An overview of topical ophthalmic drugs and the therapeutics of ocular infection

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Learning objectives
Understand basic pharmacokinetics
Appreciate the different routes of administration of ocular drugs
Discuss the mechanisms of ocular drug toxicity
Understand the mechanisms of action and side effects of commonly used ophthalmic drugs

Introduction
This review provides a brief introduction to ocular pharmacokinetics and the therapeutics of ocular infection. This review is divided into seven main areas as highlighted below.

Outline of lecture
1. Basic Pharmacokinetics
2. Practical aspects of topical therapy
3. Principles of therapeutics in ocular infection
4. Antibacterials and antibiotics
5. Antivirals and anti-acanthamoebals
6. Uses and abuses of topical corticosteroids
7. Conclusions

Ocular Pharmacokinetics
Pharmacokinetics, is by definition, the study of the time and dosage relationships of administered drugs. When considering pharmacokinetics one must assume fictional body spaces between which drugs pass, and within which drugs are equally distributed. In the systemic sense these spaces include the intravascular compartment the extracellular spaces and the intracellular spaces. However, for the purposes of ocular pharmacokinetics, we are more concerned with the ocular compartments, which comprise a) the tear film and cul-de-sac, b) the anterior chamber, c) the vitreous cavity and d) the retro or periocular space (obviously these compartments can be subdivided but this is unnecessary for the purposes of this review).

First order kinetics - most topical ophthalmic drugs exhibit first order kinetics, in first order kinetics the absorption rate and elimination rate of the drugs vary directly with the drug concentration, therefore, the drug half-life is constant regardless of the amount of drug that is present.

Zero order kinetics - in contrast to first order kinetics, in zero order kinetics, either the absorption or elimination of the drug being studied is directly related to a functional capacity which may become saturated with increasing drug concentration. Consequently when a transport mechanism is fully saturated, increasing drug concentration has no further effect. Similarly when the elimination mechanism becomes saturated, because no more drug can be eliminated, additional drug results in increasing drug concentration, and in certain cases this is associated with an increased likelihood of toxicity. Active transport or metabolism can be identified in a number of ophthalmic drugs including: propine, fluorometholone, and levobunolol. Active
transport systems operate in the cornea, the lens epithelium, the ciliary epithelium, and the retinal pigment epithelium.

Other factors may affect the pharmacokinetics of ocular drugs, for instance, binding to tissues or proteins prevents a drug from being available for elimination or metabolism and may prolong the ocular half-life. Interestingly, in the eye, binding to pigmentary structures occurs for a number of drugs, resulting in differing pharmacokinetics for brown eyed individuals compared to blue eyed individuals. Most ocular drugs exhibit first order kinetics.

From where do we obtain our data in regard to ocular pharmacokinetics? Obviously some of this comes from laboratory-based in vitro studies and other data are available from animal experiments. However, only the minority of data are actually available from human studies. It is therefore critical, when considering the available data, both from animal and human studies, to remember the limitations of extrapolation of such data since the anatomy and physiology of different species differ significantly - for example the absence of Bowman's membrane in most animals, the relatively thinner corneas of some smaller mammals, and the reduced blink rate in some species compared to man.

In consideration of topically applied drugs, theoretically, ocular penetration might be via the cornea, the conjunctiva and thereafter the sclera. However, in practice the vast majority of all topical drugs penetrate via the cornea. None-the-less, the cornea is not equally permeable to all topically applied drugs, since the basic structure of the cornea dictates the relative penetration of drugs. Effectively, the greatest barrier to drug penetration is the corneal epithelium which is rich in cellular membranes and is therefore more susceptible to penetration by drugs which are lipophilic. In contrast, since the corneal stroma is largely constituted of water, drugs pass more readily through this thickest component of the cornea if they are hydrophilic. The endothelium represents a monolayer that, once more, is lipophilic. In the absence of the corneal epithelium most drugs penetrate the cornea rapidly, however, in the intact cornea drugs which are lipophilic or biphasic, in that they can behave as either charged or non-charged, penetrate the cornea best.

This is well illustrated by homatropine which can lose its charge to be non-ionic and thereby penetrate the corneal epithelium but once through the epithelium, by picking up a positive charge it can behave in a hydrophilic manner to penetrate the stroma, before losing the charge at the level of the endothelium to become non-charged and lipophilic.

