OPHTHALMIC DRUG FORMULATIONS

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This chapter includes a review of:

- Ophthalmic dosage forms
- Drug formulation
- Preservatives
- Sterilisation of eye medications
- Shelf life and storage
- Ophthalmic drug delivery
- Administrations of eye medications

INTRODUCTION

DRUGS

Affect ocular tissues on the basis of:

- Special pharmacokinetic properties of the eye
- Absorption depends upon:
- Molecular properties of the drug
- Viscosity of its vehicle
- Functional status of the tissue forming the barrier to penetration.

The inter-relationships of the compartments and barriers of the eye can be used to predict:
Drug distribution over time and
Bioavailability at the desired site of action.

Role of metabolism:
Eliminating drugs and their toxic by-products
From the eye
From the body

PHARMACOTHERAPY OF EYE DISEASE

High local concentrations of drug at the ocular tissues

Treatment requirements:

- Ocular surface infections or inflammations — effective drug delivery to the eyelids, conjunctiva, or cornea
- Uveitis, glaucoma, or retinitis — therapeutic drug levels at appropriate target sites deep within the globe

Solutions and suspensions preferable to ointments:

- More easily instilled
- Less interference with vision
- Fewer potential complications

Disadvantages:

- Short ocular contact time
- Imprecise and inconsistent delivery of drug
- Frequent contamination
- Ocular injury with the dropper tip

Features:

- Mostly in clear plastic container with a snap off cap
- Can contain up to 7 drops
- Single uses only, discard after use
- Wafers or inserts – soluble or insoluble
- Useful for antibiotics

Available formats

- Single dose unit solutions (e.g. Minims)
- Multi-dose solutions (Aqueous or oily)/suspensions in 2.5ml-15ml plastic bottles with screw lids
- Multi-use ointments/gels (3-10g in foil tubes). They are to be used by a single individual and to be discarded after 4 weeks.
- Single use wafers or inserts in sterile packaging
- Eye lotions - used undiluted for bathing eye

See useful article on review of ocular inserts (Rathore and Nema 2009)

OPHTHALMIC DOSAGE FORMS

Route of administration

- Systemic (rest of body receives drug too)
  - Injections, e.g. lucentis for ARMD is given intravitreally
- Topical administration
  - Only route available to Optometrists

DRUG DELIVERY SYSTEMS

- Direct injection at the organ
- Periocular (subconjunctival or retrobulbar) or intravitreal
- Used when large doses of a drug are required at a site very quickly
- Systemic administration
- Uses ocular blood supply to carry drug to eye
- Topical administration
- Most common route

AQUEOUS EYEDROPS

- Topical delivery – ophthalmic route
- Fast absorption and effect
- Some drops can aAllow media and fundus viewing (cycloplegics, mydriatics)
- Brief duration (advantages and disadvantages)
- Viscous or oily drops or eye ointment increase duration and are retained in conjunctival sac for a longer period
- Are limited in volume by the conjunctival sac volume (7-10µL)

Uses:

Diagnostic or prophylactic drugs:

- Cycloplegics
- Mydriatics
- Miotics
- Topical local anaesthetics
- Staining agents
- Decongestants
- Prophylactic anti-infective agents

Therapeutic drugs:

- Treatment of glaucoma
- Treatment of infections and inflammation
- Artificial tears

DRUG FORMULATION

- Stability determined by pH
- Stabilisers maintain a stable pH
- To maintain stability drug must be properly stored and used

When drugs are made stable and sterile, sometimes slight irritation occurs upon instillation and reflex lacrimation is stimulated. To counteract this, polymers are added such as, increasing the viscosity of the drops, thereby making it less watery, e.g. cellulose polymers (hypromellose). Reducing agents act as an antioxidants, that are preferentially attacked by oxygen, leaving the active ingredient unaffected. Sequestering agents enhance the action of preservative (removes calcium ions from solution and disrupts cell wall).

Ophthalmic Pharmaceutical products tend to be composed of:

a. Buffering agents (ensure pH is equal to tears)
b. Stabilisers (maintain stable pH – e.g. sodium metabisulphate, edetate sodium)
c. Preservatives- prevents microbial contamination
d. Viscolisers
e. Reducing agents (e,g. sodium metabisulphate)
f. Sequestering agent (e.g. EDTA- forms di/ tri-valent complexes)

PRESERVATIVES

Features

- Benzalkonium chloride (BAK) sometimes used at 0.004%
- Antimicrobial agents
- To prevent contamination of multidose bottle

Ideal preservative

a. Rapidly effective against a wide range of bacteria
b. Harmless to the eye
c. Compatible with other medicaments
d. Stable during sterilisation and storage
e. Well within its solubility- to avoid crystallisation at low temperatures

Common Preservatives

- Phenylmercuric Nitrate/ Acetate 0.002%
- Benzalkonium Chloride 0.01%
- Chlorhexidine Acetate 0.01%
- Hydroxybenzoates
- Polixetonium chloride (WSCP)
- Chlorocresol 0.05%

