International Journal of PharmTech Research
CODEN(USA): IJPRIF ISSN : 0974-4304
Vol.1, No.3, pp 863-869, July-Sept 2009

MEDICAL MANAGEMENT OF GLAUCOMA: AN OVERVIEW

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ABSTRACT: The eye is considered one of the greatest gifts of God. History of diseases is as old as the civilization of human being. Various chronic eye diseases required urgent attention like glaucoma, keratoconjuctivitis sicca, diabetic retinopathy, macular degeneration etc. Glaucoma constitutes a diverse group of disorders characterized by optic neuropathy associated with field changes in which intraocular pressure (IOP) is one of the risk factors. Numerous other risk factors have been reported.
Management of all glaucoma is initiated with medical therapy. The aim of the therapy is to give complete relief to the patient. Attempts should be made to brig down the IOP to a level that will prevent further progress of damage. To achieve this, a pressure is set which is referred as target pressure i.e. approximately 19-22 mmHg, which is supposed to be the safe pressure for the patient. Though there is no single IOP level that is safe for every patient, there is aim to achieve at least 30% reduction from the initial pressure. Other therapeutic concepts are surfacing now which might prove revolutionary in future (drugs increasing optic nerve head blood flow and neuroprotective agents).
It is important in the medical management of glaucoma to understand not only the aim of the therapy, but also the mechanism of action, interactions, contraindications and side effects of individual drug. Every year March 6 is observed as World Glaucoma day.
Key words: Glaucoma, Treatment of glaucoma, medical management of glaucoma

INTRODUCTION

Worldwide, glaucoma "silent thief of the sight" is the leading cause of irreversible blindness. Most of the type it causes no pain and produces no symptoms until it becomes fetal and caused blindness. Of the 37 million people across the globe are blind due to glaucoma and in India 1.2 lakh blind patients add every year due to this menace. Ocular disorder characterized by pressure within the eyeball caused by an excessive amount of aqueous humor. This causes pressure against the optic nerve and compression of the blood vessels of the eye, the resulting impairment of vision ranges from slight abnormalities to total blindness. Glaucoma, progresses undetected until the optic nerve has already been irreversibly damaged, with varying degrees of permanent vision loss. Chronic open-angle glaucoma is the result of impeded drainage of aqueous humor. In acute angle-closure glaucoma, the anterior chamber of the eye is shallower and the iris may obstruct the meshwork at the entrance of the Canal of Schlemm. Although glaucoma is a leading cause of blindness, can be prevented by using eye drops, laser treatment or surgery if detected at an early stage.
Chronic glaucoma begins gradually over a period of months or years, usually in patients over the age of 40. There are no symptoms in the early stages, and the condition can be detected only by measurement of the intraocular pressure. Such an examination is recommended every three years for all persons over the age of 20. As the disease progresses, often the only symptom is a gradual loss of peripheral vision. Chronic glaucoma can usually be controlled with eye drops or pills that increase the outflow or decrease the production of aqueous humor; laser treatment is also effective in the early stages. If treatment is continued throughout life, useful vision will be preserved in most cases; untreated individuals will gradually become blind.
Acute closed-angle glaucoma, which accounts for only 10% of the incidence of the disease, begins abruptly with severe pain and blurred vision. It is a medical emergency that causes permanent blindness in two to five days if left untreated. Surgery is usually necessary.
Key risk factors includes: high blood pressure, family background and regional prevalence etc. High-risk groups include everyone with a family history of glaucoma, everyone over the age of 60 and any Black over the age of 40.
As many as half of the individuals with glaucoma, however, may not know that they have the disease. The reason they are unaware is that glaucoma initially causes no symptoms, and the loss of vision on the side (periphery) is hardly noticeable[1].