The conjunctiva has similar permeability characteristics to the corneal epithelium, however, since it is such a vascular structure the majority of drug that penetrates the corneal epithelium does not penetrate the eye per se but is drained into the systemic circulation.

**Practical aspects of topical ocular medication**

As previously noted the eye can be considered as a series of compartments in regard to ocular drugs. The first compartment to consider is the cul-de-sac and tear film as shown in figure 1. Normally the total tear film volume is much smaller than commonly appreciated, being in the range of 7 to 10 microlitres. With the application of a topical drop, the cul-de-sac and tear film compartment can expand transiently to perhaps 30 microlitres, however, this has to be considered in the knowledge that the average commercially prepared topical drop typically has a volume of 40 to 70 microlitres and therefore cannot be fully accommodated - even if the cul-de-sac and tear film compartment temporarily expands.
A further consideration in respect to the cul-de-sac and tear film compartment is the effect of the addition of a topical medication on the tear fluid turnover. The rate of tear film turnover varies, and it has been suggested that typically this occurs at approximately 15% per minute, this rate of tear fluid turnover (and therefore washout effect) is doubled, to at least 50 percent, after the application of a topical drop.

The "washout affect" is compounded not only by increased tear fluid turnover, but also by the addition of a second drop within a short period. For instance it has been shown in that if drug A is followed by drug B some 30 seconds later, almost 50 percent of drug A will be washed out of the eye. However, if a subject waits 120 seconds before applying drug B, then only 17 percent of drug A is washed out. The optimum practical delay between drops, in an increasingly busy society, is probably five minutes, as by this stage application of a second drug only produces a second drug washout effect of about 5% of drug A.

Of course, tear fluid turnover is also affected by blinking. With normal blinking it is estimated that only 15% of a topically applied drug remains in the eye approximately five minutes after instillation.

However, if the pouch method is utilised (wherein the lower lid is pulled away from the globe to create a pouch-like repository for drops and the patient is then commended to close the eyes gently, without force, and without blinking for approximately 2 minutes), then more than 50 percent of the drug remains five minutes after initial instillation.

**Summary: topical drugs and the cul de sac & tear film compartment**

1. The average drop size vastly exceeds capacity of tear-film & cul de sac
2. Topical drops transiently double the tear fluid turnover
3. Avoid 2nd drop wash-out – wait at least 5 minute delay between drops
4. Pouch method with closed non-blinking eye, reduces elimination

**Considering the advantages of topical compared to systemic ocular drugs**

There are several advantages of topical drugs over systemic drugs, these include: direct application to the target organ - in this case the eye, the relative ease of application for the majority of patients, and due to targeted application, the need for smaller doses of the drug associated with greater of rapidity of onset of action.

However, there are some disadvantages peculiar to topical drugs and these include: contamination of topical drops and requirement for preservatives, the subsequent toxicity of the drug or preservative to the ocular surface, limitation of the penetration of most topical drugs via the conjunctiva, cornea, and anterior chamber, and the risk of the systemic absorption of drugs which may act on other organs - such as the heart and lungs.

All drugs, topical or systemic, have a shelf life, and this is in part due to the instability of the drug formulation, the vehicle and the intrinsic degradation of the drug itself. Topical drugs can be prone to oxidation or degradation due to exposure to heat, light, and prolonged storage time beyond the specified use.
Is one drop the same as another?

Marketing of generic drugs usually follow the expiry of patent on leading drugs, a good example of this being timolol. However, drugs which are apparently identical, in terms of the stated amount of drug present, may not be therapeutically equivalent. Indeed, this has been noted in the past for a number of systemic drugs leading to the term “generic equivalence”. In respect to topical drugs this may be due to variations in the amount of the active drug, the relative solubility of the drug and the pH at which it is stored (buffers), the particle size (since microsuspensions vary in uniformity), the relative stability and degradation of the formulation as a whole, and the addition of preservatives and surfactants.

There are a number of variables in optimum topical preparations, that include the concentration of the drug, lipid solubility eg. prednisolone acetate (lipophilic) penetrates the cornea many times more effectively than prednisolone phosphate (hydrophilic), whether the drug is formulated in a microsuspension or a solution, and the type and concentration of preservative and buffering agents.

A good example of generic in equivalence is the effect of adding a preservative, in this case benzalkonium 0.01%, to a preparation of pilocarpine 2%. The simple addition of this one, apparently minor ingredient, improves the penetration of pilocarpine into the anterior chamber such that the peak concentration increases by 50 percent!

