prostatic hypertrophy.

HYTRIN, TERALFA, OLYSTER 1, 2, 5 mg tab; start with 1 mg OD, increase if required, usual maintenance dose 2–10 mg OD.

Doxazosin Another long acting ($t_{1/2}$ 18 hr) congener of prazosin with pharmacological profile, similar to terazosin, including the apoptosis promoting effect on prostate. It is used in hypertension and BHP.

Dose: 1 mg OD initially, increase upto 8 mg BD;

DOXACARD, DURACARD, DOXAPRESS 1, 2, 4 mg tabs.

Alfuzosin This short acting ($t_{1/2}$ 3–5 hours) congener of prazosin has been specifically developed for symptomatic treatment of BHP, though it is nonselective for α_{1A} , α_{1B} and α_{1D} subtypes. It is not approved as an antihypertensive. The metabolism of alfuzosin is inhibited by CYP3A4 inhibitors. Concurrent treatment with erythromycin, ketoconazole, ritonavir etc. is to be avoided.

Dose: 2.5 mg BD-QID or 10 mg OD as extended release (ER) tablet.

ALFUSIN, ALFOO 10 mg ER tab.

Tamsulosin This relatively uroselective α_{1A}/α_{1D} blocker ($\alpha_{1A} : \alpha_{1B}$ affinity 7–38 fold) has been found as effective as terazosin in improving BHP symptoms, because α_{1A} subtype predominate in the bladder base and prostate. However, it lacks the prostatic apoptosis promoting property of terazosin and doxazosin. Tamsulosin does not cause significant changes in BP or HR at doses which relieve urinary symptoms, and it is not used as an antihypertensive. No increase in adverse cardiovascular events has been noted after prolonged use. Postural hypotension is infrequent, dizziness and retrograde ejaculation are the only significant side effects. Problem of floppy iris has been encountered during cataract surgery in patients taking tamsulosin.

Plasma $t_{1/2}$ of tamsulosin is 6–9 hrs, but its modified release (MR) cap needs only once daily dosing. It may be a better tolerated α_1 blocker for BHP in patients who continue to suffer postural hypotension with terazosin/doxazosin.

CONTIFLO-OD 0.4 mg Cap, **URIMAX, DYNAPRES** 0.2, 0.4 mg MR cap; 1 cap (max 2) in the morning with meals. No dose titration is needed in most patients.

Silodosin Another selective α_{1A} blocker developed in Japan, which improves urine flow and relieves symptoms of BHP, but causes little change in BP. Incidence of postural hypotension is low. However, failure of ejaculation is frequent which can cause psychosexual distress. Oral bioavailability is ~30%. It is metabolized by glucuronidation and excreted in urine as well as in faeces. The $t_{1/2}$ averages 13 hours.

Dose: 4–8 mg OD; **RAPILIF, SILODAL** 4, 8 mg caps.

Yohimbine An alkaloid from the West African plant *yohimbe*. It is a relatively selective α_2 blocker with short duration of action. It blocks 5-HT receptors as well. Heart rate and BP are generally elevated due to increased central sympathetic outflow as well as enhanced peripheral NA release. It may cause congestion in genitals and is considered to be an aphrodisiac. This effect is only psychological, but can overcome psychogenic impotence in some patients.

There are no valid indications for clinical use of yohimbine.

Chlorpromazine and some other neuroleptics have significant α adrenergic blocking activity—cause fall in BP, nasal stuffiness and inhibition of ejaculation as side effect.

USES OF α BLOCKERS

1. **Pheochromocytoma** It is a tumour of adrenal medullary cells. Excess CAs are secreted which can cause intermittent or persistent hypertension. Estimation of urinary CA metabolites (VMA, normetanephrine) is diagnostic. In addition, pharmacological tests can be performed.

Phentolamine test Inject phentolamine 5 mg i.v. over 1 min in recumbent subject. A fall in BP > 35 mm Hg systolic and/or > 25 mm Hg diastolic is indicative of pheochromocytoma. However, it is not very reliable, both false positive and false negative results are possible.

Therapeutic Surgical removal of the tumour is the firstline therapeutic approach. Phenoxybenzamine can be used as definitive therapy for inoperable and malignant pheochromocytoma. Prazosin is an alternative. When surgical removal of the tumour is contemplated, it is desirable to give phenoxybenzamine orally for 1–2 weeks preoperatively and infuse it i.v. during surgery. The rationale is:

 - Due to excess circulating CAs blood volume is low (they shift fluid from vascular to

extravascular compartment). Treatment with α blocker normalizes blood volume and distribution of body water.

- Handling of the tumour during surgery may cause outpouring of CAs in blood $\rightarrow$ marked rise in BP. This is prevented by phenoxybenzamine given pre and intraoperatively. Alternatively, phentolamine or sodium nitroprusside (a rapidly acting vasodilator) drip can be instituted during the operation.
- Removal of the tumour is often attended by marked fall in BP, because blood vessels dilate and the blood volume is low. This does not happen if volume has been restored before hand with the aid of an α blocker.

2. Hypertension α blockers other than those selective for α_1 (prazosin-like) have been a failure in the management of essential hypertension, because vasodilatation is compensated by cardiac stimulation. Moreover, postural hypotension, impotence, nasal blockage and other side effects produced by nonselective α blockers are unacceptable. However, phentolamine/phenoxybenzamine are of great value in controlling episodes of rise in BP during clonidine withdrawal and that due to cheese reaction in patients on MAO inhibitors.

3. Benign hypertrophy of prostate (BHP) The urinary obstruction caused by BHP has a static component due to increased size of prostate and a dynamic component due to increased tone of bladder neck/prostate smooth muscle. Two classes of drugs are available:

- α_1 adrenergic blockers (prazosin like): they decrease tone of prostatic/bladder neck muscles.
- 5- α reductase inhibitor (finasteride/dutasteride) which arrest growth/reduce size of prostate (see Ch. 21).

Since activation of α_1 adrenoceptors in bladder trigone, prostate and prostatic urethra increases smooth muscle tone, their blockade relaxes these structures, reducing dynamic obstruction, increasing urinary flow rate and causing more complete emptying of bladder in many patients of BHP.

Voiding symptoms (hesitancy, narrowing of stream, dribbling and increased residual urine) are relieved better than irritative symptoms like

urgency, frequency and nocturia. The α_1 blockers afford faster (within 2 weeks) and greater symptomatic relief than finasteride which primarily affects static component of obstruction and has a delayed onset taking nearly six months for clinical improvement. The α_1 blockers do not affect prostate size, but are more commonly used. However, effects last only till the drug is given. Even with continued therapy, benefit may decline after few years due to disease progression. They may be used concurrently with finasteride.

Terazosin, doxazosin, alfuzosin and tamsulosin are the preferred α_1 blockers because of once daily dosing. There is some evidence that terazosin and doxazosin promote apoptosis in prostate. Tamsulosin appears to cause fewer vascular side effects because of relative α_{1A}/α_{1D} selectivity.

4. Peripheral vascular diseases α blockers do increase skin and to some extent muscle blood flow in normal individuals, but these drugs are largely disappointing in peripheral vascular diseases when obstruction is organic (Buerger's disease). However, when vasoconstriction is a prominent feature (Raynaud's phenomenon, acrocyanosis), good symptomatic relief is afforded by prazosin or phenoxybenzamine. Calcium channel blockers are also effective, and preferred by some due to fewer side effects.

