Antimicrobial Agents for Ocular Use

Ocular microbial infections are one of the leading causes of avoidable visual impairment in the world with higher prevalence in developing countries.

The incidence and organism responsible for ocular infections are attributed to indiscriminate use of antibiotics, corticosteroids, poor sanitary conditions, rising trend of the use of contact lens etc.

A wide variety of microorganisms; bacterial, fungal, viral and protozoal in origin are reported to be involved in ocular infections.

These ocular infections include conjunctivitis, blepharitis, endophthalmitis and corneal ulcers which are vision threatening if not treated in time.

Antifungal Agents for Ocular Use

Infectious keratitis is one of the leading causes of corneal blindness in the world with a higher prevalence in developing countries.

Infections caused by fungal organisms have been on a rise especially in developing countries where 50 % of the cases are due to fungal organisms.

The implicated factors in its causation are indiscriminate use of antibiotics and corticosteroids leading to ocular compromise.

Despite the emergence of newer drugs, the cure still remains difficult in view of poor ocular penetration of the drugs.

The common antifungals used for fungal keratitis are classified as follows:

1. Polyenes

(i) Large polyenes: Nystatin and amphotericin B

(ii) Small polyenes: Natamycin

2. Azoles

(i) Imidazoles: Miconazole, ketoconazole, and clotrimazole

(ii) Triazoles: Fluconazole, itraconazole

3. Pyrimidines

Flucytosine

4. Echinocandins

Caspofungin and micafungin

Polyenes

This class of drugs includes amphotericin B (AMB), natamycin, and nystatin.

Nystatin is not used routinely to treat ocular infection due to its low intraocular penetration, toxicity, and resistance to the drug.

However, natamycin and amphotericin B are the most commonly used drugs in cases of fungal keratitis.

Amphotericin B

AMB was the first broad-spectrum antifungal agent to be discovered. It is produced by the actinomycete *Streptomyces nodosus*.

It was approved by the FDA in the 1960s due to its great efficiency in controlling disseminated fungal infections.

Mechanism of Action: AMB works by creating pores in the cell wall by binding to ergosterol, allowing small ions such as potassium to leak out causing imbalances in the osmotic gradient and eventually cell lysis.

Its action is primarily fungistatic, with fungicidal action depending on the concentration reached in the target tissue.

AMB acts on both yeast and filamentous fungi. It has an excellent spectrum, being effective against *Candida* species, *Aspergillus* species, *Penicillium marneffei*, *Cryptococcus* species, and the causative agents of mucormycosis. It is also effective, to a lesser extent, against *Fusarium*.

Systemic administration of AMB produces little penetration into the ocular tissues and does not reach therapeutic levels in the cornea and aqueous or vitreous humor.

Also, the multiple side effects preclude its systemic administration. Ocular administration therefore is the commonly used form of treatment.

It is one of the few drugs which can be used through the subconjunctival, topical, intrastromal, intracameral, and intravitreal routes.

Dosage: AMB is prepared from the intravenous formulation diluted in distilled water. It is used at a concentration of 1.5–5 mg/ml and administered at one-hour intervals at the beginning of treatment and then every 4 h once the therapeutic response is observed. Periodic debridement of the corneal epithelium is recommended since the drug has a poor penetration in an intact epithelium.

Subconjunctival administration is used in patients not compliant to topical therapy; however, it is not preferred in view of reports of conjunctival necrosis, scleral thinning, and scleral melt.

Intrastromal administration of AMB at a concentration of 5–10 µg is administered for deep infections affecting the stroma that do not respond well to topical and systemic treatment. The interval between two doses should be at least 72 h.

Intracameral administration of the drug is suggested for infection penetrating the Descemet's membrane affecting the anterior chamber. A study compared 14 eyes who were administered intracameral AMB versus 17 eyes who were on conventional antifungal therapy.

It was noted that eyes that received intracameral AMB had an early disappearance of hypopyon and final improvement in comparison to eyes on conventional therapy.

In keratitis associated with fungal endophthalmitis, intravitreal administration of AMB is recommended in a dose of 5–10 µg and may be repeated within 48–72 h.

Side Effects: The main reason for the side effects of AMB is its binding to cholesterol which is present in the cell wall of the host cells. Systemic administration via infusion can lead to fever, chills, hyperventilation, hypotension, nausea and vomiting, and tubular injury. Intrastromal and intracameral administration of the drug may lead to pain, endothelial cell loss, iritis, and persistent corneal edema in doses greater than 15–20 µg. Intravitreal injections in higher doses can lead to retinal necrosis and toxicity.

Natamycin

Similar to amphotericin B, natamycin is a polyene antifungal and is the drug of choice for the treatment of keratitis caused by filamentous fungi.

Mechanism of Action: Natamycin binds to ergosterol in the cell wall of the fungi, forming blisters and causing lysis of the cells. This action is not concentration dependent unlike AMB.

It is used in a concentration of 5% (50 mg/ml) and is well tolerated when used topically.

Epithelial debridement is recommended as an adjuvant therapy so that higher concentrations can be achieved in the corneal stroma. For deeper infections, natamycin should be combined with other antifungals for the treatment.

Natamycin is a broad-spectrum antifungal. Although it also works against *Candida* infection, AMB remains the drug of choice for yeast infections.

The dosing interval is similar to AMB. The drug is administered at 1-h interval until the signs of resolution are visible. Once the therapeutic response is seen, the dosing interval can be increased to one drop administered every 4 h.

Natamycin is effective against Fusarium, and it has been observed that it has a lower minimum inhibitory concentration than AMB against both Aspergillus and Fusarium. Subconjunctival injections can be given but are not recommended in view of risk of scleritis and melt. There are no reports of administration of NTM through other routes (intracameral, intravitreal, intrastromal, or systemic).