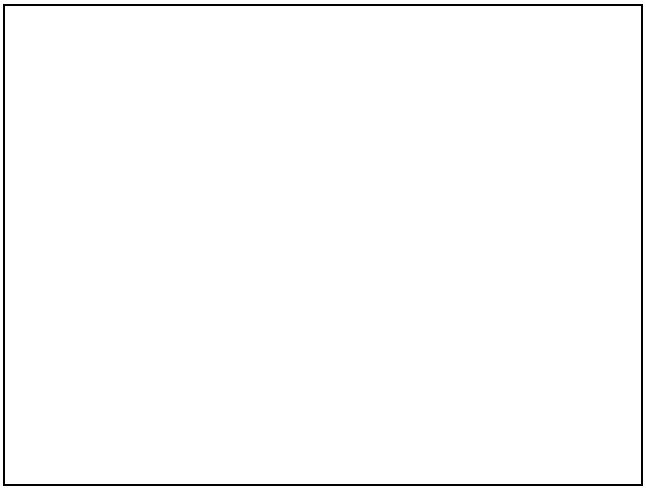

Figure: 1: Glaucoma is a condition of increased fluid pressure inside the eye. The increased pressure causes compression of the retina and the optic nerve that can eventually lead to nerve damage. Elevated pressure in the eye is the main factor leading to glaucomatous damage to the eye (optic) nerve.

(Figure: 1) The optic nerve, which is located in back of the eye, is the main seeing nerve for the eye. This nerve transmits the images we see back to the brain for interpretation. The eye is firm and round, like a basketball. Its tone and shape are maintained by a pressure within the eye (the intraocular pressure), which normally ranges between 8 and 22 mmHg. When the pressure is too low, the eye becomes softer, while a too high pressure causes the eye to become harder. It turns out that the optic nerve is the most susceptible part of the eye to high pressure because the delicate fibers in this nerve are easily damaged[2].

Before starting the treatment[3]:

1. Assess each eye individually while deciding the most appropriate therapy.
2. It is essential to involve patients as informed partners in making decisions regarding the management of their condition.
3. In order to avoid inconvenience and high cost to the patient and side effects, the least number of drugs, to achieve the therapeutic response should be a consistent goal.
4. A therapeutic medical trial on one eye first is a useful trial, although it is not always practically feasible.

Classification of drugs used in glaucoma management[4-6]:

I. Autonomic agents
(A.) Cholinergics (parasympathetic)
(B.) Adrenergics (Sympathetic)
II. Carbonic anhydrous inhibitors (CAI)
III. Prostaglandins
IV. Prostamides
V. Docosanoids
VI. Hyperosmotic agents

I. AUTONOMIC AGENTS

(A.) CHOLINERGICS (parasympathetic)

Parasympathetic innervations of anterior ocular segment

1. The anterior segment of the eye receives its parasympathetic innervations from the inferior oblique branch of III cranial nerve (preganglionic) via ciliary ganglionic via short ciliary nerve (postganglionic).

   Distribution of nerve fibers: (a) Ciliary muscles (97%), (b) Sphincter pupillae (3%)
2. VII cranial nerve innervates lachrymal gland, orbital arteries and intraocular tissue.

Physiological mediator of parasympathetic system is acetylcholine which is inactivated by enzyme cholinesterase. Acetylcholine stimulates two types of receptors, which are muscarinic and nicotinic. Muscarinic receptors are present in smooth muscles of eye[6].

Classification of parasympathetic drugs:

Direct acting cholinergic drugs

i. Choline esters: acetylcholine, carbachol (1.5%, 3%)
ii. Noncholine esters: pilocarpine (1%, 2%, 4%), aceclidine (2%)

They are not degraded by cholinesterase.

Indirect acting (anti-cholinesterase agents)

Physostigmine, ecothiophate iodate

Effects on eye: Accommodative myopia, Miosis, Increase aqueous outflow and Increase lachrymal secretion

OCULAR CHOLINERGIC AGENT

Only ocular cholinergic agent used for therapeutic purpose is pilocarpine. It is obtained from plant *pilocarpus microphyllus*. It is available as 1-4% solution for clinical use as nitrate or hydrochloride salt. It is also available as an ointment which is to be used at bed time[7].

Mechanism of action: Concentration of ciliary muscles→ tension on scleral spur→ traction of trabecular mesh work→ increase aqueous outflow.

