UNIT 26 ANTIGLAUCOMA AGENTS

Structure

26.0 OBJECTIVES

After completing this unit, you should be able to understand:

- the pathophysiology of glaucoma;
- types of different drugs used in glaucoma;
- indications and contraindications of antiglaucoma drugs; and
- doses and side effects of different antiglaucoma medications.

26.1 INTRODUCTION

Glaucoma is a condition in which intra-ocular pressure is such that causes irreversible damage to optic nerve. Damage to optic nerve causes permanent decrease of vision. In general, glaucoma can be broadly divided into two types. Glaucoma associated with open anterior chamber angle is known as Open Angle Glaucoma (OAG) and glaucoma associated with narrow angle of anterior chamber is known as Angle Closure Glaucoma (ACG). In both these conditions, basic principle of management is to'decrease Intra-ocular Pressure (IOP). Drops, laser or surgery can achieve IOP reduction. Antiglaucoma drops are the mainstay of therapy for glaucoma particularly in open angle type of glaucoma.

26.2 CLASSIFICATION

Antiglaucoma drugs are classified as under:

1) Beta Blockers
   - Timolol maleate
   - Betaxolol hydrochloride
   - Levobunolol hydrochloride
2) Cholinergic Agents
   Pilocarpine
3) Sympathomimetics
   - Epinephrine borate/bitaratrate/hydrochloride
   Dipivalyl epinephrine

4) Carbonic Anhydrase Inhibitors
   - Systemic – Acetazolamide
     Methazolamide
   - Local – Dorozolamide hydrochloride

5) Alpha-adrenergic Agonists
   - Apraclonidine
   - Brimonidine tartarate

6) Prostaglandins
   - Latanoprost
   - Bimatoprost
   - Unoprostone
   - Travoprost

7) Hyperosmotic agents
   - Intravenous – Mannitol
   - Oral – Glycerine

26.3 DESCRIPTION OF DIFFERENT ANTIGLAUCOMA DRUGS

The details of mode of action, uses and side effects of these drugs are as under:

26.3.1 Beta Blockers

Beta blockers are those drugs that antagonise beta adrenoceptors.

Mechanism of Action

These drugs decrease the intra-ocular pressure by reducing the formation of aqueous humour. There is neither a change in outflow facility nor a change in angle structure. There is antagonism of circulating catecholamines on beta-2 receptors in the ciliary epithelium, with consequent inactivation of the chloride pump and hence seduced aqueous secretion.'

Commonly used beta-blockers in glaucoma include:

1) **Timolol Maleate**

It is one of the most common and extensively used antiglaucomatous agents in ophthalmology. It is a non-selective beta-blocker, blocking both beta 1 and beta 2 receptors.

Mechanism of Action

Reduction in aqueous humour production by beta-2 receptor blockade.

Indications

- Primary open angle glaucoma
- secondary open angle glaucoma
- Ocular hypertension

Dosage

- Ophthalmic solution 0.25 per cent and 0.5 per cent
- Given 1 drop 2 times daily
- IOP decreases in 30-60 minutes and the effect lasts for 12-24 hours.

Ophthalmic gel forming solution (0.5 per cent). Because of gel formation, drug remains in contact with ocular tissue for more time and systemic absorption is reduced. Gel forming solution can be used once daily.

Adverse Reactions

Local – Irritation
Decreased Corneal Sensitivity
Allergy
Ocular cicatricial pemphigoid
Blurring and congestion
Reduction in tears
Reduced vision
Decreased ocular blood flow

Systemic – Decrease in heart rate (Bradycardia)
Heart conduction block
Induced contraction of bronchial muscle (bronchospasm)
Headache
Fatigue, Lethargy
Sexual dysfunction
Dryness of mouth

Contraindication

In patients of bronchial asthma and heart disorders, timolol should not be used.

2) Betaxolol

A selective beta 1 receptor blocking agent.

Mechanism of Action

Decrease in aqueous humour production. Betaxolol does not block beta 2 receptors, so it has no action on lungs and heart, hence can be safely given in cardiac and respiratory patients.

Indications

- Open angle glaucoma
- Ocular hypertension

Dosage

- Topical ophthalmic solution 0.25 per cent and 0.5 per cent
- Given 1 drop two times/day

Side Effects

- Allergic Reactions
- Itching and Burning Sensation
- Decreased corneal sensilivity

3) Levobunolol

Non-selective beta-blocker

Mechanism of Action

Decrease in aqueous production

Indication

- Open angle glaucoma
  Ocular hypertension

Dosage

Ophthalmic solution 0.25 per cent and 0.5 per cent, od/bd administration.