5. Papaverine/Phentolamine Induced Penile Erection (PIPE) therapy for impotence In patients unable to achieve erection, injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum has been found to produce penile tumescence to permit intercourse. However, the procedure requires skill and training. Priapism occurs in 2–15% cases, which if not promptly treated leads to permanent damage. Priapism is reversed by aspirating blood from the corpus cavernosum or by injecting phenylephrine locally. Repeated injections can cause penile fibrosis. Other complications are—local haematoma, infection, paresthesia and penile deviation. Oral sildenafil is the preferred drug now, and PIPE therapy should be reserved for selected situations with proper facilities.

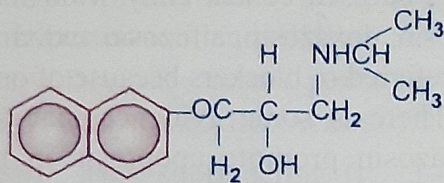
β ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the β receptors.

The dichloro derivative of isoprenaline was the first compound found in 1958 to block adrenergic responses which could not be blocked till then by the available adrenergic antagonists. However, it was not suitable for clinical use. *Propranolol* introduced in 1963 was a therapeutic breakthrough. Since then, drugs in this class have proliferated and diversified.

All β blockers are competitive antagonists. Propranolol blocks β_1 and β_2 receptors, but has weak activity on β_3 subtype. It is also an inverse agonist: reduces resting heart rate as well. Some β blockers like metoprolol, atenolol, etc. preferentially block β_1 receptors, while few others have additional α_1 receptor blocking and/or vasodilator properties.

The pharmacology of propranolol is described as prototype.



PROPRANOLOL

PHARMACOLOGICAL ACTIONS

1. CVS

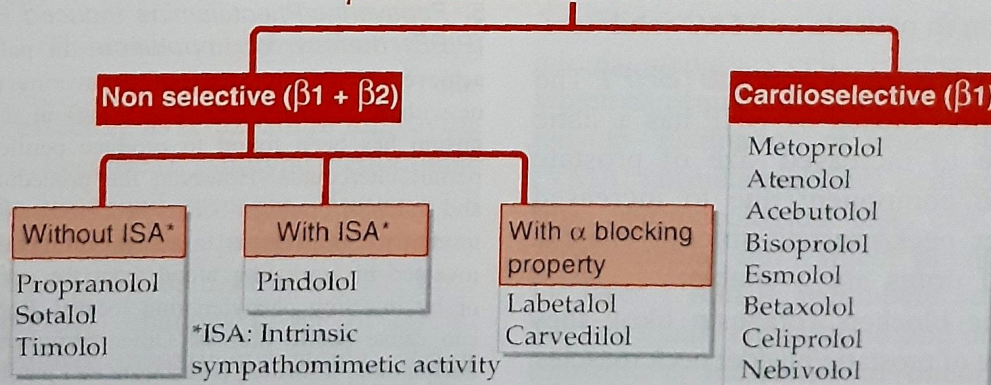
(a) *Heart* Propranolol decreases heart rate, force of contraction (at relatively higher doses)

and cardiac output (c.o.). It prolongs systole by retarding conduction so that synergy of contraction of ventricular fibres is disturbed. The effects on a normal resting subject are mild, but become prominent under sympathetic overactivity (exercise, emotion). Ventricular dimensions are decreased in normal subjects, but dilatation can occur in those with reduced reserve—CHF may be precipitated or aggravated.

Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases. Total coronary flow is reduced (blockade of dilator β receptors), but this is largely restricted to the subepicardial region, while perfusion of the subendocardial area (which is the site of ischaemia in angina patients) is not affected. The overall effect in angina patients is improvement of O_2 supply/demand status; exercise tolerance is increased.

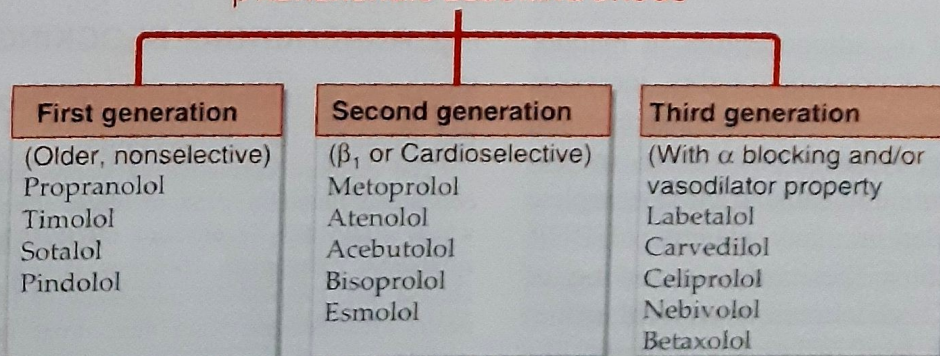
Propranolol abbreviates refractory period of myocardial fibres and decreases automaticity—rate of diastolic depolarization in ectopic foci

β ADRENERGIC BLOCKING DRUGS



GENERATION-WISE CLASSIFICATION

β ADRENERGIC BLOCKING DRUGS



is reduced, specially if it had been augmented by adrenergic stimuli. The A-V conduction is slowed. At high doses a direct depressant and membrane stabilizing (quinidine like) action is exerted, but this contributes little to the anti-arrhythmic effect at usual doses. Propranolol blocks cardiac stimulant action of adrenergic drugs but not that of methylxanthines or glucagon.

(b) Blood vessels Propranolol blocks vasodilatation and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr. There is re-reversal of vasomotor reversal that is seen after α blockade. Propranolol has no direct effect on blood vessels and there is little acute change in BP. On prolonged administration BP gradually falls in hypertensive subjects but not in normotensives. Total peripheral resistance (t.p.r.) is increased initially (due to blockade of β mediated vasodilatation) and c.o. is reduced, so that there is little change in BP. With continued treatment, resistance vessels gradually adapt to chronically reduced c.o. so that t.p.r. decreases and both systolic and diastolic BP gradually fall to some extent. This is considered to be the most likely explanation of the antihypertensive action. Other mechanisms that may contribute are:

- Reduced NA release from sympathetic terminals due to blockade of β receptor mediated facilitation of the release process.
- Decreased renin release from kidney (β_1 mediated): Propranolol causes a more marked fall in BP in hypertensives who have high or normal plasma renin levels and such patients respond at relatively lower doses than those with low plasma renin.
- Central action reducing sympathetic outflow. However, β blockers which penetrate brain poorly are also effective antihypertensives.

2. Respiratory tract Propranolol increases bronchial resistance by blocking dilator β_2 receptors. The effect is hardly discernible in normal individuals because sympathetic bronchodilator tone is minimal. In asthmatics, however,

the condition is consistently worsened and a severe attack may be precipitated.

3. CNS No overt central effects are produced by propranolol. However, subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long-term use of relatively high doses.

Propranolol suppresses anxiety in short-term stressful situations, but this is due to peripheral rather than a specific central action (see p. 495).

4. Local anaesthetic Propranolol has membrane stabilizing (Na^+ channel blocking) property and is a potent local anaesthetic. However, it is not a clinically useable local anaesthetic due to irritant action. Ocular irritation and corneal anaesthesia occurs when it is instilled in the eye, making it unsuitable for ocular use.

5. Metabolic Propranolol blocks adrenergically induced lipolysis and consequent increase in plasma free fatty acid levels. Plasma triglyceride level and LDL/HDL-CH ratio tend to increase during propranolol therapy. Glycogenolysis in heart, skeletal muscles and liver that occurs due to sympathetic stimulation is attenuated. As such, recovery from insulin hypoglycaemia that involves sympathetic stimulation is delayed. Though there is no effect on normal blood sugar level, prolonged propranolol therapy may impair carbohydrate tolerance by decreasing insulin release.