Lowers IOP in one hour and action lasts for 6-8 hours. Therefore given 3-4 times daily as 2% solution.

Contraindications: Angle recession glaucoma, malignant glaucoma, inflammatory glaucoma, neovascular glaucoma and congenital glaucoma.

To be used carefully in young patients (<40 years age) because of induced myopia, patient having previous history of retinal detachment, in myopic patients because it can cause/ predispose a patient for development of detachment and patient with angle closure glaucoma in absence of a patient iridotomy[5].

Side effects

(a) Ocular

1. Decrease vision because of miosis and accommodative myopia. Accommodative myopia can also give rise to headache.
2. Increase permeability of blood-aqueous barrier leading to inflammation.
3. Retinal detachment mainly in myopic's, aphakic's and in patient's with lattice degeneration.
4. Cataract mainly anterior subcapsular (usually seen with anticholinesterase drugs).
5. Paradoxical increase in IOP because of precipitation of angle closure.
6. Others: irritation, burning sensation and lachrymation.

(b) Systemic

Rarely seen with presently recommended doses (if dose is > 100 mg). There can be intestinal cramps and bronchospasm. These side effects mainly seen when these drops were administered at very frequent intervals in patients with acute angle closure glaucoma. They are rarely seen in dosage of 3-4 times/day.

(B.) ADRENERGICS (SYMPATHETIC)

Sympathetic innervation of eye is via superior cervical ganglion. Neurohumeral transmitters of sympathetic system are called as catecholamines which are:

1. Adrenaline(Epinephrine)
2. Noradrenaline (Norepinephrine)
3. Dopamine

They stimulate two types of receptors which are alpha (α-1 and α-2) and beta (β-1 and β-2). Adrenaline stimulates both alpha and beta receptors and noradrenaline stimulates mainly alpha receptors. Adrenaline administered in concentration range of 0.25% and 2.0% and must be instilled three times a day.

Despite the fact that sympathetic agents have been used in the treatment of glaucoma, we still lack a complete understanding of sympathetic control of aqueous humor dynamics and mechanism by which sympathetic agents reduce IOP. In fact this subject continues to generate great controversy. In general sympathetic agents act by direct combination with receptors located in cell membrane[6].

The sympathetic agents used for management of glaucoma are:

1. Non selective agonist (both α and β): dipivefrine 0.1%, epinephrine 0.25-2% ophth soln.
2. α-2selective agonist: clonidine0.125%-0.5% apraclonidine 0.5-1%, brominidine 0.2% ophth soln.
3. Non selective β- antagonist (β-blockers): timolol 0.25-0.5% ophthalmic soln and gel, levobunolol 0.25-0.5% ophth soln, carteolol 0.5%,1.0%, 2.0% ophth soln, pindolol, carteolol 1 and 2% ophth soln, metipranolol 0.1,0.3 and 0.6% ophthalmic soln.
4. Selective β-1 antagonist: betaxolol, 0.25 and 0.5%as ophth solution and suspension.

Non selective agonist (both α andβ): Dipivefrine 0.1%, Epinephrine 0.25-2%

The clinical use of epinephrine (adrenaline) is limited because of its side effects and therefore, to enhance the corneal penetration and to decrease toxicity, dipivephrine, a prodrug, which is more lipophilic than epinephrine is, used whose passage through cornea is facilitated 17 times. This compound is hydrolyzed to epinephrine after getting absorbed in to the eye.

Mechanism of action:

1. increase aqueous outflow
   a.) from trabecular pathway
   b.) from uveoscleral pathway
2. decrease aqueous production

The action starts in one hour, peaks in 4 hours, and lasts for 12-24 hours. The average fall of IOP is 20-24%.tachyphylaxis is rare. The recommended dose is twice daily.

Dose response: optimal dose strength is 0.1%, balancing significant efficacy with minimal mydriasis, 0.1% dipivephrin being equally effective to 1% ephinephrine, suggesting a 10:1 potency relationship. There is no significant difference between 0.1 and 0.25% concentrations. Since betaxolol has selective β-1 action, it does not block the effect of epinephrine; a combination of betaxolol with epinephrine has an ocular hypotensive effect similar or better than a combination of timolol with epinephrine.