Antimicrobial Agents for Ocular Use

Lecture 4

Azoles

This class of drugs has a broader spectrum of activity as compared to AMB and fewer side effects. They are divided into two classes: **imidazoles** which were first to be introduced in the market, and followed by **triazoles**.

The imidazoles used more often include miconazole (MCZ), econazole (ECZ), and ketoconazole (KCZ).

Among the first-generation triazoles, the most often used are itraconazole (ICZ) and fluconazole. Second-generation triazoles were introduced into clinical practice in the past decade and include voriconazole and posaconazole (PCZ).

Azoles act on cytochrome P450 enzymes and block the synthesis of ergosterol in the plasma membrane, thus inhibiting fungal growth.

Imidazoles

The imidazoles have various mechanisms of action for their antifungal activity.

At low concentrations, they affect the formation of ergosterol present in the cell membranes.

At higher concentrations, they can disrupt lysosomes, causing direct damage.

Also, most imidazoles inhibit catalase and cytochrome C peroxidase intracellularly, causing accumulation of hydrogen peroxide leading to cell death.

Miconazole is a broad-spectrum antifungal with activity against *Cryptococcus*, *Fusarium*, *Aspergillus*, *Curvularia*, *Candida,* and *Trichophyton*.

It not only acts on the synthesis of ergosterol but also leads to inhibition of peroxidases, resulting in the accumulation of free radicals in the fungal cytoplasm which leads to cell death.

Topical use at a dose of 10 mg/ml or a 1% solution is effective especially if associated with epithelial scraping.

Compared to polyenes, MCZ is less effective but provides better penetration into ocular tissues.

Econazole is primarily used in the treatment of superficial mycosis and not used routinely for the treatment of ocular infections.

In a clinical trial, 116 eyes with fungal keratitis were randomized to either econazole 2% or natamycin 5%, and it was found that econazole is as efficacious as natamycin for the treatment of fungal keratitis.

However, the drug is not commercially available for ocular administration which prevents its ophthalmic use.

Ketoconazole was the first systemic imidazole to be used successfully for the treatment of fungal infections.

It is available in 200mg tablets with a recommended dose of 200–400 mg daily.

Its oral absorption depends on the gastric pH (pH < 3); therefore, it should be taken on empty stomach and without gastric acid suppressives.

KCZ is available in a topical formulation of 1–5 % concentration, but other drugs have been shown to be superior in comparative studies.

Currently, systemic KCZ is indicated only for the adjuvant treatment of deep fungal keratitis.

The systemic side effects include pruritus, nausea, vomiting, diarrhea, cramps, reversible gynecomastia, and elevation in liver enzymes.

Triazoles

Itraconazole is used in a dose of 400 mg/day in the treatment of infections by *Candida* spp.

However, when administered orally, it exhibits lower bioavailability, solubility, and penetration into ocular tissues than other azoles.

However, ICZ has not been found to be very effective against *Fusarium*.

In a randomized controlled trial involving 100 patients, topical itraconazole 1% was found to be inferior when compared to natamycin 5%.

The study concluded that when natamycin is unavailable, topical itraconazole therapy could be used.

The MIC of ICZ is higher than both AMB and KCZ; hence, systemic use should be limited only to the adjuvant treatment of eye infections by yeasts.

Fluconazole oral use at 200–400 mg per day is effective in the treatment of eye infections, with or without topical NTM.

Unlike KCZ and ICZ, FCZ shows excellent absorption from the gastrointestinal tract unaffected by gastric acidity.

Its penetration into the ocular tissue is effective and reaches aqueous concentration similar to that of plasma.

FCZ achieves good intracorneal levels at a dose of 2 mg/ml with penetration being better after epithelial scraping.

However, it is less effective in the treatment of fungal endophthalmitis.

The ocular penetration of FCZ has been shown to be superior to KCZ.

However, the antifungal spectrum of FCZ is narrow.

In many studies, it has shown to be effective against yeasts like *Candida,* whereas filamentous fungi like *Aspergillus* and *Fusarium* have shown to exhibit marked resistance to it.

Topical FCZ 2% was found to be effective in six eyes with microbiologically proven *Candida* keratitis with abscess formation.

The average duration of healing was found to be 22.6 ± 2.3 days.

Combination Therapy

In order to broaden the antifungal spectrum and increase the efficacy of treatment, two or more drugs are often combined in the treatment of fungal keratitis.

Azoles are often combined with NTM or AMB. However, several studies showed an antagonistic effect between these drugs.

The introduction of an azole decreases the synthesis of ergosterol in the cell membrane, a binding site for polyenes, whose action is therefore decreased.

However, polyenes such as natamycin and triazoles such as voriconazole are often combined in the treatment of filamentous fungi and have shown a synergistic effect.

The combination of two drugs of the same class is often discouraged such as NTM and AMB since it increases local and systemic toxicity and fails to increase therapeutic efficacy.

Conclusion

A variety of antifungal drugs are available in the market for topical and systemic use, the choice of which depends upon the causative organism, the location, and the extent of infection.

Standard therapy with polyenes remains the first choice of treatment for fungal keratitis.

New-generation triazoles act as an add-on therapy in cases of poor responsiveness to the former.

Studies until date lack the demonstration of superiority of the newer-generation triazoles over the conventional therapy with polyenes.