6. Skeletal muscle Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on the muscle fibres (through β_2 receptors). Propranolol also tends to reduce exercise capacity by attenuating β_2 mediated increase in blood flow to the exercising muscles, as well as by limiting glycogenolysis and lipolysis which provide fuel to working muscles.

7. Eye Instillation of propranolol and some other β blockers reduces secretion of aqueous humor, i.o.t. is lowered. There is no consistent effect on pupil size or accommodation.

8. Uterus Relaxation of uterus in response to isoprenaline and selective β_2 agonists is blocked

by propranolol. However, normal uterine activity is not significantly affected.

PHARMACOKINETICS

Propranolol is well absorbed after oral administration, but has low bioavailability due to high first pass metabolism in liver. Oral: parenteral dose ratio of up to 40:1 has been found. Interindividual variation in the extent of first pass metabolism is marked, therefore equieffective oral doses vary considerably. Propranolol is lipophilic and penetrates into brain easily.

Metabolism of propranolol is dependent on hepatic blood flow. Chronic use of propranolol itself decreases hepatic blood flow: its own oral bioavailability is increased and its $t_{1/2}$ is prolonged (by about 30%) on repeated administration. Bioavailability of propranolol is higher when it is taken with meals because food decreases its first pass metabolism. Since metabolism of propranolol is saturable, higher bioavailability and prolongation of $t_{1/2}$ is noted when high doses are given.

A number of metabolites of propranolol have been found, of which the hydroxylated product has β blocking activity. The metabolites are excreted in urine, mostly as glucuronides. More than 90% of propranolol is bound to plasma proteins.

Dose: Oral—10 mg BD to 160 mg QID (average 40–160 mg/day). Start with a low dose and gradually increase according to need; i.v.—2 to 5 mg injected over 10 min with constant monitoring. It is not injected s.c. or i.m. because of irritant property.

INDERAL, CIPLAR 10, 40, 80 mg tab, 1 mg/ml inj., BETABLOC 10, 40 mg tab.

INTERACTIONS

1. Additive depression of sinus node and A-V conduction with digitalis and verapamil — cardiac arrest can occur. However, propranolol has been safely used with nifedipine and its congeners.
2. Propranolol delays recovery from hypoglycaemia due to insulin and oral antidiabetics. Warning signs of hypoglycaemia mediated through sympathetic stimulation (tachycardia, tremor) are suppressed.

3. Phenylephrine, ephedrine and other α agonists present in cold remedies can cause marked rise in BP due to blockade of sympathetic vasodilatation.
4. Indomethacin and other NSAIDs attenuate the antihypertensive action of β blockers.
5. Propranolol retards lidocaine metabolism by reducing hepatic blood flow.

ADVERSE EFFECTS AND CONTRAINDICATIONS

Propranolol can produce many adverse effects, but mostly they are mild; β blockers are, in general, well tolerated drugs.

1. Propranolol can accentuate myocardial insufficiency and can precipitate CHF/edema by blocking sympathetic support to the heart, especially during cardiovascular stress. However, when compensation has been restored, careful addition of certain β_1 blockers is now established therapy to prolong survival.
2. Bradycardia: It is the most common side effect, resting HR may be reduced to 60/min or less. Patients of sick sinus are more prone to severe bradycardia.
3. Propranolol worsens chronic obstructive lung disease, can precipitate life-threatening attack of bronchial asthma: contraindicated in asthmatics. The β_1 selective agents may be safer in this regard.
4. Propranolol exacerbates variant (vasospastic) angina due to unopposed α mediated coronary constriction. In some patients, even classical angina may be worsened if ventricular dilatation and asynergy of contraction occurs—specially with high doses.
5. Propranolol is better avoided in diabetics, because risk of hypoglycaemic episodes may be increased. However, the β_1 selective agents may be less risky. Carbohydrate tolerance may be impaired in prediabetics.
6. Plasma lipid profile is altered on long-term use: total triglycerides tend to increase while HDL-cholesterol falls. This may enhance risk of coronary artery disease. Cardio-selective β blockers and those with intrinsic

sympathomimetic activity have little/no deleterious effect on blood lipids.

7. Withdrawal of propranolol after chronic use should be gradual, otherwise rebound hypertension, worsening of angina and even sudden death can occur. This appears to be due to upregulation of β receptors occurring as a result of long-term reduction in agonist stimulation.
8. Propranolol is contraindicated in partial and complete heart block: arrest may occur.
9. Tiredness and reduced exercise capacity may be felt due to blunting of β_2 mediated increase in blood flow to the exercising muscles as well as attenuation of glycogenolysis and lipolysis.
10. Cold hands and feet may be noticed during winter due to blockade of vasodilator β_2 receptors. Peripheral vascular disease is worsened.
11. Side effects not overtly due to β blockade are—g.i.t. upset, lack of drive, nightmares, forgetfulness. Incidence of mental depression was found to be higher among patients taking β blockers, especially the lipid soluble agents like propranolol. Male patients more frequently complain of sexual distress.

OTHER β BLOCKERS

A number of β blockers have been developed having some special features. Their comparative properties are presented in Table 10.2. The associated properties alongwith their significance can be summarized as:

Cardioselectivity (in metoprolol, atenolol, acebutolol, bisoprolol, nebivolol).

These drugs are more potent in blocking cardiac (β_1) than bronchial (β_2) receptors. However, selectivity is only relative and is lost at high doses. Their features are:

1. Lower propensity to cause bronchoconstriction, but even these drugs should usually be avoided in asthmatics and COPD patients. However, a coexisting cardiac condition may warrant their use, which may be initiated at low dose and under supervision.
2. Less interference with carbohydrate metabolism and less inhibition of glycogenolysis during hypoglycaemia—safer in diabetics.

However, tachycardia in response to hypoglycaemia is blocked.

3. Lower incidence of cold hands and feet, less chances of precipitating Raynaud's phenomenon.
4. No/less deleterious effect on blood lipid profile.
5. Ineffective in suppressing essential tremor (it occurs through β_2 action on muscle fibres).
6. Less liable to impair exercise capacity.

Partial agonistic (intrinsic sympathomimetic) action (in pindolol, celiprolol, acebutolol). These drugs themselves activate β_1 and/or β_2 receptors submaximally. The benefits of this property are controversial.

1. Bradycardia and depression of contractility at rest are not prominent, but exercise tachycardia is blocked; may be preferred in those prone to severe bradycardia (elderly patients; sick sinus) or with low cardiac reserve.
2. Withdrawal is less likely to exacerbate hypertension or angina; continued agonistic action on β receptors (of the drug itself) prevents development of supersensitivity.
3. Plasma lipid profile is not/less worsened.
4. Not effective in migraine prophylaxis—they dilate cerebral vessels.
5. Not suitable for secondary prophylaxis of MI.

Membrane stabilizing activity (in propranolol, oxprenolol, acebutolol). This activity is claimed to contribute to the antiarrhythmic action, but appears to be insignificant. β blockers with membrane stabilizing action cannot be used topically for glaucoma, because they anaesthetize cornea.

Low lipid solubility (atenolol, celiprolol, bisoprolol, sotalol)

1. They are less likely to produce sleep disturbances, nightmares, or to increase the incidence of mental depression.
2. They are incompletely absorbed orally, but do not undergo first pass metabolism and are primarily excreted unchanged in urine: are longer acting ($t_{1/2}$ 6–20 hours) and tend to be effective in a narrow dose range. In contrast, the lipid soluble agents are primarily metabolized in liver and have shorter $t_{1/2}$ (2–6 hours).