We are subliminally informed by a constant flow of pharmaceutical advertising, but the clinician needs to remain better informed than this. The informed clinician needs to be aware that there are distinct differences between topical ophthalmic products in the context of the key fundamentals of ocular pharmacokinetics, specifically differences in apparently similar preparations should always be considered.

There is a fundamental difference between topical drops, which are presented as a solution and those that are presented as microsuspensions. Microsuspensions prolong ocular residency time and therefore tend to produce higher drug peaks, and equally important, longer drug action. Of course in the practical sense, it should be noted that microsuspensions tend to settle to the bottom of the bottle, and therefore, it is good standard practice to tell all patients to “shake the bottle before use” since suspensions will benefit from this and solutions will come to no harm. If bottles containing microsuspensions are not shaken, some subjects may be simply applying mainly vehicle to the eye, rather than the active drug ingredient!

Ophthalmic ointments compared to topical drops

Ophthalmic ointments have a number of advantages and a few disadvantages in comparison to topical drops.

The advantages include: prolonged retention in the cul-de-sac and longer drug action, no stinging on application (important in children), lack of preservatives, a lesser likelihood of bacterial contamination, and due to their lubricant nature they may prevent ocular surface drying and minimise morning lid stickiness in cases of infective conjunctivitis.

However, there are a few minor disadvantages in comparison to topical drops: since the drug tends to leave the vehicle less readily, there is a less rapid onset of action and lower peak
concentration compared to topical drops, and the rather greasy appearance on the lid margins is generally less acceptable.

Ointments are a particularly useful adjunct to topical drops to maintain treatment at night time during sleep.

**Sub-conjunctival injection of drugs**

Generally subconjunctival injection is reserved to post operative prophylaxis and the treatment of severe infections or uveitis where subjects’ compliance is in doubt and a high concentration, sustained release effect, is required. Generally, subconjunctival injection may produce higher initial intraocular levels of poorly soluble drugs e.g. antibiotics, secondly, since the drug accesses the eye by leaking via the injection track there may also be a slow release over 12 to 24 hours or more (of course specific delayed-release drugs can provide much longer coverage) and thirdly the eye can be padded if necessary between injections. However the injections are variably painful, a number of patients are understandably apprehensive, and there is a small risk of globe perforation, furthermore, for many of the commonly used topical drugs, subconjunctival injection is not superior to intensive half hourly to hourly topical application.

**Elimination of topical drugs from the eye**

As has been highlighted in earlier sections, the standard topical drop volume is greater than the tear film and cul-de-sac can contain, so a significant fraction of any topically applied drug is lost by initial overflow onto the cheek, and due to the pumping action of the lids, another significant fraction is lost through the naso-lacrimal system. Much of the drug that enters via the conjunctiva drains via blood vessels away from the eye, and drug that reaches the anterior chamber via the cornea is drained by the aqueous humour outflow. Drug is also lost due to the production of inactive metabolites.

Methods to prevent or minimise initial overflow and loss have already been discussed, however, if normal blinking occurs most of the excess drug is lost via the naso-lacrimal system within 15 seconds. Therefore, to maximise retention in the eye and to prevent systemic absorption of drugs, compression of the nasolacrimal sac during, or immediately after, application of the topical drop can be beneficial.

Nasolacrimal flow is often underestimated, whereas, some studies have demonstrated that only approximately 2% of the applied drop is actually retained in the cul-de-sac and tear film compartment, and the majority of an applied drop actually leaves the compartment without ever entering the eye by overspill onto the lid or drainage via the nasolacrimal system. Applying two or three drops, rather than the single drop, therefore does not increase the effective ocular dose, but does increase the systemic those and therefore the risk of systemic side-effects e.g from betablockers or phenylephrine 10%.

Apart from the methods of elimination which have already been outlined, as previously noted, a number of drugs undergo metabolism in the eye. Some of these drugs are metabolized by enzymes in the tears and ocular tissues, including lysosomal enzymes, esterases, oxidases and acetyl-transferases. In contrast some drugs are delivered in an inactive form and their subsequent metabolism in ocular tissues produces an active metabolite such as follows the application of propine and levobunolol.
Local and systemic toxicity of topically applied ocular drugs

Topical ophthalmic drugs can produce local toxicity for a number of reasons, some have inherent toxicity such as topical anaesthetics and adrenaline. Some drugs are more prone to produce hypersensitivity reactions such as neomycin. Since the majority of multi-use topical drops contain preservatives, these can prove toxic to the corneal epithelium, particularly in dry eyes. It should always be remembered that topically applied ocular drugs can also produce systemic side-effects.