Drug	Route	Dosing	Indication
Amphotericin B	Topical	1.5–5 mg/ml	First choice in keratitis by yeasts
	Intrastromal	5–10 µg/0.1 ml	Deep keratitis with partial response to topical treatment
	Intracameral	5–10 µg/0.1 ml	Keratitis affecting anterior chamber/lens
	Intravitreal	1–10 µg/0.1 ml	First choice in fungal endophthalmitis (yeast/ filamentous fungi)
Natamycin	Topical	50 mg/ml	First choice in filamentous fungi
Miconazole	Subconjunctival	1.2–10 mg/1 ml	Associated with topical therapy in low adherence to treatment
Econazole	Topical	20 mg/ml	Alternative to NTM for filamentous fungi
Ketoconazole	Oral	100–400 mg every 12 h	Deep keratitis along with topical therapy
Itraconazole	Oral	400 mg/day	Deep keratitis by yeasts
Fluconazole	Topical	2 mg/ml	Alternative to polyenes in Candida keratitis
	Subconjunctival	2 mg/1 ml	Associated with topical therapy in low adherence to treatment
	Oral	200–400 mg/day	Deep keratitis

Ocular Pharmacology (Introduction)

Dr. Ahmed Faisal

Drug

- A drug is defined as any chemical that can affect living processes.
- All chemicals can be considered drugs, since, when exposure is sufficiently high, all chemicals will have some effect on life.

Pharmacology

- Pharmacology can be defined as the study of drugs and their interactions with living systems.
- Pharmacology encompasses the study of the physical and chemical properties of drugs as well as their biochemical and physiologic effects.
- Pharmacology includes knowledge of the history, sources, and uses of drugs as well as knowledge of drug absorption, distribution, metabolism, and excretion.

Clinical Pharmacology

- Clinical pharmacology is defined as the study of drugs in humans.
- This discipline includes the study of drugs in patients as well as in healthy volunteers (during new drug development).
- Thus, clinical pharmacology encompasses all aspects of the interaction between drugs and people.

Routes of Drug Administration

- **Enteral**
  - Oral
  - Sublingual
- **Parenteral**
  - Intravenous (IV)
  - Intramuscular (IM)
  - Subcutaneous (SC)
- **Other**
  - Inhalation
  - Intranasal
  - Intrathecal
  - Topical
  - Transdermal
  - Rectal

Principles of Ocular Therapy

After the Second World War, sterility of drug for eye has been recognized as a mandate for topical eyedrops.

Usage of preservatives came into picture to avoid bacterial contamination or growth in the multi-dose eyedrop vial for their use up to 30 days after opening.

However, few fundamental aspects need emphasis while administering them to the patients or self-administration.

One need to remember the appropriate way of application of an eyedrop.

How to apply eyedrops:

- Clean hands with soap solution and dry it.
- Open the dropper cap.
- Do not touch the tip of the dropper.
- Slightly tilt the head backwards.
- Gently pull the lower eyelid with one hand.
- Place only one drop of the drug solution into the lower fornix (do not apply two drops).
- Close the eyes and sit quietly for 1 min.

- If possible apply a gentle pressure on the tear duct by pressing near medial canthus with index finger for a while, this will avoid the immediate entry of drug solution into the lacrimal drainage system.

- If two different drops need to administered, it should be done by with the interval of at least 15 min between them.

- Close the eyedropper without touching the dropper tip and store it in a cool and dry place.

- Unpreserved eyedrops must be kept in refrigerator at 2–6°C.

Most of the eyedrops are clear-colored or colorless solutions with or without preservatives, iso-osmotic and buffered to have neutral pH, with exception in suspensions like prednisolone acetate, dexamethasone, etc.

Application of eyedrops with lesser volume (drop size) or single drop is known to have better ocular bioavailability as compared to larger volume or multiple drops.

Cornea is a specialized tissue, devoid of blood vessels having hydrophobic epithelium followed by hydrophilic stroma thereby restricting the entry of both hydrophobic and hydrophilic compounds for gaining access to aqueous humor.

Cornea is highly sensitive for pH of the ingredients, osmolarity (hypo and hyper), nonspecific irritants, and pH of the formulations.

The pH and nonspecific irritation can induce reflux tearing which in turn washes away the pre-corneal drugs.

Predominately, drugs applied topically take transcellular diffusion pathway as corneal epithelium is reported to have tight intracellular junctions; therefore, less than 5% of the topically applied drug dosage reaches aqueous humor.

As less amount of drug reaches into aqueous humor, conventionally, drug concentrations are increased considerably in the applied drops to reach adequate levels for the pharmacological activity.

However, the modern understanding for the transfer of drugs across cornea is explained much better by the presence of drug transporter proteins in corneal epithelium and endothelium.

These transporters are physiologically responsible for the uptake of nutrients for the survival of cornea and to maintain its transparency by regulating its homeostasis.

Systemically, administered drug seldom reaches adequate concentration into the tissues of the eye with the considerable concentration for expected pharmacological action.

Most of the systemically administered antibiotics were reported to fail to reach adequate concentration due to the presence of blood-ocular barriers.

Therefore, selecting appropriate route of drug administration to the eye is expected to having better pharmacodynamic profiles.

Based on requirement, subtenon, retrobulbar, subconjunctival, intracameral, intravitreal, and peribulbar routes are preferred to comply required drug concentration at a particular site in the eye.

Challenges in Ocular Therapeutics

Ocular therapeutics is the only area in which the drugs used more than 100 years ago are still having its presence in clinical practice.

Despite the multidimensional drug development approaches of the contemporary period, it is rare to see any specific agent being developed for ocular use considering the penetration constraints exerted by the eye after topical or systemic administration.

Most of the drugs, approved for systemic use, are often exploited for ocular use without rationalizing the penetration characteristics in the drug development stage.