Indications: it is used as a first line drug. It is used as an additive agent in cases of primary open angle glaucoma (POAG), angle closure glaucoma with a patent iridotomy and some secondary glaucoma.

Contraindications: to be used with caution in patients with occludable angle and aphakic and pseudophakic patients as it may produce CME.

To be used with caution in patients with cardiac problems and patients on tricyclic antidepressants and MAO inhibitors.

Side-effects: (a) **Ocular-** rare with dipivefrine as compared to epinephrine. The most common is reactive hyperaemia i.e. an initial vasoconstriction followed by vasodilation. There is a high incidence of local allergic reactions also. Mydriasis, blurring of vision and cystoid macular edema have also been reported.

(b) Systemic- these effects are less acute than with epinephrine. It can cause tachycardia, cardiac arrhythmias, hypertension and headache.

α-2 selective adrenergic agonist: Apraclonidine 0.5-1%, Brominidine0.2%

Apraclonidine 0.5-1%: apraclonidine use is limited because of high incidence of local allergic reactions (seen in 50% of patients with chronic use) and tachyphylaxis

(33%) and other side effects. apraclonidine 0.5% is used for chronic management of glaucoma and apraclonidine 1% is useful for short term treatment of IOP elevation in patients undergoing anterior segment laser procedures. It is used only when patients is unable to tolerate other anti-glaucoma drugs.

Brominidine0.2%: brominidine0.2% is more than 1000 times more selective for the α-2 over the α-1 receptors and 28 times more selective for α-2 receptors than apraclonidine. Low activity of alpha-1 receptor means brominidine should have less vasoconstriction and mydriasis.

Mechanism of action: dual mechanism of action: 1. decrease aqueous production 2. Increase uveoscleral outflow

The mechanism of action starts in 30 minutes and peak effect occurs in two hours with trough at 12 hours. There fore, the recommended dose is 2-3 times daily depending on the mid-day spike of IOP. The IOP lowering efficacy is 15-30%. Evidences from animal studies have suggested its neuroprotective role for optic nerve. However, neuroprotection in human has not yet been proved.

Dose response: the 0.2% formulation demonstrated the best combination of efficacy and safety for long term use and 0.5% was chosen to reduce the number of IOP spikes that occur after argon laser trabeculoplasty.

Safety: Brominidine can be used safely in patients with bronchial asthma and systemic hypertension. They have minimal effect on cardiovascular parameters but should be used cautiously in patients with severe cardiovascular diseases. No tachyphylaxis has been reported.

Side-effects: (a) **Local:** burning, foreign body sensation and ocular allergy (12-13%) lower ocular allergy compared to apraclonidine is because of its oxidative stability.

(b) Systemic: headache, dry mouth, depression and anxiety, fatigue, drowsiness and hypotension are rarely seen. They should be used cautiously in patients receiving tricyclic antidepressants and MAO inhibitors. It should also be used with caution in pediatric patients as apnoea has been reported.

Non selective β- antagonist: Timolol 0.25-0.5%, Levobunolol 0.25-0.5%

Timolol 0.25% and 0.5%:

It is a milestone in ocular pharmacology since 1978 and it has been a gold standard in medical treatment of glaucoma since then. It has minimal intrinsic sympathomimetic activity and membrane stabilizing property[7].

Mechanism of action: Timolol decreases aqueous production. Action starts in 30-60 minutes, peaks at 2 hours and lasts for 12-24 hrs. Dose given as two times a day. It is believed that aqueous production is below baseline in night, so it is not so effective in night hours. It reduces IOP by approximately 25-30% and has minimal cross over effect[8].

Efficacy: Timolol have short term escape because increase number of β-receptors (?) therefore it is good clinical practice to wait approximately for one month after initiating timolol to determine the efficacy of therapy because it has been determine the efficacy of therapy because it has been demonstrated that the number of β-receptors in ocular tissues increases during the first few days of timolol therapy which is known as short term escape. It can also have long term drift because of adaptation of ciliary body to timolol usually beginning three month to one year after starting treatment hence long term follow-up is also a must[9].