- Chlorbutol 0.5%
- Thiomersal 0.01%
- Phenylethyl alcohol 0.5%
- Polidronium chloride (POLYQUAD)

STERILISATION OF EYE MEDICATIONS

- 2.5-15ml
- Plastic bottle with screw cap
- Usually clear plastic or white or opaque if light sensitive product
- Multiple uses by a single individual
- Dispose after 4 weeks of use unless indicated for a shorter time

Methods of sterilization

- Heating in an autoclave (121 deg for 15 mins)
- Heating with preservative at 98-100 deg C for 30 mins
- Filtration using bacterial filter of pore size 0.22 +/- 0.02 Micrometers (ensure no Pseudomonas persists)- smallest bacteria 0.5 Micrometers diameter
- Ionising radiation- Gamma rays 2.5-3.5 mRad used to sterilise Fluorescein strips (Fluorets)
- Ultrasonic- High power required- utilised in C/L Cleaning

SHELF LIFE AND STORAGE

Fig. 1.1 Instillation of eye drops on a child.

In order to ensure that stability requirements are realised, a pharmaceutical has a specified shelf-life (the time period between manufacture and expiration date)- during which the pharmaceutical will always contain within 10% of the specified medicament concentration.

Storage

- Most Ophthalmic preparations may be stored at room temperature (8-25 deg C)
- Some must be refrigerated (4 deg C)
- E.g. chloramphenicol must be stored in fridge
- All multiple use containers of ophthalmic products should be discarded 1 month after opening.

OPHTHALMIC DRUG DELIVERY

TOPICAL ADMINISTRATIONS

Features:

- The most common route of administration for ophthalmic drugs
- Convenient
- Simple
- Noninvasive
- Patients can self-administer the medication
- Note : Topically applied anesthetics are the primary anesthetic for contemporary cataract surgery

Disadvantages:

- Diffusion into the circulating blood — the primary source of drug loss in topical administration
- Drug losses through the systemic circulation —
- Do not typically penetrate in useful concentrations to the posterior ocular structures
- Are often of no therapeutic benefit for diseases of the posterior segment
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- Route of diffusion into the blood:
- Blood vessels of the conjunctiva and episclera
- Intraocular vessels
- Vessels of the nasal mucosa and oral pharynx after drainage through the nasolacrimal system

SOLUTIONS AND SUSPENSIONS

Solutions

Features:

- Most commonly used mode of delivery for topical ocular medications
- Usually preferred over ointments
- More easily instilled
- Interfere less with vision
- Fewer potential complications

Disadvantages:

- Short ocular contact time
- Imprecise and inconsistent delivery of drug
- Frequent contamination
- Possibility of ocular injury with the dropper tip

Suspension

Features:

- Must be re-suspended by shaking to provide an accurate dosage of drug
- Degree of re-suspension varies considerably among preparations and among patients

Disadvantages:

- Inadequate re-suspension — corticosteroid formulations
- Poor suspension — some generic steroid suspensions
- Development of clogged dropper tip — some generic products

ADMINISTRATION OF EYE MEDICATIONS

TOPICAL ADMINISTRATION

Method

Eye drops- Generally 1-2 drops are instilled into conjunctival sac (0.05-0.1 ml). The patient should lift his chin up while looking up as well and the drop should be placed in the lower conjunctival sac, without the tip of the bottle touching any of the ocular structures.

In the case of multiple instillation- leave 3 minutes between instilling drops

Eye ointments are applied by placing approx 0.5cm ribbon of ointment to the inside of lower lid. With clean hands, the ribbon is first placed on the tip of the index. The patient then looks up and the lower lid is pulled down to expose the lower conjuctival sac. The ribbon of ointment is then gently slided in the conjuctival sac.

If they are used together, the ointment should used after drops.

DRUG DELIVERY TO THE EYE

- Drug entering the eye is absorbed by the ocular tissues
- Absorption occurs both in corneal epithelium and conjunctival epithelium – drug crosses epithelial barriers into aqueous humour and then iris tissue and ciliary body
- Unless cornea is compromised, only very small amounts of drug actually enter eye
- Drug entering eye, due to aqueous humour flow, enters systemic circulation
- In normal lens containing eye, there is no diffusion into vitreous
- If cataract surgery, drugs can diffuse but no clinical consequences

- More lipophilic drug is expected to penetrate cells of cornea more effectively than lipophobic
- pH influences how readily drug penetrates cornea
- Drug instilled into lower cul-de-sac
    - Solution mixes with tears
    - Small proportion absorbed (<5%)