Table 10.2: Comparative properties of β blockers

β -BLOCKER	Potency (on β_1)	Partial agonis- tic action	Membrane stabilizing action	Lipid solubility	Daily dose (mg)	Oral bioavailability (%)	First pass metabo- lism	Major route of elimina- tion	Plasma $t_{1/2}$ (hours)
NONSELECTIVE									
1. Propranolol	1	—	++	+++	40–480	~30	Yes	Hep.*	3–5
2. Sotalol	1/3	—	—	±	160–480	~80	No	Ren. ¹	6–12
3. Timolol	6	—	—	++	10–40	50–75	Partial	Ren.+Hep.	4–5
4. Pindolol	6	+++	±	+	10–30	90	No	Ren.+Hep.	3–4
CARDIOSELECTIVE									
1. Metoprolol	1	—	±	++	100–400	40–50	Yes	Hep.	3–6
2. Atenolol	1	—	—	—	25–100	50–60	No	Ren.	6–9
3. Acebutolol	1/3	+	+	±	400–1200	40–60	Yes	Hep.+Ren.	3–4
4. Bisoprolol	6	—	—	—	2.5–10	80	No	Hep.+Ren.	9–12
$\alpha + \beta$ BLOCKER									
1. Labetalol	1/3	+	+	±	300–600	~30	Yes	Hep.	4–6

*Hep—Hepatic metabolism; ¹Ren.—Renal excretion

Salient features of important β blockers are given below.

1. Sotalol A nonselective β blocker with low lipid solubility. It has additional cardiac rectifier K^+ channel blocking and class III antiarrhythmic property.

SOTAGARD 40, 80 mg tab.

2. Timolol Due to absence of local anaesthetic activity and good lipid solubility, it is the first ocular β blocker to be used topically for glaucoma (see p. 167).

Orally it is a potent β blocker which is indicated in hypertension, angina and prophylaxis of myocardial infarction.

Betaxolol, Levobunolol, Cartiolol and Metipranolol are β blockers employed exclusively for topical application to the eye (see p. 168).

3. Pindolol A potent β blocker with prominent intrinsic sympathomimetic activity. It has been used primarily as antihypertensive which may be advantageous in patients who develop marked bradycardia with propranolol. Chances of rebound hypertension on withdrawal are also less. Plasma lipid profile may not worsen.

PINADOL 5 mg tab, VISKEN 10, 15 mg tab.

4. Metoprolol It is the prototype of cardio-selective (β_1) blockers; nearly 50 times higher dose is needed to block isoprenaline induced

vasodilatation. Some measure of inverse agonistic activity on β_1 receptors has also been demonstrated. It is less likely to worsen asthma, but is not entirely safe. It may be preferred in diabetics receiving insulin or oral hypoglycaemics. Patients who complain of cold hands and feet while on propranolol do better on metoprolol.

First pass metabolism of metoprolol is less marked than propranolol, but 90% or more is ultimately hydroxylated by CYP2D6 before excretion. There are 'extensive' and 'poor' hydroxylators of metoprolol (CYP2D6 alleles); the latter may require a lower dose.

Side effects of metoprolol are milder. It is generally given orally for hypertension, angina and CHF, but i.v. injection (5–15 mg) has been used in myocardial infarction provided bradycardia is absent.

BETALOC 25, 50, 100 mg tab, 5 mg/ml inj. LOPRESOR, METOLAR 50, 100 mg tab.

S(–) Metoprolol is the active enantiomer, now available as a single enantiomer product. It is to be used at half the dose as the racemate. Dose: 12.5–50 mg OD–BD.

METPURE-XL 12.5, 25, 50 mg extended release tabs.

5. Atenolol A relatively selective β_1 blocker having low lipid solubility. It is incompletely absorbed orally, but first pass metabolism is not significant. Because of longer duration of

action, once daily dose is often sufficient. Side effects related to CNS action are less likely. No deleterious effects on lipid profile have been noted. Effective dose for most individuals falls in a narrow range. It is one of the most commonly used β blockers for hypertension and angina, but is not approved for CHF.

BETACARD, ATEN, TENORMIN 25, 50, 100 mg tab.

S(-) Atenolol This pure active enantiomer is effective at half the dose and may be better tolerated.

Dose: 12.5–50 mg OD;

ATPURE, ADBETA 12.5, 25, 50 mg tabs.

6. Acebutolol Another cardioselective agent with significant partial agonistic and membrane stabilizing properties. The side effect profile is like that of metoprolol, but resting heart rate is not decreased as much. Acebutolol is rapidly metabolized to an active metabolite diacetolol which is primarily excreted by kidney and has a longer $t_{1/2}$ (8–12 hours). As such, a single daily dose is sufficient in many patients.

SECTRAL 200, 400 mg tab., 10 mg/2 ml amp. Intravenous dose for arrhythmias 20–40 mg.

7. Bisoprolol A cardioselective β_1 blocker lacking intrinsic sympathomimetic activity; suitable for once daily administration in angina, hypertension and CHF.

CONCOR, CORBIS 5 mg tab; $\frac{1}{2}$ to 2 tab OD.

8. Esmolol It is an ultra-short acting β_1 blocker devoid of partial agonistic or membrane stabilizing actions. Due to inactivation by esterases in blood its plasma $t_{1/2}$ is < 10 min; action disappears 15–20 min after terminating i.v. infusion. The degree of β blockade can be titrated by regulating the rate of infusion. Rapid onset, short lasting fall in BP attends i.v. infusion of esmolol.

A loading dose of 0.5 mg/kg is given followed by 0.05–0.2 mg/kg/min infusion. It has been used to terminate supraventricular tachycardia, episodic atrial fibrillation or flutter and arrhythmia during anaesthesia. Esmolol is also very useful for reducing HR and BP during and after cardiac surgery, in aortic dissection and in early treatment of myocardial infarction.

MINIBLOCK 100 mg/10 ml, 250 mg/10 ml inj.

9. Nebivolol This highly selective β_1 blocker is regarded as a *third generation* β blocker, because in addition to β receptor blockade, it activates endothelial nitric oxide (NO) synthase and enhances NO production. It thus causes vasodilatation and has the potential to improve endothelial function, which may delay atherosclerosis. Absence of deleterious effect on plasma lipids and on carbohydrate metabolism is another advantage. It tends to increase insulin sensitivity, instead of decreasing it. In contrast to older β blockers, hypotensive response to nebivolol has a rapid onset. Nebivolol is indicated in hypertension as well as in CHF.

Dose: 5 mg (elderly 2.5 mg) OD;

NEBICARD 2.5, 5 mg tabs, **NODON** 5 mg tab.

10. Celiprolol Another third generation selective β_1 blocker having additional weak β_2 agonistic activity which reduces vascular resistance and holds promise of safety in asthmatics. Nonadrenoceptor mediated vasodilatation (due to NO production) adds to its antihypertensive action.

Dose: 200–600 mg OD; **CELIPRES** 100, 200 mg tab.

USES

1. Hypertension β blockers are relatively mild antihypertensives. All agents, irrespective of associated properties, are nearly equally effective. They were one of the first choice drugs, but are less favoured now for initiating therapy as the single drug (*see* Ch. 41).

2. Angina pectoris All β blockers benefit angina of effort. Taken on a regular schedule they decrease frequency of attacks and increase exercise tolerance. High doses, however, may worsen angina in some patients by increasing ventricular size and reducing coronary flow. β blockers are not suitable for variant (vasospastic) angina (*see* Ch. 40).

3. Cardiac arrhythmias β blockers (mainly propranolol) suppress extrasystoles and tachycardias, both supraventricular and ventricular, especially those mediated adrenergically (during anaesthesia, digitalis induced). Propranolol may be used i.v. for this purpose. It also controls ventricular rate in atrial fibrillation and flutter,

but only occasionally restores sinus rhythm. Esmolol is an alternative drug for paroxysmal supraventricular tachycardia (see Ch. 39).