Lack of considerable market size for drugs other than for glaucoma and retinal neovascular conditions could have been the major limiting factor for not getting much of industrial emphasis for ocular-specific drug discovery.

Due to the application of modern techniques on traditional knowledge, ocular applications of herbal drugs are continuously increasing.

However, in most of the cases, there are isolated publications on animal models or human studies which are not having any big impact for their wider use in ocular therapeutics.

Therefore, developing drug specific for the eye with the consideration of its constraints would be beneficial for the further development of ocular pharmacology and its application to therapeutics.

Ocular Pharmacology and Its Practice

Ocular applications of many drugs are due to their mutual borrowings from several fields of medicine.

However, all of them may not been approved for its ocular use due to the lack of initiation for the application to the regulatory authorities for their use in ophthalmology.

Off-label use of drugs is commonly evident in ophthalmology; therefore, requirement of a compounding pharmacy in the final translation of drugs approved for other systemic use for ocular therapeutics.

One of the chapters in this book deals with extensively about this aspect in detail.

Along with the increasing knowledge about the pathology of ocular disease, we are sure that usage of extemporaneously prepared drugs might increase further in the future.

During such attempts, a rational approach is expected to justify their appropriate usage in ocular therapeutics.


Question

Antimicrobial Agents for Ocular Use

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Antibacterial Agents in Ocular Infections

Antibiotics are the substances produced by microorganisms which selectively inhibit the growth of microorganisms (bacteriostatic drugs) or kill the microorganisms (bactericidal drugs).

When bacteriostatic drugs are used to treat ocular infection, the host defense mechanisms are ultimately responsible for clearing and eradicating the infective organism.

In bacterial keratitis, the infection develops in the avascular cornea, and in endophthalmitis it develops in the fluid-filled aqueous or vitreous cavity.

In either case, the immune system may be unable to control the microorganism fast enough to prevent the sight-threatening complications.

Within the first 24 h, pathogens may multiply and release toxins and degradative enzymes that destroy the function and integrity of ocular tissues.

Therefore, the bactericidal drugs are preferred for the treatment of severe ocular infections.

Sometime, for severe systemic infections involve ocular components, systemic antibiotics are instituted with adjunctive topical therapy.

Systemic antibiotics have poor penetration into the anterior chamber of the eye, and thus, both systemic and topical aminoglycoside antibiotics, and occasionally subconjunctival injections, are required for effective treatment.

General Classification of Antibacterial Agents

The antibiotics are classified on the basis of the following:

- Chemical structure (sulfonamides, diaminopyrimidines, quinolones, β-lactam antibiotics, tetracyclines, nitrobenzene derivatives, macrolides, lincosamides, glycopeptides, oxazolidinones, polypeptides, nitrofuran derivatives, nitroimidazoles, azoles, and nicotinic acid derivatives).

- Mechanism of action (inhibit cell wall synthesis, disrupt cell membrane, inhibit protein synthesis, inhibit DNA topoisomerase, interfere with DNA function or synthesis, and interfere with intermediary metabolism)

- Spectrum of activity (narrow spectrum and broad spectrum)
- Type of action (bacteriostatic and bactericidal), origin (from bacteria, fungi, etc…)
- Type of organism against which they are primarily active (antibacterial, antifungal, antiviral, antiprotozoal, and anthelmintic).
- Site of action (usually target against cell wall, cytoplasmic membrane, intermediate metabolites, and DNA synthesis in microorganisms)

Cell Wall Synthesis Inhibitors

Penicillins

The penicillins structurally consist of a thiazolidine ring with a β-lactam ring connected to a side chain.

Several of the penicillins are used in ophthalmic preparations, these are as follows: penicillin G, penicillin V (acid-resistant penicillin), methicillin, cloxacillin (penicillinase-resistant penicillins), carbenicillin, mezlocillin, piperacillin, and ticarcillin (extended-spectrum penicillins).

Spectrum of Activity Penicillins have higher susceptibility against Gram-positive bacteria.

Mechanism of Action Penicillins act by interfering with synthesis of bacterial cell wall.

They inhibit the transpeptidases so that cross-linking (which maintains the close knit structures of the cell wall) does not occur.

Indications Topical use of penicillins for treatment of eye disease is limited by their narrow spectrum and high incidence of allergic reaction to these drugs.

Penicillin G has a narrow spectrum of activity though used for the treatment of patients with keratitis caused by susceptible *Streptococcus pneumoniae*.

A 14-day course of high-dose intravenous penicillin G is first-line therapy for all stages of ocular syphilis and chorioretinitis.

Ticarcillin and piperacillin are used with an aminoglycoside antibiotic topically and subconjunctivally for the treatment of bacterial corneal ulcers caused by Pseudomonas and other Gram-negative rods.

Carbenicillin is useful in corneal ulcer caused by the opportunistic organism Achromobacter xylosoxidans which developed during chronic topical steroid treatment of an eye with neovascular glaucoma.

Topical piperacillin/tazobactam is used as an option for the treatment of therapy-resistant P. aeruginosa keratitis.

Also, methicillin is preferred in combination with aminoglycoside for the treatment of keratitis.

Antimicrobial Agents for Ocular Use

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Cephalosporins

Cephalosporins are semisynthetic antibiotics derived from a fungus, cephalosporium.

It shares its pharmacology with penicillins in structure and mechanism of action.

The compounds are commonly classified to generations based on their clinical uses and varying spectrum of activity.

The cephalosporins that belong to each generation used in ophthalmic preparations are the following:

First generation cephalosporins (cefazolin, cephalexin and cefadroxil).

Second-generation cephalosporins (cefamandole, cefaclor, cefprozil, cefoxitin and cefuroxime).