Side-effects:

(a) ocular

1. local irritation
2. dry eye because of decrease in goblet cell density
3. corneal anesthesia
4. allergic reaction (rare)

(b) systemic

Systemic side effects are more common than local side effects. Systemic absorption occurs from the nasolachrymal mucosa and can cause following side effects.

1. Exacerbation of bronchial asthma: mainly in patients with asthma, COPD and chronic bronchitis. Few cases of death have also been reported because of status asthmaticus following use of timolol in patients with asthma.
2. Cardiovascular: decrease heart rate and myocardial contractility, hypotension and arrhythmias. Therefore it should be used carefully in patients with congestive heart failure, heart block, fibrillation or infarction and patients on oral calcium antagonist and digitalis. Worsening of angina has also been reported.
3. CNS: fatigue, depression, anxiety, mood swinging, lethargy, impotency and even suicidal tendencies.
4. Lipid profile: decreases high density lipoproteins and increase low density lipoproteins.
5. Blood glucose: no effect in normal individuals but can mask symptoms of hypoglycemia in diabetic patients.
6. Myasthenia gravis: timolol can cause exacerbation in this condition.
7. timolol may mask the sign of hyperthyroidism (e.g. tachycardia)

Systemic side-effects can be minimized by applying finger pressure to inner corner of the eye to occlude the lachrymal passage or closing the eye for two minutes.

Levobunolol 0.25-0.5%

Effects are similar to timolol but it has no intrinsic sympathomimetic or membrane stabilizing property. levobunolol 0.25-0.5% has a longer duration of action as compared to timolol[7].

Selective β-1 antagonist: Betaxolol 0.5%

This category is less effective than non-selective β-1 blockers (15 to 20% efficacy)

Mechanism of action: betaxolol decreases aqueous production. The dose recommended is 0.5% twice daily.

Side-effects: (a) local: - same as nonselective β-blockers but compared to non-selective β-blockers more burning and stinging have been reported.

(b) Systemic: - same as nonselective β-blockers but can be used relatively safely in patients with respiratory diseases.

Note: β-1 selectivity is not 100%. Betaxolol can block β-2 receptors also but with less affinity than timolol. Bronchial asthma can be precipitated or aggravated in some patients with betaxolol. This should be explained to the patients and betaxolol should be discontinued if this happens.

II. CARBONIC ANHYDROUS INHIBITORS (CAI)

Classification

1. Oral: Acetazolamide (250-1000mg/day), methazolamide (50-100mg p.o. bid in divided dosage), dichlorfenamide (50mg p.o. bid-tid)
2. Topical: Dorzolamide 2%, Brinzolamide 1%
3. Topical in combination with β-blockers: Dorzolamide 2% with Timolol 0.5%.

1. Oral CAI: Acetazolamide

Mechanism of action: CAI decreases aqueous production by decreasing the formation of bicarbonate ions.

$$CO_2 + OH \overset{CA}{\longleftrightarrow} HCO^-_3$$

A significant physiological response requires greater than 99% decrease in carbonic anhydrase (CA) in target tissue. CA is found in RBC's, Kidney, lungs, GIT, CNS and various secretory tissues. In eyes it is found in corneal endothelium, ciliary epithelium and retina (muller cells and RPE). There are seven isoenzymes of CA. CA II (isoenzyme C) is predominant in ciliary epithelium. Membrane bound CA IV is also present in nonpigmented epithelium[8].

Oral medication decreases IOP in one hour and peak occurs in 2-4 hours. Actions last for 6-8 hours. With intravenous administration, peak reaches in 10-15 minutes. Dose is 125 mg BD to 250 mg QID or 500 mg SR 1-2 times daily. IV dose is 5 mg/kg. It decreases aqueous production by 20-40%. Pretreatment with loading dose has significant additional decrease in IOP by 1.5 to 3 mmHg. Plasma level of more than 10 μg/ml does not correlate with additional pressure reduction[6].