4. Myocardial infarction (MI) In relation to MI, β blockers, particularly propranolol and metoprolol, have been used for two purposes:

(a) *Secondary prophylaxis of MI*: There is now firm evidence of benefit. Long-term use after recovery from MI has been found to decrease subsequent mortality by 20%. They may act by:

- Preventing reinfarction
- Preventing sudden ventricular fibrillation at the subsequent attack of MI.

High risk patients (those who had large infarcts) should be put on these β blockers (if there are no haemodynamic contraindications) for at least 2 years. Other β blockers, especially those with partial agonistic action, are considered less suitable for this purpose.

(b) *Myocardial salvage during evolution of MI*: Administered i.v. within 4–6 hours of an attack followed by continued oral therapy, one of the above two β blockers—

- May limit infarct size by reducing O_2 consumption—marginal tissue which is partially ischaemic may survive.
- May prevent arrhythmias including ventricular fibrillation.

However, β blockers can be given to only those patients not in shock or cardiac failure and who have heart rate $> 50/\text{min}$ along with not higher than first degree heart block (P-R interval < 0.24 sec). In megatrials such therapy has been found to reduce mortality by 20–25%.

5. Congestive heart failure Although β blockers can acutely worsen heart failure, several studies have reported beneficial haemodynamic effects of certain β blockers, namely *metoprolol*, *bisoprolol*, *nebivolol* and *carvedilol* over long-term in selected patients with dilated cardiomyopathy. Introduced gradually and maintained for long term, these drugs retard the progression of CHF and prolong life. The benefit may result from antagonism of deleterious effects of sympathetic overactivity (invoked reflexly by heart failure) on the myocardium. Overactivation of cardiac β_1 receptors has been

found to exert toxic effects on the heart by accelerating myocyte apoptosis and promoting functionally unfavourable remodeling. One of the above named β blockers, used appropriately along with other measures, is now established as standard therapy for most mild to moderate CHF patients. However, these drugs should not be given to patients with marked fluid retention and to those who worsen on initiating the β blocker, or to those requiring i.v. vasodilators/inotropic drugs (see Ch. 38).

6. Dissecting aortic aneurysm β blockers help by reducing cardiac contractile force and aortic pulsation. Nitroprusside infusion is often added.

7. Pheochromocytoma β blockers may be used to control tachycardia and arrhythmia, but should never be administered unless an α blocker has been given before, otherwise dangerous rise in BP can occur. They suppress cardiomyopathy caused by excess CAs.

8. Thyrotoxicosis Propranolol rapidly controls the sympathetic symptoms (palpitation, nervousness, tremor, fixed stare, severe myopathy and sweating) without significantly affecting thyroid status. It also inhibits peripheral conversion of T_4 to T_3 and is highly valuable during thyroid storm. Major use, however, is preoperatively and while awaiting response to antithyroid drugs/radioactive iodine.

9. Migraine Propranolol is the most effective drug for chronic prophylaxis of migraine (see p. 195).

10. Anxiety Propranolol exerts an apparent antianxiety effect, especially under conditions which provoke nervousness and panic, e.g. examination, unaccustomed public appearance, etc. This is probably due to blockade of peripheral manifestations of anxiety (palpitation, tremor) which have a reinforcing effect. Propranolol is largely ineffective in anxiety neurosis, but may benefit the somatic symptoms.

11. Essential tremor Nonselective $\beta_1 + \beta_2$ blockers have now an established place in treating essential tremor. However, they do not benefit parkinsonian tremor.

12. Glaucoma Ocular β blockers are widely used for chronic simple (wide angle) glaucoma. They are also used as adjuvant in angle closure glaucoma (see p. 167, 170).

13. Hypertrophic obstructive cardiomyopathy The subaortic region is hypertrophic. Forceful contraction of this region under sympathetic stimulation (exercise, emotion) increases outflow resistance which has incapacitating haemodynamic consequence. β blockers improve c.o. in these patients during exercise by reducing left ventricular outflow obstruction, though they have little effect while at rest.

$\alpha + \beta$ ADRENERGIC BLOCKERS

Labetalol It is the first adrenergic antagonist capable of blocking both α and β receptors. There are 4 diastereomers of labetalol, each of which has a distinct profile of action on subtypes of α and β receptors. The commercial racemic preparation has equal parts of each diastereomer and displays $\beta_1 + \beta_2 + \alpha_1$ blocking as well as weak β_2 agonistic activity. The β blocking potency is about 1/3 that of propranolol, while α blocking potency is about 1/10 of phentolamine.

Labetalol is 3–5 times more potent in blocking β than α receptors. As such, effects of a low dose resemble those of propranolol alone while at higher dose they are like a combination of propranolol and prazosin. Fall in BP (both systolic and diastolic) is due to α_1 and β_1 blockade as well as β_2 agonism (vasodilatation). Relatively high doses reduce both c.o. and t.p.r. Heart rate is unchanged or slightly decreased or increased. In contrast to propranolol, limb blood flow increases with labetalol. It has also been shown to inhibit NA uptake by adrenergic nerve endings.

Labetalol is orally effective but undergoes considerable first pass metabolism.

It is a moderately potent antihypertensive that is particularly useful in pheochromocytoma, clonidine withdrawal, pregnancy induced hypertension (preeclampsia) and hypertensive emergencies, as well as in essential hypertension.

Most important side effect is postural hypotension, but this is significant only in some patients. Failure of ejaculation and other side effects of α and β blockers can also occur, but plasma lipid levels are not altered. Rashes and liver damage have been reported.

Dose: Start with 50 mg BD, increase to 100–200 mg TDS oral. In hypertensive emergencies 20–40 mg i.v. every 10 min till desired response is obtained.

NORMADATE 50, 100, 200 mg tab, LABESOL, LABETA 50 mg tab, 20 mg/amp and 100 mg/amp inj.

Carvedilol It is a $\beta_1 + \beta_2 + \alpha_1$ adrenoceptor blocker which produces vasodilatation due to α_1 blockade as well as calcium channel blockade. Antioxidant property has also been demonstrated, but its clinical relevance is uncertain. It has been used in hypertension and is the β blocker especially employed as cardioprotective in CHF. Oral bioavailability of carvedilol is 30%. It is primarily metabolized CYP2D6 of which there are 'poor' or 'extensive' metabolizer alleles. Interaction with CYP2D6 inhibitors can occur. Carvedilol has a $t_{1/2}$ of 6–8 hrs.

CHF: Start with 3.125 mg BD for 2 weeks, if well tolerated gradually increase to max. of 25 mg BD.

Hypertension/angina: 6.25 mg BD initially, titrate to max. of 25 mg BD.

CARVIL, CARLOC, CARVAS 3.125, 6.25, 12.5, 25 mg tabs; ORICAR 12.5, 25 mg tabs.

DRUGS FOR GLAUCOMA

Glaucoma is a group of diseases characterized by a progressive form of optic nerve damage. This is generally, but not necessarily, associated with raised (> 21 mmHg) intraocular tension (i.o.t), but the etiology is unknown and there are many risk factors. The chief therapeutic measure is to lower i.o.t., either by reducing secretion of aqueous humour or by promoting its drainage. Lowering of i.o.t. retards progression of optic nerve damage even in normal/low i.o.t. glaucoma. The site of formation and pathway of drainage of aqueous humour as well as sites of action of antiglaucoma drugs is illustrated in Fig. 10.1. Major amount of aqueous (~90%) drains through the *trabecular route*, while ~10% fluid passes into the connective tissue

spaces within the ciliary muscle—then *via* suprachoroid into episcleral vessels (*uveoscleral outflow*). Glaucoma is seen in two principal clinical forms; *viz.* 'open angle' and 'angle closure' glaucoma.