Third-generation cephalosporins (ceftriaxone, cefixime, cefoperazone, ceftazidime, ceftibuten and cefdinir).

Fourth-generation cephalosporins (cefepime and cefpirome) appear more active against Gram-negative organisms and appear more active against Gram-negative enteric bacteria.

All are effective against Gram positive bacteria, but their activity against Gram-negative bacteria is relatively modest.

The activity of cephalosporins increased toward Gram-negative bacteria along with generations.

Spectrum of Activity Second-generation cephalosporins appear more active against Gram-negative enteric bacteria.

Third-generation cephalosporins are more active against Gram-negative organisms.

Mechanism of Action All cephalosporins are bactericidal and inhibit bacterial cell wall synthesis, similar to the penicillins, but bind to other proteins than penicillin.

Indications Cefazolin is used to treat bacterial corneal ulcers as part of a broad spectrum approach in combination with an aminoglycoside or fluoroquinolone such as ciprofloxacin.

It is used due to its activity against Gram-positive cocci, including penicillin-resistant Staphylococci.

The clinical response is variable in infections caused by the group of Streptococci.

Cefazolin is not available as an ophthalmic preparation so it is administered topically as a specially prepared solution or subconjunctivally.

It is found to be highly active against Gram-positive bacteria, a common cause of bacterial keratitis.

Cefazolin and cefuroxime are resistant to staphylococcal β-lactamases and used in combination with aminoglycosides in the empirical treatment of keratitis.

Cefazolin and cefuroxime intracameral injection are used to decrease the risk of endophthalmitis at the end of cataract surgery.

Second-generation cephalosporins have limited use in ophthalmic practice.

Ceftazidime shows excellent activity against Gram-negative bacteria including Pseudomonas aeruginosa and remains the most popular mode of antibiotic prophylaxis in cataract surgery patients for prophylaxis from endophthalmitis.

Ceftazidime is also suggested as an alternative for intravitreal amikacin in the treatment of endophthalmitis.

It possesses high therapeutic index with a lower risk of retinal toxicity than amikacin.

Antibacterial Agents in Ocular Infections

Lecture
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Polypeptide Antibiotic
(Cell Wall Synthesis Inhibitors)

Bacitracin, gramicidin, and colistin are the polypeptide antibiotics used in ophthalmic topical formulations.

Bacitracin

Spectrum of Activity It is active against Gram-positive bacteria, including Streptococci and Staphylococci.

Mechanism of Action It inhibits cell wall synthesis of bacteria by a different mechanism than do the β-lactam antibiotics.

Indications Because of its systemic renal toxicity, it is used topically alone and in fixed combination products.

It is unstable in solution, thus available only as an ointment in combination with neomycin, effective against Gram-negative bacteria, and polymyxin B.

The inclusion of bacitracin produces broad antibacterial spectra against most common ocular pathogens.

Bacitracin appears useful to clear corneal wound infection caused by Gram-positive organisms after phacoemulsification is a serious complication of cataract surgery.

Bacitracin is found useful for perioperative antibiotic prophylaxis.

Vancomycin

It is a glycopeptide antibiotic first isolated in 1953 from a soil bacterium *Amycolatopsis orientalis* (formerly known as *Nocardia orientalis*).

Spectrum of Activity It possesses broad-spectrum activity against Gram-positive bacteria including methicillin- and cephalosporin-resistant Staphylococci.

Also, it shows activity against coagulase-negative Staphylococcus, Gram-positive cocci, including Streptococcus, Staphylococcus, Clostridium, and Corynebacterium.

Mechanism of Action It acts by inhibiting cell wall synthesis by binding to the peptide chains preventing them from interacting properly with the cell wall cross-linking enzyme and crosslinks are not formed and the cell wall falls apart.

Indications It is reserved for serious infections for which less toxic antibiotics are not indicated, not effective, or not tolerated.

It is an excellent empiric antibiotic for treating endophthalmitis and an alternative to penicillins or cephalosporins for serious infections.

It is used as the final choice in serious cases of methicillin-resistant Staphylococcus aureus (MRSA) or methicillin-resistant Staphylococcus epidermidis (MRSE) keratitis.

It is recommended as intravitreal, topical, or subconjunctival for treatment of bacterial endophthalmitis.

Antibacterial Agents in Ocular Infections

Lecture
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Cytoplasmic Membrane Inhibitors

Polymyxin B

Spectrum of Activity: It is active against Gram-negative bacteria except Proteus, Serratia, and Neisseria.

It is also active against Pseudomonas, Salmonella, and Shigella.

Mechanism of Action: It is surfactant in nature that disrupts the osmotic integrity of bacterial cell membranes.

Indications: Currently, it used as a last resort antibiotic for the treatment of infections caused by Gram-negative bacteria.

Topical neomycin/polymyxin B is found effective in reducing the conjunctival bacterial load given before cataract surgery.

The combination of topical trimethoprim/polymyxin B and topical moxifloxacin is found to effectively control the corneal ulcer in keratitis caused by Elizabethkingia meningosepticum.

Polymyxin B and trimethoprim are found useful in infectious keratitis after photorefractive keratectomy.

Polymyxin B-trimethoprim continues to be an effective treatment for acute conjunctivitis and bacterial keratitis and may combine with chloramphenicol and gentamicin.

Polymyxin B may be used for multidrug-resistant Pseudomonas spp.

It is available in combination with various other agents such as bacitracin (ointment), trimethoprim (eye drops and ointment), and neomycin plus gramicidin (eye drops).

Colistin

Spectrum of Activity: It is active against the multidrug-resistant (MDR) Gram negative organisms except Proteus, Serratia, and Neisseria. It is also active against Pseudomonas, Salmonella, and Shigella.