Unfortunately some eyes, and some individuals, have a genetic predisposition to allergic reactions, particularly those subjects who suffer from atopy or allergy affecting other systems. Others may have known but atypical and undesirable reactions to topical drops, such as marked elevation of intraocular pressure (IOP) associated with topical corticosteroids.

The systemic toxicity of topical ocular drugs can be significant, and topical betablockers have been associated with marked respiratory and cardiac depression and exacerbation of respiratory conditions such as asthma. Other drugs are more likely to prove toxic to small children, for example, the fatal adult dose of atropine is 100 mg, however, for a four kilogram baby the lethal dose may be as little as 10 mg which represents only 20 drops (1ml) of the 1% solution. Since a 5 ml bottle of atropine contains 50 mg of active drug, these bottles must obviously be kept safely out of the reach of children, as should all ophthalmic and systemic drugs.

Having perfected the optimum dosage and formulation of the topical agent, it would be marvellous if patients fully complied with the dosage regimen. However, in the real world, many have problems complying with, and remembering to take, medication, and this is no less so in regard to topical drops, which in chronic disease such as glaucoma, may be required for life.

Perhaps, unsurprisingly, non-compliance with ocular medication is very common. Some studies have demonstrated non-compliance in the range of 30 to 40%, with compliance being less likely when medication is required four times per day rather than twice per day. Women would appear to be more attentive to their health and application of drops than men, and those that do not attend for regular review, as one would suspect, are much less likely to comply with ocular medication.

The therapeutics of ocular infection

The external eye has an intrinsic protection constituted by such elements as the mechanical sweeping of the lids and the washout effect of the tears. The tears also contain a number of enzymes and immunoglobulins to protect the eye from pathogens and the intrinsic bacterial flora of the conjunctiva and lid margin have a protective function.

The tear film contains a number of components, including lysozyme, lactoferrin, and immunoglobulins which have an intrinsic antibacterial function.

When considering the therapeutics of ocular infection one must first of all base the choice of agent on the nature of the infection that has been identified, thereafter, the most appropriate dosage for the drug to produce the maximum therapeutic effect with minimum toxicity, and finally a balanced regimen to ensure effective treatment.
The best choice of therapeutic agent depends primarily on the nature and site of the infection. One must always determine whether the infection is bacterial, viral, chlamydial, fungal, or due to other pathogens, preferably by isolating the organism and testing the sensitivity of the organism to appropriate antimicrobials. The severity of the infection, and the position e.g. whether the infection is extra or intraocular determines the method of treatment – topical, subconjunctival or intravitreal injection.

Differentiating between infective and allergic conjunctivitis can be difficult, however, the appropriate treatment can only be instigated if diagnostic differentiation can be made with confidence. Follicles are more common in viral conjunctivitis and chlamydial infections, whereas, papillae are more commonly found in bacterial infections and chronic allergy, such as giant papillary conjunctivitis. In bacterial infections the discharge is typically purulent, whereas, in viral infections the discharge is usually watery. Chlamydia can produce mucopurulent infection, however, this diagnosis is often made in retrospect due to the non-responsiveness and chronicity of infection when treated with standard topical antibiotics. Allergic conjunctivitis is usually associated with other symptoms of allergy and often a prior history of systemic allergies e.g. hayfever, asthma, and atopic dermatitis. If viral conjunctivitis is suspected, examination of the pre-auricular lymph nodes should be made, since these will often be enlarged.

**Diagnosis and therapeutics of presumed microbial keratitis**

Infective keratitis has a much greater visual morbidity than conjunctivitis, and therefore will usually will fall under the management of an ophthalmologist. Common causes of microbial keratitis include bacteria and viruses, with acanthamoeba and fungi being less common.

Any assessment of acute keratitis must involve careful assessment of the relevant history. This should include consideration of: whether the disease is unilateral or bilateral, the presence or absence of discharge and its nature, whether recurrent episodes have occurred, the use of the current topical medication (including over-the-counter drugs), a contact lens history, exclusion of trauma and recurrent erosions, an exploration of relevant past ophthalmic surgery, and delineation of any history of allergy. In discriminating between infective and non-infective cases, one should always consider recent systemic symptoms. Common predispositions to severe keratitis are highlighted below.