A. Open angle (wide angle, chronic simple) glaucoma

It is probably a genetically predisposed degenerative disease affecting patency of the trabecular meshwork which is gradually lost past middle age. The i.o.t. rises insidiously and progressively. Ocular hypotensive drugs are used on a

long-term basis and constitute the definitive treatment in majority of cases. The mode of ocular hypotensive action of topical antiglaucoma drugs is summarized in Table 10.3.

1. β Adrenergic blockers

Topical β blockers have been the first line drugs till recently, but PG F_{2a} analogues are the preferred drugs now. In contrast to miotics, the β blockers do not affect pupil size, tone of ciliary muscle or outflow facility, but lower i.o.t. by reducing aqueous formation. This probably results from down regulation of

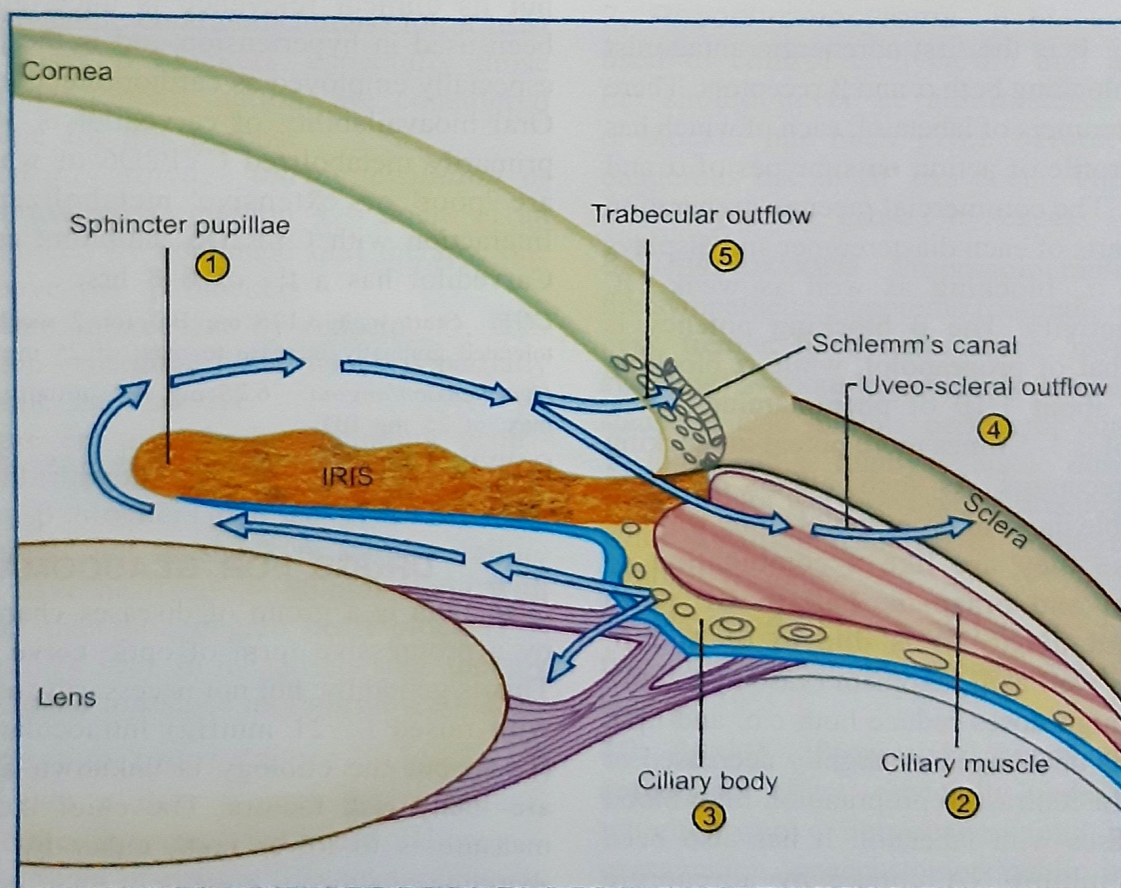
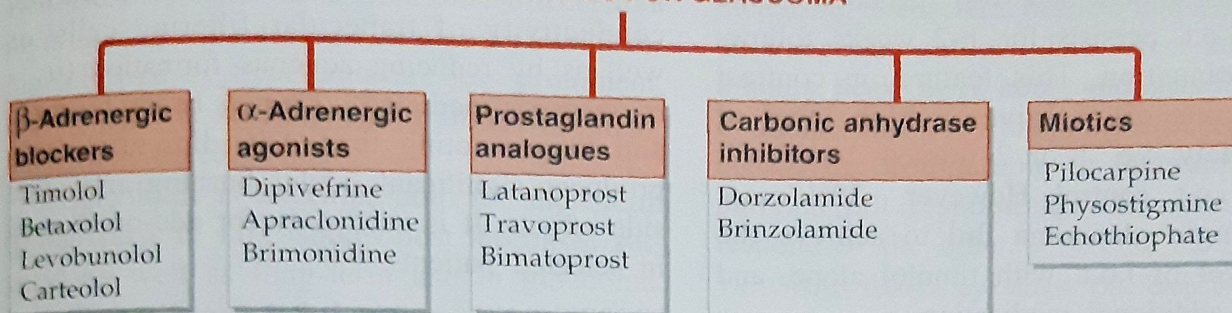


Fig. 10.1: Illustration of aqueous humour dynamics and the sites of action of ocular hypotensive drugs

- (1) Site of action of miotics in angle closure glaucoma: contraction of sphincter pupillae removes pupillary block and reverses obliteration of iridocorneal angle
- (2) Site of action of miotics in open angle glaucoma: contraction of ciliary muscle pulls on scleral spur and improves trabecular patency
- (3) Site of action of (a) β blockers (b) α_1 agonists (c) α_2 agonists (d) carbonic anhydrase inhibitors: all reduce aqueous secretion by ciliary body
- (4) Site of action of prostaglandins and adrenaline (α agonist action): increase uveoscleral outflow by altering permeability and/or pressure gradients
- (5) Site of action of adrenaline (β_2 agonist action): possibly increases aqueous conductivity of trabecular filtering cells

TOPICAL DRUGS FOR GLAUCOMA



adenylyl cyclase due to β_2 receptor blockade in the ciliary epithelium (see Fig. 10.2) and a secondary effect due to reduction in ocular blood flow. They are as effective as miotics and produce less ocular side effects. Ocular β blockers are lipophilic with high ocular capture (to reduce systemic effects) and have no/weak local anaesthetic activity (to avoid corneal hypoesthesia and damage).

Ocular side effects of β blockers These are generally mild and infrequent—stinging, redness and dryness of eye, corneal hypoesthesia, allergic blepharoconjunctivitis and blurred vision.

Systemic adverse effects These are the major limitations in the use of ocular β blockers, and occur due to absorption through nasolacrimal duct. Life-threatening bronchospasm has been reported in asthmatic and COPD patients. Bradycardia, accentuation of heart block and CHF are likely to occur, especially in the elderly. In fact all adverse effects and contraindications of systemic β blocker therapy (see p. 160-61) apply to ocular β blockers as well. Systemic adverse effects can be minimized by applying mild pressure on the inner canthus of the eye for about 5 min. after instilling the eye drop to prevent entry of the drug into nasolacrimal duct from where it is mainly absorbed.