Mechanism of Action: Its rapidly acting bactericidal agent exhibits a surfactant-like action on the cell membrane and causes distortion or pseudopod formation.

Indications: Topical colistin 0.19 % found a safe and effective alternative in the management of multidrug-resistant P. aeruginosa bacterial keratitis.

Gramicidin

Spectrum of Activity: It is active against Gram-positive bacteria, except for the Gram-positive bacilli, and against select Gram-negative organisms, such as Neisseria.

Mechanism of Action: It is bactericidal and causes cell membrane leakage in the microorganisms.

Indications: It replaces bacitracin in some fixed combination formulations used topically for eye infections. It is used in therapeutics in the name of tyrothricin which is a mixture of gramicidin (20 %) and tyrocidine (80 %). Its use is limited to topical application only, as it is very toxic on systemic use.

Fusidic Acid

Spectrum of Activity: It is a narrow-spectrum antibiotic effective against Streptococci, Haemophilus, and methicillin-susceptible Staphylococcus aureus.

Mechanism of Action: It inhibits protein synthesis in bacteria.

Indications: It achieves high concentrations at the surface of the eye. It is available as 1 % viscous drops which liquefy in contact with the eye and results in a relatively better half-life in the tear film, therefore reducing the frequency of application compared to other formulations.


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Antibacterial Agents in Ocular Infections

Lecture

9

Protein Synthesis Inhibitors

Aminoglycosides, **tetracyclines**, and **macrolide** antibiotics as well as the individual drugs **clindamycin** and **chloramphenicol** inhibit the protein synthesis in bacteria.

Aminoglycosides

Gentamicin, **neomycin**, **netilmicin**, **tobramycin**, and **amikacin** are the aminoglycoside antibiotics used in ocular preparations.

Gentamicin was discovered in 1963 and was introduced into parenteral usage in 1971.

Since then, it has been widely used in medicinal applications including eye diseases.

Spectrum of Activity

These are effective against most Gram-negative bacteria and Staphylococci with lesser activity against Streptococci.

Aminoglycosides showed differences in the type and doses associated with toxic reactions; thereby, the following order of toxicity can be described (from most toxic to least toxic): gentamicin > netilmicin = tobramycin > amikacin = kanamycin.

Aminoglycosides display concentration-dependent bactericidal activity and are the cornerstone of therapy against serious Gram-negative bacterial infections.

Mechanism of Action

These inhibit protein synthesis by binding to 30S bacterial ribosomes and cause inaccurate mRNA translation and so inhibit the biosynthesis of proteins.

Indications

Gentamicin and tobramycin are more active than neomycin and framycetin, particularly against P. aeruginosa.

The rapid bactericidal action of gentamicin and tobramycin and their potential activity against P. aeruginosa make them useful in the treatment of bacterial keratitis.

They do not penetrate the cornea well; therefore, they are generally used at fortified concentrations until the condition of the cornea improves.

Gentamicin is used to treat many bacterial infections such as conjunctivitis, blepharitis, and dacryocystitis.

It is also used for the initial treatment of bacterial corneal ulcers or prophylaxis of endophthalmitis after cataract surgery by intracameral antibiotics or subconjunctival injection, though it is considered inadequate for the initial treatment of serious bacterial keratitis.

The solutions containing fortified concentrations are prepared from sterile products to be intended for parenteral use.

The fortified gentamicin or tobramycin solution is combined with a penicillinase-resistant cephalosporin and considered a useful initial empiric treatment for serious bacterial keratitis.

The initial loading dose of fortified aminoglycosides is given to increase the antibiotic concentrations in the cornea, followed by regular applications.

Neomycin is most commonly administered topically in combination with other antibiotics or corticosteroids.

Topical application frequently results in sensitization to the drug; therefore, long-term use should be avoided.

Netilmicin appears the most effective antibiotic tested against both MRSA and MRSE and may curtail the emergence, spreading, and persistence of antibiotic-resistant bacteria.

Netilmicin appears a safe and broad-spectrum antibiotic comparable with that of ciprofloxacin, ofloxacin, norfloxacin, and gentamicin that can be used as first-line therapy for the treatment of acute bacterial conjunctivitis.

Tobramycin is used similar to gentamicin; however, Staphylococci are generally susceptible to tobramycin, whereas Streptococci are not susceptible to tobramycin.

Amikacin is usually effective for most strains of Klebsiella, Enterobacter, E. coli, and Serratia.

However, for bacterial keratitis, tobramycin is often preferred in combination with ticarcillin.

Dual therapy with a β-lactam agent is recommended for empirical therapy to cover streptococcal infection and improve activity against Staphylococci.

The aminoglycosides are slowly inactivated in the presence of some β-lactams; thus, they should be administered separately, preferably at least 5 minutes apart.

Tobramycin 1.4% topical is found useful in mycobacterial keratitis after laser in situ keratomileusis (LASIK) and infectious keratitis after photorefractive keratectomy.

Tobramycin also may be useful as prophylactic topical antibiotics for preventing secondary corneal infections or recurrent corneal erosion syndrome.

Amikacin, the first semisynthetic aminoglycoside, has been chemically modified to be protected from aminoglycoside-inactivating enzymes.

It is popular as a primary antibiotic for intravitreal injection along with vancomycin for the treatment of bacterial endophthalmitis due to its broad spectrum against resistant Gram-negative organisms and reduced toxicity.


Any
questions

Antibacterial Agents in Ocular Infections

Lecture

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Protein Synthesis Inhibitors

Tetracyclines

Tetracyclines were first acknowledged in 1948 as the natural fermentation product of the soil bacterium *Streptomyces aureofaciens* and, 6 years later, were chemically purified for the first time.