Adverse effects: more commonly observed in elderly patients

Systemic effects: 50% of the patients develop intolerable side effects.

i. Malaise Complex (most common) generalized malaise, fatigue, weight loss, depression, anorexia and loss of libido.
ii. GIT: distress with nausea, epigastric burning, abdominal cramps and diarrhea.
iii. Paresthesia of extremities.
iv. Transient urinary frequency. There is increase incidence of urolithiasis.
v. Blood discrasias (most lethal): Aplastic anemia mainly within six months of therapy. It is idiosyncratic.
vi. Respiratory acidosis: especially in diabetics, corticosteroids and on digitalis
vii. Cross reaction in patients allergic to sulpha drugs.
viii. Interaction with salicylates because of competitive binding to plasma proteins.
ix. Rarely teratogenicity is reported.

Ocular side effects: Ocular side effects are rare. Rarely transient myopia and a choroidal detachment leading to angle close glaucoma have been reported mainly related to sulphonamide related idiosyncratic reactions.

To be used with caution in patients with history of sulpha allergy, in patients with kidney or liver dysfunction, patients with low potassium level and in patients with hyperchloremic acidosis.

2. Topical CAI: Dorzolamide 2%, Brinzolamide 1%

Mechanism of action: it decreases aqueous production by inhibiting CA II enzyme. Peak action starts in two hours and trough is reached in 12 hours therefore should be given in dose of 2-3 times daily. It decreases IOP by 18-22%. The drug is excreted unchanged in urine. IOP lowering efficacy of topical CAI's is half that of oral CAI's. The concomitant use of topical and oral CAI is not additive and not recommended.

Side effects: rarely produces systemic side effects. They should be used carefully in patients allergic to sulpha drugs and patients with renal impairment.

Local side effects are stinging, burning (due to low pH i.e.5.6), bitter taste, SPK, blurred vision, transient myopia. Contact lenses should be removed before instilling the drop and reinserted 15 minutes later.

Brinzolamide 1% is given 2-3 times daily as suspension form therefore has lower incidence of ocular discomfort (neutral pH i.e.7.5) but efficacy is similar to dorzolamide 2%.

III. PROSTAGLANDINS (latanoprost 0.005%, travoprost 0.004%)

Prostaglandins are 20 carbons chain biologically active products of arachidinic acid. The enzyme cyclooxygenase (COX) converts arachidonic acid to prostaglandin[10].

The drug available in this group for commercial use is latanoprost 0.005%. It is isopropyl ester a prodrug which is per se inactive but after hydrolysis to acid of latanoprost becomes active. It is hydrolyzed during its passage through cornea. Other drugs available are unoprost 0.12%, bimatoprost0.03% and travoprost 0.004%[11].

Mechanism of action: it is selective FP receptor agonist and does not cause a breakdown of blood-aqueous barrier. It comes in contact with prostaglandin receptors, causing ciliary muscle cells to produce matrix metalloprotienases, which in turn induce degradation and remodeling of collagen in between muscle bundle in ciliary muscle and decreases IOP by increasing the uveoscleral outflow. It decreases IOP by 25-32%. Its action lasts for more than 24 hours therefore given as once daily preferably at bed time. Action start in 3-4 hours and maximum effect is in 8-12 hours. No tachyphylaxis has been reported. Use of pilocarpine with

prostaglandins is controversial (pilocarpine causes contraction of ciliary muscles whereas latanoprost reduces the resistance around the muscle fibers) [12].

Side-effects: systemic adverse effects are rare as it is rapidly metabolized.

Ocular side effects:

i. Increases iris pigmentation: this is the most serious side effect which is due to prostaglandin induced dispersion of melanin pigment. Light colored eyes are more likely to change color.

ii. Increase in length of eyelashes with darkening and thickening of eyelashes and periocular skin pigmentation.

iii. Conjuctival hyperaemia and punctuate epithelial keratopathy.

iv. Rarely it can cause iritis and hypotony in eyes with multiple risk factors.

v. Herpes simplex keratitis recurrence can be precipitated.