**Common associations with infective keratitis**

- Dry eye disease
- Lid malposition – especially entropion
- Corneal exposure – e.g. dysthyroid eye disease
- Corneal trauma
- Previous ocular surgery and retained sutures
- Neurotrophic cornea
- Herpes Simplex Keratitis
- Poor contact lens hygiene
- Recurrent corneal erosion
- Infective blepharitis
Assessment of acute, presumed infectious keratitis

The standard examination should include estimation of corneal sensation, size, location and colour of any corneal lesion, and the presence of hypopyon. However, the microbial agents cannot really be identified by the clinical appearance of the keratitis/corneal ulcer and therefore the diagnosis should be made by sampling of the infected material.

In relation to conjunctivitis, empirical treatment is often commenced without confirmation of the infectious agent, however, a swab will be more usually taken if the infection appears severe or recalcitrant to first-line treatment. In contrast, in all cases of presumed infective keratitis a diagnostic corneal scrape should be performed and this might be extended to microbial culture of both contact lenses and contact lens cases.

Although the eye can be infected by innumerable organisms, 87% of all bacterial keratitis is caused by a relatively small group of bacterial pathogens that include: staphylococcus, Streptococcus, Pseudomonas, and enterobacteriaceae species. Although Acanthamoeba remains an ongoing concern in contact lens practice, they often represent less than 1% of infective keratitis although they are strongly associated with soft contact lens wear and poor lens hygiene or swimming in contact lenses. Interestingly the relative risk of any form of bacterial keratitis associated with soft contact lenses appears to be greater with overnight and extended wear.

Antibacterials and antibiotics

As previously noted, when considering any antibacterial or antibiotic, the basic therapeutics should be considered. It must be remembered that drops provide more rapid onset of action with higher peak concentrations but a relatively shorter half-life. Ointments, on the other hand have a slower onset of action but will provide a longer duration of action and may provide a useful lubricant function on inflamed tissue and prevent lid stickiness in the morning. Therefore, the combination of topical drops by day and ointment last thing at night, before retiring, is used in moderate conjunctivitis. Systemic tablets are seldom used in external or corneal infections, but subconjunctival injection has a limited role.

Having determined organism sensitivity, the short residency time of drops must be considered and the drug regime tailored to the severity of the disease. Therefore, mild conjunctivitis may be treated by four times per day application, whereas, severe keratitis may require hourly or even half hourly drop application. One must also remember, even with conjunctivitis, that infections do not sleep, and overnight treatment utilising an ointment preparation, of the same antibiotic used by day, can shorten the length of the infective episode.

Commonly used antibacterials

A large number of an antibacterials are readily available, although some are reserved for more severe infections. Commonly used antibiotics and antibiotic groups are listed below.

1. Chloramphenicol
2. Fusidic acid
3. Aminoglycosides
4. Sulphonamides
5. Cephalosporins
6. Fluoroquinolones
7. Miscellaneous others

**Chloramphenicol**

This remains the most commonly used topical antibiotic in the UK and Australasia for the prophylaxis of ocular bacterial infections and is a very useful first-line treatment for bacterial conjunctivitis. Chloramphenicol is a bacteriostatic antibiotic which inhibits protein synthesis, it has activity against a wide range of bacteria, including Streptococci, Pneumococci and Corynebacteria, however, most Pseudomonas are resistant and resistance can develop via acetyltransferase.

Chloramphenicol is widely available as 0.5% drops and a one percent ointment, in addition to a reasonable spectrum of antibacterial activity it has low topical toxicity, and since it has extremely limited use in the community - other than for ophthalmic conditions - there is very limited bacterial resistance. However, it is not used routinely for more severe infections such as bacterial keratitis, and there is a theoretical risk of aplastic anaemia, although McGhee et al have noted that this risk is in the same region a patient suffering a fatal anaphylactic response to penicillin, and is therefore extremely unlikely.

Fusidic acid (Fucithalmic) is a useful alternative to chloramphenicol in the treatment of conjunctivitis. Fusidic acid acts in both a bacteriastatic and bacteriacidal manner and is very effective against Gram positive bacteria, however, most Gram negative bacteria are resistant. This antibiotic also inhibits protein synthesis in bacteria to produce its antibiotic effect.

Fusidic acid is available as a viscous gel, and requires only two to three times daily application, this may produce a better compliance than the four times daily application needed for chloramphenicol. Fucithalmic should be considered as the first-line treatment for bacterial conjunctivitis and blepharitis, although it has been noted that resistant strains develop quickly, and it is ineffective against Gram negative bacteria.