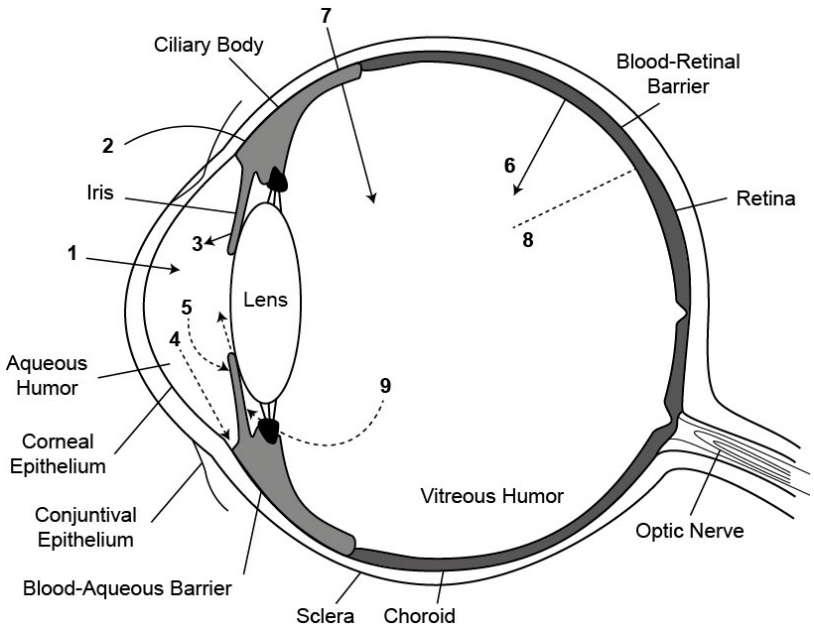

Fig. 1.2:

Schematic presentation of the ocular structure with the routes of drug kinetics illustrated.

The numbers refer to following processes:

1. Trans-corneal permeation from the lacrimal fluid into the anterior chamber
2. Non-corneal drug permeation across the conjunctiva and sclera into the anterior uvea
3. Drug distribution from the bloodstream via blood–aqueous barrier into the anterior chamber
4. Elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal
5. Drug elimination from the aqueous humor into the systemic circulation across the blood–aqueous barrier
6. Drug distribution from the blood into the posterior eye across the blood–retina barrier
7. Intra-vitreal drug administration
8. Drug elimination from the vitreous via posterior route across the blood–retina barrier
9. Drug elimination from the vitreous via anterior route to the posterior chamber

OCULAR DRUG DELIVERY

- Volume of a drop estimated to be between 50-70µl
- Conjunctival sac estimated 7-10µl
- Eye closure for 30-60 seconds recommended to reduce wash out
- One study suggested that approximately 1.5% of pilocarpine was absorbed by the ocular tissues
- Immediate loss

FACTORS AFFECTING DELIVERY

- Stinging sensation, irritation and crying will increase tearing which will increase washout of the drug
- 30-60 sec of eye closure recommended or occlude puncta for 30-60sec
- 50% of many drugs washed from ocular surface after 1 minute
- 1 drop contains 35micro litres
- If more than one dose – 3 to 5 mins between drops

- Melanin pigments in iris
- Not available for use on receptors
- Slow release prolonged effects
- Viscosity – inclusion of viscolisers (certain polymers) increases residence time on surface of eye
- Increases chance of drug being absorbed into corneal and conjunctival tissues
- Gels or ointments increase surface time – good for irritated eye
- Compromised cornea will cause increased absorption
- Reflex lacrimation and drug wash out
- Tear volume and naso-lacrimal drainage
- Absorption by melanin pigments
- Viscosity of product
- Ocular surface health and age related effects on ocular pharmacokinetics.

REFERENCES

Optometrists formulary 2007 edition. The College of Optometrists Handbook.

British National Formulary 54th edition.

ABPI Compendium of data sheets (Association of the British Pharmaceutical Industry).

Martindale: The virtual pharmacy, pharmacology and toxicology centre. Martindalecenter.com

Doughty M. 2006. Drugs, Medications and the Eye. 14th Edition.

Hopkins G, Pearson R. Ophthalmic Drugs – 4th and 5th edition 1998 and 2008. Butterworth Heinemann.

Liew and Hammond. Optometry Today. 2 Dec 2005. Therapeutics in practice.

Buckley, Lawrenson, Hennelly. Optometry Today. 14 Jan 2005. Therapeutics in clinical practice. Recent developments in drug legislation for optometrists.

Lawrenson. Optometry Today. 3 June 2005. Recent changes in the use and supply of medicine by the Optometrist.

Needle, Petchey, Lawrenson. A survey of the scope of therapeutic practice by UK optometrists and their attitudes to an extended prescribing role. Ophthalmic and Physiological Optics. 2008 28: 193-203.

Hopkins and Pearson. Ophthalmic Drugs. Fifth edition. Butterworth Heinemann.

Rathore KS, Nema RK. Review on Ocular Inserts. International Journal of Pharm Tech Research. Vol.1, No.2, pp 164-169, April-June 2009.

Prog Retin Eye Res. 1998 Jan;17(1):33-58.

Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems--recent advances. Progress in Retinal and Eye Research. Volume 17, Issue 1, January 1998, Pages 33-58.