Adverse Reaction

Local – Burning
Decreased corneal sensitivity
Allergic blepharoconjunctivitis
Dendritic keratopathy

Systemic – Decrease in heart rate (Bradycardia)
Heart conduction Block
Congestive cardiac failure

26.3.2 Cholinergic Agents

Most common oholinergic agent used as an antiglaucoma agent is pilocarpine.

Pilocarpine

Most common and widely used topical antiglaucoma drug.

Mechanism of Action

1) Increase in drainage of aqueous from the eye (by ciliary muscle contraction and hence putting traction on the scleral spur and the trabecular meshwork).
2) Constriction of pupil (Miosis)
3) Decreased aqueous production

Indications

Angle Closure Glaucoma

i) *Acute Angle Closure Glaucoma*

In this condition, the intraocular pressure is very high. The drug acts by constricting the pupil, tightening the iris, decreasing the volume of iris tissue at the angle and pulling the iris periphery away from trabecular tissue.

ii) *Chronic Angle Closure Glaucoma*

In this condition, pilocarpine is mainly used to control the IOP.

Dosage

Ophthalmic solution – Pilocarpine hydrochloride 1 per cent, 2 per cent, 4 per cent
Pilocarpine Nitrate 1 per cent, 2 per cent, 4 per cent
It is used tds-qid topically,

Alternate Delivery Systems

- Soft contact lens used as drug reservoirs
- Pilocarpine gel prolongs the contact time and enhances the drug penetration
  Pilocarpine polymer
- Membrane controlled delievery — the ocusert can be placed in the lower conjunctival fornix to release the drug in a constant concentration of 20µg/hr or 40µg/hr.

Adverse Reaction

Local side effects include periocular pain, allergic blepharoconjunctivitis, ocular pseudopemphigoid,' irritation, lacrimation, punctal stenosis, vascular dilation and hyperemia, corneal epithelial staining and vascularisation, band keratopathy, iris hyperemia and pigment epithelial cyst formation, ciliary muscle spasm, cataract, retinal hole, detachment and vitreous hemorrhage. The pupillary constriction leads to diminished dark vision and constriction of peripheral visual field.

Systemic side effects are sweating, salivation and lacrimation, nausea, vomiting and abdominal cramps, weakness, fatigue and muscular spasm, paresthesia, nightmare and depression, prolonged respiratory paralysis after general anaesthesia, bronchial spasm, asthma and pulmonary edema.

26.3.3 Sympathomimetics

Sympathomimetics used in glaucoma management include:

Epinephrine (Adrenaline)

Mechanism qf Action

- Stimulates both alpha and beta-receptors.
- Increased drainage of aqueous humour through the conventional pathway
- Decrease in production of aqueous humour

Indication

- Open angle glaucoma
- Angle closure glaucoma after iridectomy
- Useful in glaucomas with immature cataract where dilatation improves vision

Contraindication

- Severe hypertension, cardiac diseases, tliyrotoxicosis and patients taking reserpine/MAO inhibitors
- Hypersensitivity to Epinephrine
- Aphakic/pseudophakic glaucoma

Dosage

Epinephrine is available as hydrochloride, borate and bitartrate salts. Available as 0.5 per cent, 1 per cent and 2 per cent solution. Given 1 drop 2 times/day.

Adverse Reaction

Local – Conjunctival hyperemia, burning, tearing, blepharoconjunctivitis, adrenochrome deposits on conjunctiva, cornea and lids, ocular pemphigoid, lacrimal punctal stenosis, epidermalisation of puncta, lacrimal stones, corneal epithelial edema, endothelial toxicity, mydriasis and angle closure, visual distortion/blurred vision, photophobia, oedema of the macular area of retina particularly in aphakic patients (epinephrine maculopathy).

Systemic – Increased heart rate (palpitation), increased blood pressure, cardiac arrhythmia, headache, anxiety, nervousness, tremors, cerebrovascular accident, myocardial infarction and death.