Tetracycline analogues are classified as short-, intermediate-, and long-acting based on duration of action.

Analogues in each category have generally similar patterns of bacterial susceptibility and resistance.

Spectrum of Activity

Tetracyclines are the broad-spectrum antibiotics, active against Gram-positive, Gram-negative, aerobic, and anaerobic bacteria as well as Mycoplasma, Rickettsia, Chlamydophila, Brucella, and a few protozoa.

Mechanism of Action

Primarily these are bacteriostatic in action, inhibit protein synthesis by binding to 30S ribosomes, and interfere with attachment of aminoacyl-tRNA to the mRNA-ribosome complex and inhibition of growth of peptide chain required for protein synthesis.

Indications

Tetracyclines also interact with matrix metalloproteinases (MMP), tissue inhibitors of MMPs, growth factors, and cytokines; therefore, tetracyclines are capable of affecting inflammation, immunomodulation, cell proliferation, and angiogenesis.

Slow-release doxycycline 40 mg given daily appears an effective and safe therapy of ocular rosacea.

Oral minocycline or doxycycline can provide clinical benefits in treating moderate and severe meibomian gland dysfunction by reducing inflammatory cytokine levels.

Oral doxycycline is also used with topical amikacin, oral ketoconazole in the treatment of keratitis caused by Nocardia organisms.

Oral doxycycline and topical corticosteroid are used in the treatment of recurrent corneal erosion syndrome.

Tetracycline and chlortetracycline both are available in the ophthalmic preparations and indicated for the treatment of chlamydial infections.

Macrolides

These antibiotics have macrocyclic lactone ring attached with sugar.

Erythromycin, clarithromycin, and azithromycin are the popular macrolide antibiotics used in ocular preparations.

Spectrum of Activity

It is narrow spectrum and active mainly against Gram-positive cocci, Streptococcus, Staphylococcus, Gram-positive rods, and a few Gram-negative bacteria.

It is also effective against Mycoplasma, Rickettsia, and Chlamydophila.

Mechanism of Action

These are primarily bacteriostatic at low concentration but become bactericidal at high concentration.

They act by inhibiting protein synthesis through binding to the bacterial 50S ribosomal subunit and interfering with translocation in protein synthesis.

Indications

The first-generation macrolide, erythromycin, is a widely used macrolide antibiotic for human external ocular infections because of its lack of toxicity and good activity against microorganisms.

Erythromycin decreases the risk of gonococcal ophthalmia neonatorum in newborns.

The American Academy of Pediatrics recommends a 14-day course of systemic erythromycin (50 mg/kg/day, divided in 4 doses).

The second-generation macrolide, azithromycin, is available as a 1.5 % ophthalmic solution for use in the treatment of bacterial or trachomatous conjunctivitis.

Azithromycin 1.5 % ophthalmic solution for 3 days (1 drop twice daily) is found non-inferior to tobramycin 0.3 % ophthalmic solution for 7 days (1 drop every 2 h) in pediatric and adult patients with bacterial conjunctivitis, with regard to clinical cure and bacteriological resolution.

Azithromycin administered orally is rapidly absorbed and widely distributed.

A single oral dose of azithromycin can eliminate trachoma infection, but cannot be used in infants under 6 months old, and needs to be given every few years in communities with a high prevalence of disease.

Azithromycin 1 % ophthalmic solution is also used in the treatment of blepharitis and blepharitis-associated ocular dryness.

Topical azithromycin is also used in meibomian gland dysfunction, a common problem associated with evaporative dry eye disease.

Mass azithromycin treatments are highly effective for the ocular strains of chlamydia causing trachoma.

A short course of oral azithromycin (20 mg/kg once daily for 3 days) appears an effective treatment alternative for Chlamydia trachomatis.

Macrolides are considered bacteriostatic, but clarithromycin may provide a bactericidal effect against non-tuberculous mycobacteria keratitis if used at a high concentration.

Clarithromycin 1 % topical is found useful in mycobacterial keratitis after laser in situ keratomileusis (LASIK).

Chloramphenicol

It was first obtained from Streptomyces venezuelae in 1947.

Spectrum of Activity

It is a broad-spectrum antibiotic and active against most Gram-positive and Gram-negative bacteria, Rickettsia, Chlamydophila and Mycoplasma except P. aeruginosa or Chlamydia trachomatis.

It is effective against Haemophilus influenzae and Haemophilus parainfluenzae, Neisseria meningitidis, and Streptococcus pneumonia.

Mechanism of Action

It binds to 30S bacterial ribosomes and hinders the access of aminoacyl-tRNA to the acceptor site for amino acid incorporation and inhibits protein synthesis. Primarily, it is bacteriostatic in action.

Indications

It is one of the oldest and commonest antibiotics, available over the counter and considered least expensive.

It is used for the treatment of methicillin resistant Staphylococcus aureus ocular surface infections and bacterial conjunctivitis and available as 0.5 % drops and 1 % ointments.

A high incidence of resistance was reported, and even topical use also may cause bone marrow toxicity and aplastic anemia.

Antibacterial Agents in Ocular Infections

Lecture

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Bacterial DNA Synthesis Inhibitors

Fluoroquinolones antibiotics have quinolone moiety with one or more fluorine substitutions, divided into generations based on their antibacterial spectrum.

Nalidixic acid belongs to first generation.

Second generation fluoroquinolones include ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, nadifloxacin, and pefloxacin.

Third-generation fluoroquinolones include balofloxacin, levofloxacin, grepafloxacin, and sparfloxacin.