It should be used with caution in children, inflammatory conditions, NVG, congenital glaucoma, patients with light pigment iris pseudophkia, uveitis and drops containing thiomersal as preservative (if such drugs are used they should be administered with an interval of at least five minutes).patients wearing contact lenses should remove it before instilling the drop and may reinsert it after 15 minutes. It should be stored at temperature of 2 to 8º C. once open the container should be used within four to six weeks and may be stored at room temperature up to 25º C[10].

IV. PROSTAMIDES (bimatoprost 0.03%)

It belongs to group of agents lowering IOP known as prostamides. Their mechanism of action is similar to that of latanoprost except that it acts on different receptors, efficacy, indications, contraindications and side effects are almost similar to latanoprost. It is indicated to reduce IOP in patients with primary open angle glaucoma and ocular hypertension. It has not been evaluated in treatment of angle closure, inflammatory or neovascular glaucoma. It is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product[10].

Side-effects: conjuctival hyperemia, growth of eyelashes and ocular pruritis (15-45%). Approximately 3% of patients discontinue therapy due to conjuctival hyperemia. Iris pigmentory changes are less as compare to latanoprost.

Studies comparing bimatoprost with timolol and has shown its superiority in controlling diurnal IOP. Unlike latanoprost, bimatoprost is not a prodrug, and no refrigeration is required to storage. There is no restriction of six weeks shelf-life after opening the drops as in case of latanoprost. Bimatoprost is able to achieve considerable lower target IOP in most patients[11].

V. DOCOSANOIDS (unoprostone isopropyl 0.12%)

It reduces IOP less than prostaglandins' analogs. It is applied twice daily in a 0.155 concentration. Several studies shows unoprostone might have a neuroprotective and endothelin-antagonizing effect. Adverse reactions are less frequent than with prostaglandins' analogs[12].

VI. HYPEROSMOTIC AGENTS

1. Oral agents: glycerol(Glycerin) 1-2 g/kg/ dose PO
2. Intravenous agents: Mannitol 20%: 1-2 g/kg IV infusion over 30-60 min

Mechanism of action:

i. Increases plasma osmolality (20 to 30 mOsm/L) this leads to withdrawal of fluid from vitreous (3-4% i.e. 0.12-0.16 ml).

ii. Posterior movement of lens iris plane.

iii. Central action (via hypothalamus)

Indications:

i. In acute angle closure attacks.

ii. Very high pressure glaucomas like neovascular glaucoma, traumatic glaucoma, malignant glaucoma, lens induced glaucoma and some time before combined procedure[13].

1. Oral agents: Glycerol

Dose: 1-1.5 gm /kg body weight (two tablespoons t.i.d.). When given orally drops in IOP usually begin within 10 minutes and is maximum in 30 minutes and the effect lasts for four to five hours. The addition of lemon or orange juice with ice makes it more palatable[14].

Note: when given intravenously in saline it causes hematuria due to severe vasoconstriction of glomerular arterioles, hence contraindicated.

Metabolism: rapidly absorbed through GIT and distributed in extracellular space and metabolized in liver (therefore less diuresis).

Side effects:

i. Unpalatable sweet taste which leads to nausea and vomiting.

ii. Increase chance of hyperglycemia and ketosis in diabetic patients. Therefore should be used carefully in diabetics.

2. Intravenous agents: Mannitol

Dose: 1-1.5 gm/kg body weight of 10-20% solution. It is given i.v. over a period of 30-45 minutes. Onset of action starts in 10-30 minutes with peak action in 30-60 minutes and the action lasts for six hours[15].

Metabolism: rapidly absorbed through GIT and is confined to extracellular space and excreted unchanged in urine.

Side-effects:

1. Patient with compromised renal or cardiac function may develop circulatory overload with chest pain, pulmonary edema, CCF and intracranial hemorrhage.

2. Tendency for developing crystals, therefore we should warm the solution before use.
3. Headache, giddiness, confusion, chills, fever and anaphylactic reaction may develop.

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