Dipivefrin Hydrochloride

It is pro-drug of epinephrine. It penetrates better (17 times) than epinephrine (more lipid solubility). Within the cornea, dipivefrin is bio-transformed into epinephrine by the esterase enzyme. Because of increased corneal penelration, there are less chances of systemic absorption, and hence systemic side efl'ects are less with dipivefrin as compared to epinephrine (can bc safely used in patients with cardio-vascular disorders).

Mechanism of Action and Indication

- Same as Epinephrine.

Dosage

- Ophthalmic solution 0.1 per cent
- Given 1 drop 2 times/day

Adverse Reaction

- Burning/stinging sensation
- Follicular conjunctivitis

26.3.4 Carbonic Anhydrase Inhibitors

These are the drugs that inhibit carbonic anhydrase.

Mechanism of Action

Carbonic Anhydrase inhibitors decrease aqueous humour production by direct and indirect mechanisms. The direct action involves the inhibition of ciliary epithelial carbonic anhydrase with reduced bicarbonale movement (which is linked to the movement of sodium ions and water) from the plasma into the posterior chamber and hence reduced aqueous production. The indirect action involves interference with the buffer action of carbonic anhydrase, thus indirectly decreasing aqueous production.

Acetazolamide

Indication

- Primary open angle glaucoma
- Secondary glaucoma
- Congenital glaucoma
- Pre-operatively to reduce Intra-ocular Pressure
- Acute glaucoma

Dosage

Oral: Tablet –125 mg and, 250 mg given 3 to 4 times/day

Sustained Release Capsule –250 mg and 500 mg given once daily

Adverse Reaction

Systemic side effects are common due to dehydration and metabolic acidosis. Paresthesias and urinary frequency are virtually universal. Metallic taste, abdominal cramps, nausea, vomiting, diarrhoea or constipation can occur. Nocturia, hypersensitivity nephropathy, urolithiasis, renal colic, hematuria, anuria may be seen. Drowsiness, excitement, increased intracranial tension, vertigo, headache, insomnia, tremors, depression and imitability have been reported. Fatigue, malaise, weight loss, anorexia, decreased libido may be reported. Exfoliative dermatitis, alopecia, hirsuitrism, Steven Johnson syndrome are also seen occasionally. Thrombocytopenia, agranulocytosis and aplastic anemia are rarely seen.

Dorozolamide

Topical carbonic anhydrase inhibitor.

Inhibits carbonic anhydrase enzyme in the ciliary body, by which it decreases aqueous humour production. As systemic absorption is less through this route, most of the side effects associated with systemic use are reduced with dorozolamide.

Indication

- Primary open angle glaucoma
- Secondary open angle glaucoma
- Angle closure glaucoma

Dosage

- Ophthalmic solution (2 per cent) 1 drop 2 times/day.

Adverse Reaction

- Ocular burning/stinging

26.3.5 Alpha Adrenergic Agonists

The drugs which are alpha adrenoceptor agonists are as below:

Brimonidine Tartrate

It is a selective alpha-2 receptor agonist.

Mechanism of Action

- Decrease in aqueous production
- Increase in uveoscleral out Flow (extra-canalicular pathway)
- It is a neuro-protective agent. It protects the nerve fibres from damage because of raised intra-ocular pressure.

Indication

- Primary open angle glaucoma
- Ocular hypertension
- Used to control the post Yag laser capsulotomy rise of IOP

Dosage

- Ophthalmic solution 0.2 per cent -0.5 per cent
- 1 drop 2 times/day

Adverse Reaction

- Burning
- Stinging
- Allergic Reaction
- Systemic— dry mouth, fatigue, reduction of systolic BP

Apraclonidine

It is a selective alpha-2 adrengic agonist.

Mechanism of Action

- Decreased aqueous humour production.
- Increased aqueous production.
- Reduced episcleral venous pressure.

Indications

Specifically used to check intra-ocular pressure rise following laser surgery.

Dosage

- Ophthalmic solution 0.5 per cent and 1 per cent
- 1 drop 1 hour before laser surgery and 1 drop immediately after laser surgery.
- Otherwise usecl bd/tds

Adverse Reaction

Local – Upper lid elevation (1-2 per cent of case)
Burning, Itching
Conjunctival blanching
Mydriasis
Follicular conjunctivitis

Systemic – Gastrointestinal reactions
Bradycardia
Insomnia
Dry nose and mouth

26.3.6 Prostaglandins

Various prostaglandins used in glaucoma management are as below:

Latanoprost

Mechanism of Action

Increases uveoscleral out flow by relaxation of ciliary muscle and loss of extracellular material from among the ciliary muscle. It is one of the most potent antiglaucoma drugs.