Fourth-generation fluoroquinolones include gatifloxacin, moxifloxacin, gemifloxacin, and trovafloxacin.

Spectrum of Activity

They are active against the majority of ocular pathogens, including Staphylococci, Haemophilus spp., Chlamydia trachomatis, Neisseria gonorrhoeae, Enterobacteriaceae, Listeria, Legionella, Brucella, Shigella, Proteus, Klebsiella, Bacillus anthracis, and Pseudomonas aeruginosa, but modest activity against Streptococci.

These drugs have bactericidal action and relatively confer higher potency against Gram-positive bacteria.

Most of the fluoroquinolone drugs penetrate corneal stroma and exhibit MICs against Gram-positive and Gram negative bacteria.

Fluoroquinolones have greater efficacy and a broader spectrum of activity than some other antibacterial drugs, including bacitracin, erythromycin, tobramycin, and gentamicin against ocular pathogens.

Mechanism of Action

The fluoroquinolones inhibit the bacterial enzyme DNA gyrase, which required for nicking double-stranded DNA and introducing the negative supercoils.

Indications

Quinolones, such as ciprofloxacin, ofloxacin, norfloxacin, levofloxacin and moxifloxacin, are available as topical ophthalmic solution, and application remains the most popular mode of antibiotic prophylaxis in cataract surgery patients for prophylaxis from endophthalmitis.

They are also effective agents for non-tuberculous mycobacterial keratitis.

They are well tolerated and effective in the treatment of patients with superficial eye infection.

Therapy of bacterial keratitis with ciprofloxacin or ofloxacin eye drops is found superior over conventional regimens of multiple fortified agents.

Topical ciprofloxacin is effective for bacterial conjunctivitis and is also used to treat bacterial keratitis caused by a variety of pathogens.

It is found effective in perioperative prophylaxis for endophthalmitis after cataract surgery.

Ciprofloxacin is also available as an ointment too.

Ciprofloxacin may be useful as prophylactic topical antibiotics for preventing secondary corneal infections or recurrent corneal erosion syndrome.

Topical formulation with intravenous ofloxacin achieves aqueous and vitreous levels that inhibit many common pathogens and hold promise for treating intraocular infections.

The empiric use of second-generation fluoroquinolones (ciprofloxacin and ofloxacin) seems to be contraindicated in the treatment of MRSA keratitis.

Norfloxacin is indicated for the treatment of bacterial conjunctivitis but is not useful for bacterial keratitis due to lesser penetration of the cornea than ofloxacin.

Levofloxacin recently became available as a 0.5 % ophthalmic solution.

It exhibits high solubility in comparison with ciprofloxacin.

It possesses greater activity against Streptococcus species than ciprofloxacin or ofloxacin.

Moxifloxacin has an impressive spectrum of coverage, and this pharmacokinetic study reinforces its potential as a prophylactic drug against intraocular infections, given the high aqueous level post topical administration.

Intravitreal moxifloxacin is found useful for the treatment of bacterial endophthalmitis.

Topical moxifloxacin with tobramycin is found effective in postoperative prophylaxis against infectious keratitis after laser in situ keratomileusis (LASIK) and surface ablation.

Intracameral moxifloxacin appears most suitable for the prevention of endophthalmitis.

Topical use of fluoroquinolones is considered to be safe leading to their widespread use.

Common indications include blepharitis, conjunctivitis, and corneal ulcers.

However, unsupervised prolonged use is associated with deposition of crystalline material in the epithelial and anterior stromal layers of the cornea.


QUESTIONS

CHEMOTHERAPY

for Eye Cancer

Cancers that are in the eye are called **intraocular cancers**.

- Primary intraocular cancers start in the eye.
- Secondary intraocular cancers start in another part of the body and spread to the eye.

In adults, the most common primary intraocular cancers are:

- Melanoma
- Non-Hodgkin lymphoma

In children, the most common primary intraocular cancers are:

- Retinoblastoma
- Medulloepithelioma

Intraocular melanoma is the most common type of cancer that develops within the eyeball in adults, but it is still fairly rare.

Melanomas that start in the skin are much more common than melanomas that start in the eye.

Melanomas develop from pigment-making cells called **melanocytes**.

Chemotherapy is the use of drugs to treat cancer.

The drugs can be injected into a certain part of the body (such as the liver), or they can be injected into a vein (through an IV line) or taken by mouth (as a pill) to reach most of the body, making this treatment very useful for many types of cancer that have spread.

Unfortunately, chemotherapy is usually not as helpful for melanoma as it is for some other types of cancer, but it can shrink tumors in some people.

Chemotherapy might be an option if uveal (eye) melanoma has spread to other parts of the body, although other treatments such as **immunotherapy** or **targeted drugs** might be tried first.

If chemotherapy is an option, the drugs used are generally the same as for melanoma of the skin.

Several drugs can be used to treat melanoma:

- Dacarbazine (also called DTIC)
- Temozolomide
- Nab-paclitaxel
- Paclitaxel
- Cisplatin
- Carboplatin

Possible side effects of chemotherapy:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Diarrhea or constipation
- Increased risk of infection (from having too few white blood cells)
- Easy bruising or bleeding (from having too few blood platelets)
- Fatigue (from having too few red blood cells)

These side effects usually go away once treatment is finished.

There are often ways to lessen side effects, for example, drugs can help prevent or reduce nausea and vomiting.

Some chemotherapy drugs can have other side effects, for example, some drugs can damage nerves, which can lead to symptoms (mainly in the hands and feet) such as pain, burning or tingling sensations, sensitivity to cold or heat, or weakness.

This condition is called **peripheral neuropathy**. It usually goes away once treatment is stopped, but for some people it can last a long time.