Timolol It is the prototype of ocular β blockers; is nonselective ($\beta_1 + \beta_2$) and has no local anaesthetic or intrinsic sympathomimetic activity. The ocular hypotensive action (20–35% fall in i.o.t.) becomes evident within 1 hour and lasts for ~12 hours. After chronic dosing,

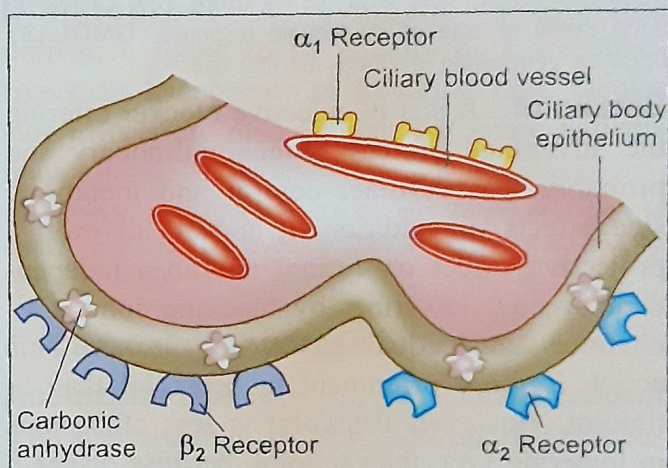


Fig. 10.2: Location of α_1 , α_2 and β_2 adrenergic receptors and of carbonic anhydrase enzyme (molecules which are targets of drug action for reducing aqueous formation) in the processes of the ciliary body

α_1 adrenoceptors constrict ciliary vessels and reduce aqueous production: are activated by adrenaline.

α_2 adrenoceptors located on ciliary epithelium reduce aqueous secretion: are activated by adrenaline/apraclonidine/brimonidine.

β_2 adrenoceptors located on ciliary epithelium enhance aqueous secretion via increased cAMP. Their blockade by timolol/betaxolol reduces secretion.

Carbonic anhydrase present within ciliary epithelial cells generates HCO_3^- ion which is secreted into aqueous humor. Acetazolamide/dorzolamide inhibit it and reduce aqueous secretion.

Advantages of topical β blockers over miotics

- No change in pupil size: no diminution of vision in dim light and in patients with cataract
- No induced myopia which is especially troublesome in young patients
- No headache/brow pain due to persistent spasm of iris and ciliary muscles
- No fluctuations in i.o.t. as occur with pilocarpine drops
- Convenient twice/once daily application sufficient

the action is smooth and well sustained. Some effect on i.o.t. persists for 1–2 weeks following discontinuation. This feature, in contrast to pilocarpine drops, gives a high level of clinical safety, i.e. 1 or 2 missed doses will not affect i.o.t. control. However, ~30% cases of open angle glaucoma fail to achieve the desired level of i.o.t. with timolol alone, and may need additional medication.

GLUCOMOL, OCUPRES, IOTIM, LOPRES 0.25% and 0.5% eye drops; start with 0.25% drops BD, change to 0.5% drops in case of inadequate response. TIMOLAST 0.5% as gelforming eyedrop for OD use.

Betaxolol It is a β_1 selective blocker offering the advantage of less bronchopulmonary and probably less cardiac, central and metabolic side effects. In addition, it appears to exert a protective effect on retinal neurones independent of i.o.t. lowering, by blocking some Ca^{2+} channels and reducing $\text{Na}^+/\text{Ca}^{2+}$ influx. This action is more prominent in betaxolol than in timolol. However, betaxolol is less efficacious in lowering i.o.t. than timolol, because ocular β receptors are predominantly of the β_2 subtype. Transient stinging and burning in the eye is more common with it. Most ophthalmologists prefer to start with betaxolol and change over to timolol (or a similar drug) only if i.o.t. control is insufficient or there is local intolerance to betaxolol.

OPTIPRESS, IOBET, OCUBETA 0.5% eye drops; 1 drop in each eye BD.

Levobunolol It has been introduced as a once daily alternative to timolol. The ocular and systemic effects are very similar to timolol except for longer duration of action.

BETAGAN 0.5% ophthalmic soln., 1 drop OD.

Carteolol and Metipranolol are the other ocular β blockers.

2. α Adrenergic agonists

Dipivefrine It is a prodrug of Adr; penetrates cornea and is hydrolysed by the esterases present there into Adr, which itself has poor corneal penetration and causes ocular smarting, reactive hyperemia. The released Adr (from dipivefrine) lowers i.o.t. by augmenting uveoscleral outflow,

β_2 receptor mediated increase in hydraulic conductivity of trabecular filtering cells, as well as by reducing aqueous formation ($\alpha_1 + \alpha_2$ receptor mediated). Though better tolerated and longer acting than Adr, dipivefrine still produces significant ocular burning and other side effects. It is used only for add-on therapy in selected patients.

PROPINE 0.1% eye drop; 1 drop in each eye BD.

Apraclonidine It is a polar clonidine congener which does not cross blood-brain barrier, but applied topically (0.5–1%) it lowers i.o.t. by ~25%. It decreases aqueous production by primary α_2 and subsidiary α_1 action in the ciliary body. Itching, lid dermatitis, follicular conjunctivitis, mydriasis, eyelid retraction, dryness of mouth and nose are common side effects. Its use is restricted to short-term control of spikes of i.o.t. after laser trabeculoplasty or iridotomy.

ALFADROPS DS 1% eyedrops.

Brimonidine This clonidine congener is more α_2 selective and more lipophilic than apraclonidine. It lowers i.o.t. by 20–27% by reducing aqueous production and by increasing uveoscleral flow. Peak effect on i.o.t. occurs after 2 hours of instillation. Allergic conjunctivitis and other ocular side effects are similar to but less frequent than with apraclonidine.

Table 10.3: Mode of action of ocular hypotensive drugs

Drug/class	Aqueous secretion	Trabecular outflow	Uveoscleral outflow
1. β -blockers (Timolol)	↓	–	–
2. Adrenaline/Dipivefrine	↓	↑	↑
3. Brimonidine/apraclonidine	↓	–	↑
4. Prostaglandins (Latanoprost)	–	↑	↑
5. Miotics (Pilocarpine)	–	↑	–
6. Carbonic anhydrase inhibitors	↓	–	–

Because of weaker α_1 action, side effects like mydriasis, eyelid retraction, conjunctival blanching followed by hyperemia are less prominent, but dry mouth, sedation and a small fall in BP have been noted.

Brimonidine is indicated both for short-term (prophylaxis of i.o.t. spikes post laser/post surgery) as well as long-term use in glaucoma. It is generally used for add-on therapy only.

ALPHAGAN-P, BRIMODIN-P 0.15% eye drops, IOBRIM 0.2% eyedrops; 1 drop in each eye TDS.

3. Prostaglandin analogues

Low concentration of $\text{PGF}_{2\alpha}$ was found to lower i.o.t. without inducing ocular inflammation. It acts by increasing uveoscleral outflow, possibly by increasing permeability of tissues in ciliary muscle or by an action on episcleral vessels. An effect on trabecular outflow has also been demonstrated, but is less marked. Ciliary body COX-2 has been found to be down regulated in wide angle glaucoma indicating a physiological role of PGs in aqueous humour dynamics.

Latanoprost Instilled in the eye, this $\text{PGF}_{2\alpha}$ derivative has shown efficacy similar to timolol (i.o.t. reduction by 25–35%) and the effect is well sustained over long-term. It reduces i.o.t. in normal pressure glaucoma also. Though ocular irritation and pain are relatively frequent, no systemic side effects are reported. Blurring of vision, increased iris pigmentation, thickening and darkening of eyelashes have occurred in some cases. Macular edema can develop during treatment with any $\text{PGF}_{2\alpha}$ analogue, especially in aphakic patients; a watch should be kept to detect it early.

Because of good efficacy, once daily application and absence of systemic complications, PG analogues have become the first choice drugs for open angle glaucoma. High cost is a disadvantage.

