Ocular Pharmacology

68

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Abstract

Ocular Pharmacology deals with the treatment of ocular disorders by administering drugs through the eye or systemically. Various pharmacokinetic considerations and proper understanding of the anatomy of the eye are needed. It is important to properly select a drug formulation, account for drug absorption through various structures in the eye, local drug metabolism, and possible systemic spread following ocular administration. This chapter discusses the various drugs used in various conditions including infections, cancers, allergies, glaucoma. Certain systemically administered drugs can result in ocular toxicity. A brief note of these is also made.

Keywords

Ocular pharmacology · Glaucoma · Ocular toxicity

68.1 Pharmacokinetic Considerations

68.1.1 Drug Formulation

Since the amount of drug absorption is proportional to the amount of time the drug remains over the surface of the eye and below the eyelids, various formulations have been developed.

They include ointments (e.g., penicillin), gels (e.g., pilocarpine), ocular inserts (e.g., ganciclovir), and collagen shields.

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68.1.2 Absorption into the Eye

- The rate of drug absorption is determined by the time the drug is present and available for absorption in the palpebral space. The drug absorption is directly proportional to its concentration in the tear film as the tear film is in contact with the absorptive surfaces of the cornea.
- Factors that help in increasing absorption into the eye include corneal and conjunctival suffusion, binding to tear proteins. Factors that decrease absorption into the eye include elimination by the drainage into nasolacrimal duct, drug metabolism by tear and tissue proteins.
- Drug absorption can be increased by blocking the nasolacrimal ducts by silicon plugs.
- Alternatively, closing the eyes for 10–15 min after drug administration reduces nasolacrimal drainage by reducing the suction pressure by the lacrimal apparatus.
- Nasolacrimal drainage increases the systemic absorption of the drug and results in increased toxicity.
- The drug absorption through the corneal surface has to pass through the layers of the cornea. The layers of the cornea vary in hydrophilicity. The outer epithelium and the inner endothelium are hydrophobic while the central stroma is hydrophilic. Hence drugs must have both lipophilicity and hydrophilicity to achieve optimal absorption rates into the eye.
- Certain drugs may not be absorbed because of the ionic nature of the drug. This can be circumvented by administering the ester formulation of the drug with more lipophilicity.

68.1.3 Distribution

- Systemic distribution of drugs administered for ophthalmic purposes increases the side effects and toxicity.
- As the drugs reach the nasal mucosa through the drainage via the nasolacrimal duct, due to high vascularity and the increased surface area, systemic absorption is maximum. Further, drugs absorbed through the nasal mucosa do not undergo any first pass metabolism.
- Drug binding to proteins within the eye can affect its actions. Drugs like the alpha agonists bind avidly to melanin and hence, its action is slower in patients with higher melanin content in their iris.
- Accumulation of certain drugs in the retinal pigment epithelium is responsible for the long-term toxicity of some of the drugs like chloroquine. Chloroquine accumulation in the retinal pigments causes bull's eye maculopathy.

68.1.4 Metabolism

- Various enzymes are present in the ocular tissues which degrade drugs as they are absorbed into the eye.
- The esterases break down the prodrugs thus activating the parent drug in the eye.
- Use of a drug with local anaesthetic effect must be avoided as it predisposes the patient's cornea for microabrasions leading to corneal ulceration.

68.2 Chemotherapeutic Drugs in the Eye

68.2.1 Bacterial Infections (Box 68.1)

Box 68.1 Antibiotics Used in Bacterial Infections and Various Infective Conditions of the Eye

Antibiotics	Conditions requiring antibiotic therapy
Macrolides	Conjunctivitis
Erythromycin	Dacryoadenitis
Azithromycin	Dacryocystitis
Aminoglycosides	Hordeolum
Gentamicin	Blepharitis
Tobramycin	Conjunctivitis
Sulfonamides	Keratitis
Sulfacetamide	Endophthalmitis
Fluoroquinolones	Panophthalmitis
Ciprofloxacin	
Ofloxacin	
Levofloxacin	
Moxifloxacin	
Besifloxacin	
Gatifloxacin	
Miscellaneous	
Bacitracin	
Chloramphenicol	
Polymyxin	

68.2.2 Viral Infections (Box 68.2)

Box 68.2 Antivirals Used in Viral Infective Conditions of the Eye

Antivirals	Conditions requiring antiviral therapy
Trifluridine Ganciclovir Valganciclovir Acyclovir Valacyclovir Famciclovir Foscarnet Cidofovir	Viral keratitis Herpes zoster ophthalmicus Viral retinitis

68.2.3 Fungal Infections (Box 68.3)

Box 68.3 Antifungals Used in Fungal Infective Conditions of the Eye

Antifungals	Conditions requiring antifungal therapy
Amphotericin B Natamycin	Fungal corneal ulcer Fungal injections of other parts of the eyeball Fungal keratitis
Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole	

68.2.4 Protozoal Infections

- Treatment of Acanthamoeba Keratitis.
  Antiseptics: Propamidine isethionate, Polyhexamethylene biguanide, and Chlorhexidine.
  Administered as topic therapy.
  Oral imidazoles: Added on to the topical medications.
- Treatment of Toxoplasmosis
  Treatment is indicated when the inflammatory reaction reaches the macula and might interfere with visual acuity. The drugs that are commonly used are combinations of a dihydrofolate reductase inhibitor with a sulphonamide (e.g., pyrimethamine + sulfadiazine).