Indication

- Open angle glaucoma
- Ocular hypertension

Dosage

Ophthalmic solution-0.005 per cent, 1 drop in the affected eye once daily preferably in the evening.

Adverse Reaction

- Burning, irritation
- Conjunctival hyperemia
- Increased iris pigmentation
- Punctate epithelial keratopathy
- Aqueous cells and flare
- Miosis

Bimatoprost

Mechanism of Action

Increase in uveoscleral outflow.

Indication

- Open angle glaucoma
- Ocular hypertension

Dosage

Ophthalmic solution 0.03 per cent 1 drop daily preferably at night time.

Adverse Reaction

- Iris pigmentation
- Hypertrichosis

Unoprostone

Mechanism of Action

Increases uveoscleral outflow. It has no effect on aqueous humour production.

Indication

Open Angle Glaucoma and Ocular hypertension not responding to other antiglaucomatous agents.

Dosage

Ophthalmic solution 0.15 per cent, once daily dose.

Adverse Reaction

- Iris pigmentation
- Irritation
- Conjuntival hyperemia

Travoprost

Mechanism of Action

Increase uvea-scleral outflow.

Indication

- Open angle glaucoma
- Ocular hypertension

Dosage

Ophthalmic solution 0.004 per cent 1 drop once or twice daily

Adverse Reaction

- Hyperemia
- Iris pigmentation
- . Foreign body sensation

26.3.7 Hyperosmotic Agents

Hyperosmotic agents decrease intra-ocular pressure mainly by increasing osmolarity of plasma.

Mechanism of Action

Hyperosmolar agents increase the osmolarity of plasma, leading to absorption of water from ocular tissues. In addition, they may act by the central pathway by involving osmo-receptors in the hypothalamus, thus decreasing aqueous production. Hyperosmotic agents cause immediate reduction in intra-ocular pressure. When the intra-ocular pressure is very high and needs immediate control, hyperosmotic agents are the drug of choice.

- Oral hyperosmotic agent – Glycerine
- Intravenous hyperosmotic agent – Mannitol

Glycerine

50 per cent solution, given orally in a dose 1-1.5 g/kg body weight.

Mannitol

20 per cent concentration is used, 1-2 g/kg body weight given intravenously over a period of 30-45 minutes at a rate of 1 drop per second.

Adverse Reaction

- Systemic hypertension particularly with mannitol use.
- Increased urination and 'urinary retention
- Cardiac failure
- Electrolyte imbalance

Check Your Progress

1) Name at least five antiglaucoma drugs.

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2) Classify antiglaucoma medications.

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26.4 LET US SUM UP

In this unit you have studied various antiglaucoma agents used in ophthalmology, their classification, mode of action, uses, contraindications and adverse reactions.

You know that in the last decade, antiglaucoma therapy has undergone revolution. A number of new potent ocular hypotensive agents are now available commercially for the effective and better medical management of all type of glaucomas. These new ocular hypotensive drugs have excellent efficacy with least side effects. They are highly effective in lower doses and lower concentration making the compliance of patients more treatment oriented and practical.

In next unit you will study various anti-inflammatory and anti-allergy drugs used in ophthalmology with their full details.

26.5 ANSWERS TO CHECK YOUR PROGRESS

1) Pilocarpine, Betaxolol, Dorzolamide, Latanoprosl, Glycerol.

2) Classification of commonly used antiglaucoma agents:

i) Beta Blockers
- Timolol maleate
- Betaxolol hydrochloride
- Levobunolol hydrochloride

ii) Cholinergic Agents
- Pilocarpine

iii) Sympathomimetics
- Epinephrine borate, bitartarate, hydrochloride
- Dipivalyl epinephrine

iv) Carbonic Anhydrase Inhibitors
- Systemic- Acetazolamide
  Methazolamide
- Local-Dorozolamide hydrochloride

v) Alpha-adrenergic Agonists
- Apraclonidirie
  Brimonidine tartarate

vi) Prostaglandins
- Latanoprost
- Bimatoprost
- Unoprostone
- Travoprost

vii) Hyperosmotic agents
- Intravenous—Mannitol
- Oral—Glycerine