LACOMA, XALATAN, LATOPROST, 0.005% eye drops, one drop in each eye OD in the evening; LACOMA-T, LAPROST PLUS, LATOCHECK-T eye drops with timolol 0.5% eye drops. (To be stored in cold)

Travoprost Another selective FP-prostanoid receptor agonist which lowers i.o.t. mainly by

increasing uveoscleral outflow and a minor effect on trabecular outflow. The effect starts within 2 hours, peaks at 12 hours and lasts for 24 hours or more. The i.o.t. lowering efficacy and side effects are comparable to latanoprost. Some patients not responding well with one may respond to the other.

TRAVATAN 0.004% eye drops. One drop in each eye in the evening; refrigeration of the eye drop is not required; TRAVACOM 0.004% with timolol 0.5% eye drop.

Bimatoprost A synthetic prostamide derivative found to be equally or more effective than latanoprost in lowering i.o.t. Ocular side effects are also similar, but some patients may tolerate it better.

LUMIGAN, CAREPROST 0.03% eye drops; one drop in each eye OD in the evening. The eye drop need not be stored in refrigerator.

4. Carbonic anhydrase inhibitors

Acetazolamide (see Ch. 42) Oral treatment with acetazolamide (0.25 g 6–12 hourly) reduces aqueous formation by limiting generation of bicarbonate ion in the ciliary epithelium. It is used to supplement ocular hypotensive drugs for short-term indications like angle closure, before and after ocular surgery/laser therapy. Systemic side effects—paresthesia, anorexia, hypokalaemia, acidosis, malaise and depression restrict long-term use to few cases in which target i.o.t. is not achieved even by concurrent use of 2–3 topical drugs.

Dorzolamide (2% eye drops BD-TDS) It is a topically useful carbonic anhydrase inhibitor developed to circumvent systemic side effects of acetazolamide. It lowers i.o.t. by ~20%; somewhat less efficacious than timolol. Ocular stinging, burning, itching, corneal edema and bitter taste are the usual side effects. Systemic adverse effects are also possible. Dorzolamide is used only as add on drug to topical β blockers/PG analogues, or when these drugs are contraindicated.

DORTAS, DORZOX 2% eye drops.

Brinzolamide is another ocular carbonic anhydrase inhibitor.

5. Miotics: Till the 1970s topical pilocarpine alone or combined with antiChEs were the standard antiglaucoma drugs (see Ch. 7). However, because of several drawbacks (see box on p. 167), they are now used only as the last option. In open angle glaucoma, they lower i.o.t. by increasing ciliary muscle tone thereby improving patency of trabeculae.

The current approach to treatment of open angle glaucoma can be summarized as—start monotherapy with latanoprost/another PG analogue, or a topical β blocker; if target i.o.t. is not attained, either change over to the alternative drug or use both the above concurrently. Brimonidine/dorzolamide (occasionally dipivefrine) are used only when there are contraindications to PG analogues and/or β blockers, or to supplement their action. Topical miotics and oral acetazolamide are added only as the last resort.

B. Angle closure (narrow angle, acute congestive) glaucoma

It occurs in individuals with a narrow iridocorneal angle and shallow anterior chamber. The i.o.t. remains normal until an attack is precipitated, usually by mydriasis (Fig. 10.3A,B). The i.o.t. rises rapidly to very high values (40–60 mmHg). It is an emergent condition with marked congestion of eyes and severe headache. Failure to lower i.o.t. quickly may result in loss of sight.

Vigorous therapy employing several measures to reduce i.o.t. is instituted.

1. *Hypertonic mannitol (20%) 1.5–2 g/kg or glycerol (10%):* infused i.v. decongest the eye by osmotic action. A retention enema of 50% glycerine is also some times used.
2. *Acetazolamide:* 0.5 g i.v. followed by oral twice daily is started concurrently.
3. *Miotic:* Once the i.o.t. starts falling due to the above i.v. therapy, pilocarpine 1–4% is

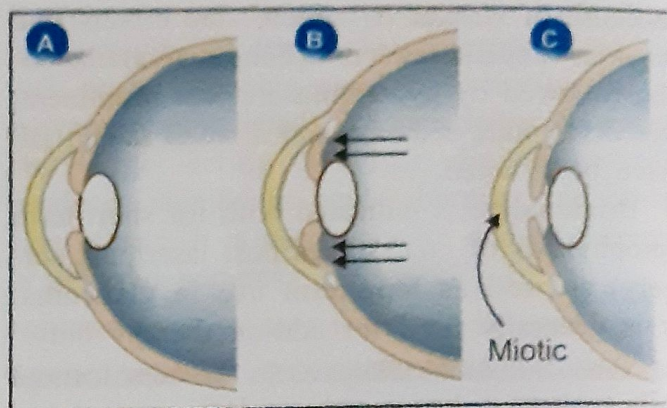


Fig. 10.3: Development of angle closure glaucoma and its reversal by miotic

- A. Mydriasis occurs in an eye with narrow iridocorneal angle and iris makes contact with lens blocking passage of aqueous from posterior to anterior chamber.
- B. Pressure builds up behind the iris which bulges forward and closes the iridocorneal angle thus blocking aqueous outflow.
- C. Miotic makes the iris thin and pulls it away from the lens removing the pupillary block and restoring aqueous drainage

instilled every 10 min initially and then at longer intervals. Contraction of sphincter pupillae changes the direction of forces in the iris to lessen its contact with the lens and spreads the iris mass centrally → pupillary block is removed and iridocorneal angle is freed (Fig. 10.3C). However, when i.o.t. is very high, the iris muscle fails to respond to miotics; tension should be reduced by other measures before miotics can act.

4. *Topical β blocker:* Timolol 0.5% is instilled 12 hourly in addition.
5. *Apraclonidine (1%)/latanoprost 0.005%:* instillation may be added.

Drugs are used only to terminate the attack of angle closure glaucoma. Definitive treatment is surgical or laser iridotomy. Few cases, who have chronic narrow angle glaucoma, may be treated with a miotic/other ocular hypotensive drug for long periods, but often surgery/laser therapy is ultimately required.

PROBLEM DIRECTED STUDY

10.1 A 70-year-old male presented with the complaints of weak stream of urine, sense of incomplete bladder voiding, urinary frequency and nocturia. After physical examination and ultrasound, he was diagnosed to have developed benign hypertrophy of prostate and was prescribed:

Tab. Terazosin 5 mg, one tab daily at bed time.

He took the medicine as advised and went off to sleep. At night, when he got up to pass urine, he felt giddy and fainted. On being laid flat on the bed, he regained consciousness within 2 minutes. Later, he was gradually propped up on the bed to the sitting position and then got up slowly and walked without any problem.

- (a) What is the rationale of prescribing terazosin to this patient?
- (b) What is the likely explanation for the fainting attack?
- (c) What precautions could have avoided the fainting episode?

10.2 A lady aged 55 years was brought at night to the hospital emergency with severe breathlessness and wheezing. Chest auscultation revealed marked bronchoconstriction. She was managed with 100% O₂ inhalation and nebulized salbutamol + ipratropium bromide. The asthmatic attack was controlled in about 6 hours. Next day, history taking revealed that she was having mild episodic asthma off and on, but never had such a severe attack. Day before she had visited an ophthalmologist for visual difficulty and frontal headache. The intraocular pressure was measured to be 24 and 25 mmHg in right and left eye respectively. She was prescribed:

Timolol 0.5% eye drops in each eye twice a day.

- (a) What is the most likely explanation for the precipitation of severe attack of asthma?
- (b) How could such a complication be avoided?

(see Appendix-1 for solutions)