68.3 Drugs Used in Glaucoma

The established strategy in treating patients with open angle glaucoma is to reduce the intraocular pressure. Recent research has shown that a proportion of patients experience optic nerve damage without ocular hypertension. Further, reducing the IOP does not completely treat the disease. This has led to the development and active search for drugs that will have potent neuroprotective action.

The drugs of choice for maintenance therapy of open angle glaucoma are the prostaglandin analogues as they have the following beneficial actions.

- Potent IOP lowering.
- Once a day dosing.
- Reduced systemic side effects.

Fixed dose combinations of these eye drops improve compliance by reducing the number of eye drops the patient has to self-administer (Table 68.1).

Table 68.1 Drugs for glaucoma

Drug class	Mechanism of action	Notes
PG analogues Latanoprost Travoprost Bimatoprost Tafluprost Unoprostone	Act on the FP receptors to increase the drainage of aqueous humor through the uveoscleral outflow. Other proposed mechanisms include increased metalloproteinase release to digest blockade of the outflow tract	*Advantages*: Once a day dosing Less systemic side effects Potent and stable lowering of IOP
Beta blockers Timolol Levobunolol Metipranolol Carteolol Betaxolol	Non selective beta blockade results in reduction of production of aqueous humor. Majority of the receptor subtype is beta 2. Other proposed mechanism includes decrease in ocular blood flow	While betaxolol is beta 1 selective and hence less efficacious, it reduces the risk of bronchospasm in susceptible individuals
Alpha 2 agonists Apraclonidine Brimonidine	Decreases the aqueous humor production by acting on postsynaptic receptors in the ciliary epithelium. Other proposed mechanisms include increase in the uveoscleral outflow and decrease in NE release from the sympathetic neurons	Apraclonidine does not enter the CNS because it is ionized and cannot cross the blood brain barrier
Topical carbonic anhydrase inhibitors Dorzolamide Brinzolamide	Inhibits the carbonic anhydrase (CA) isoform II present in the ciliary epithelium which is responsible for pumping bicarbonate and fluid into the aqueous humor	Generally not used as the first line therapy
Parasympathomimetic agents Pilocarpine Carbachol Echothiophate	Stimulates muscarinic receptors in the ciliary epithelium resulting in contraction and opening of the angle of the eye and outflow tract	*Disadvantages*: Very high risk of adverse effects mostly related to increased ciliary muscle strain Short duration of action and hence less sustained effect on the IOP High dosing frequency

68.4 Anti-Inflammatory and Immunomodulatory Drugs (Table 68.2)

Table 68.2 Anti-inflammatory and immunomodulatory drugs

Drug	Uses	Special considerations/toxicity
Glucocorticoids Difluprednate Fluorometholone Prednisolone Dexamethasone	Ocular pemphigoid Uveitis Postoperative inflammation to reduce scarring ARMD Diabetic retinopathy and macular oedema	Implants are available for the treatment of macular oedema and ARMD Loteprednol has to lowest risk of secondary glaucoma *Toxicity*: Posterior subcapsular cataracts Secondary glaucoma Infections
NSAIDs Flurbiprofen Diclofenac Ketorolac	Ocular inflammation Cystoid macular oedema Postoperative inflammation Seasonal allergic conjunctivitis	Rare toxicity Sterile corneal ulceration

68.5 Antihistamines and Mast Cell Stabilizers Used in Allergic Conditions

- *H_1 antagonists*
  Pheniramine
- *Mast cell stabilizer*
  Cromolyn sodium
- *H_1 antagonist with mast cell stabilization*
  Olopatadine
  Ketotifen
- *H_1 and H_2 antagonist with mast cell stabilization*
  Epinastine

68.6 Ocular Toxicity of Systemic Agents (Table 68.3)

Table 68.3 Ocular toxicity of systemic agents

Drug	Toxicity
Anticholinergics or drugs with anticholinergic effects (antihistamines, antipsychotics, antidepressants)	Dry eye syndrome
Tamoxifen	Intraoperative floppy Iris syndrome (IFIS)
Sildenafil and other PDE5, 6 inhibitors	Bluish discoloration of vision NAION (Nonarteritic anterior ischemic optic neuropathy)
Topiramate	Transient myopia Secondary angle closure glaucoma
Vigabatrin	Peripheral visual field defects
Phenytoin	Fine gaze-evoked nystagmus (horizontal) Ophthalmoplegia and diplopia
Alkylating agents and nitrosoureas	Retinal toxicity
5-Fluorouracil	Lacrimal duct stenosis and intractable epiphora
Vincristine	Hyperesthesia of the cornea
Paclitaxel and taxanes	Photopsia
Interferon	Retinopathy
Tamoxifen	Whorl-like keratopathy
Corticosteroids	Posterior subcapsular cataracts Secondary glaucoma
Thioridazine Chlorpromazine	Retinal deposition Decreased night vision
Amiodarone	Whorl-like keratopathy Blue green halos NAION
Digoxin	Yellow blue discoloration of vision
Chloroquine	Verticillate keratopathy Bull's eye maculopathy
Ethambutol	Optic neuritis
Vitamin A, Tetracyclines, OCPs, Lithium	Idiopathic intracranial hypertension and subsequent ophthalmoplegia
Rifabutin, sulfonamides Bisphosphonates	Drug-induced uveitis
Trazodone, clomiphene	Palinopsia
Cetirizine	Oculogyric crisis

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