Bacterial conjunctivitis is often a self-limiting condition, and may resolve within 10 days without any treatment. Nonetheless, sticky eyes and blurred vision are unpleasant, and infected individuals often seek treatment. Useful first-line treatment is the application of chloramphenicol drops four to eight times daily, depending on the severity of the conjunctivitis, with chloramphenical ointment at night. The treatment regime can be reduced after two to three days to a four times per day application for 10-14 days. This should ensure complete eradication of the infecting pathogens. An alternative treatment is fusidic acid three times daily, with perhaps an increased regime for the first few days if the conjunctivitis is severe. Failure to respond to either of these treatments, presuming compliance, should be managed by swabbing of any bacterial discharge to culture for bacterial analysis, followed by a course of whichever of the two antibiotics was not used as the first-line treatment. If after consecutive treatment by each of these antibiotics there is not complete resolution of conjunctivitis then alternative causes such as allergic conjunctivitis, or chlamydia infection, should be considered.

**Aminoglycosides**

There are a number of aminoglycosides in use including framycetin, neomycin, tobramycin, gentamicin, amikacin and streptomycin. However, the most popular of these are neomycin (often
in combination with a corticosteroid), tobramycin which has a wide spectrum of activity against bacteria, and gentamicin which is usually reserved for severe corneal infections.

All of the aminoglycosides are rapidly bactericidal and inhibit protein synthesis, ultimately producing cell membrane destruction in bacteria, however, these are a generally toxic group of antibiotics that are of restricted utility in systemic disease due to ototoxicity and nephrotoxicity. Topical agents are toxic to corneal epithelium, but did not have any systemic toxicity.

**Tobramycin** is a superior antibacterial than gentamicin and is active against a spectrum of Gram positive and Gram negative bacteria, including pseudomonas. It is active against most ocular staphylococci and is the first-line antibiotic for ocular bacterial infections in parts of the United States because of medico-legal concerns in respect to the very rare possibility of aplastic anaemia associated with the use of chloramphenicol.

**Penicillins** are seldom used as topical agents in ocular infections, however cephalosporins are penicillin-like antibiotics, unfortunately, there are no commercial ocular preparations of cephalosporins, though these are often made up by pharmacies, in a five percent solution, for the treatment of severe infective keratitis. For this reason cephalosporins are generally restricted to hospital use.

** Fluoroquinolones** are widely used systemically and are efficacious against Gram positive and Gram negative bacteria, particularly staphylococci, although these are less effective against certain streptococci. They have variable effectiveness against pseudomonas species. They generally exhibit low toxicity and work by enzymic inhibition of bacterial DNA production.

Two fluoroquinolones are widely available for severe ocular infections and these are ciprofloxacin and ofloxacin. They provide good ocular penetration and are at least as effective as chloramphenicol or tobramycin in bacterial conjunctivitis, however, since they are more powerful antibiotics, being the only monotherapy for severe bacterial keratitis, they are best reserved for this function.

Although ciprofloxacin is a more potent antibiotic, ofloxacin penetrates into the eye more readily, and both appear to be equally useful in the treatment of bacterial keratitis. One of the side-effects of ciprofloxacin is deposit of whitish material in the base of corneal ulcers which can make monitoring of the progress of the disease more difficult. (Figure 9)

Tetracyclins have poor intra-ocular penetration and are best reserved for treatment of diseases such as blepharitis, trachoma and ophthalmia neonatorum.

**First-line antibiotic therapy in severe keratitis** is either dual-therapy with fortified cephalosporins and aminoglycosides or monotherapy with one of the fluoroquinolones. Second line antibiotic therapy is based upon further information such as the organisms that are cultured and their sensitivity to a battery of antibiotics.

**Antivirals**

Unlike bacteria, viruses are more difficult to treat since the infecting agent actually inhabits the host cell, therefore, at the present time there are only a handful of specific antivirals suitable for use in the eye or elsewhere. Fortunately, herpes simplex virus, a common pathogen in the eye
was one of the first viruses to succumb to treatment. In addition to causing dendritic ulcers and stromal keratitis, the herpes simplex virus is also associated with cold sores and genital herpes.

Herpes simplex in the eye can present with myriad manifestations including: dendritic, geographic/amoeboid, stromal, disciform, endothelitis, metaherpetic and trophic forms of corneal disease.

The earliest anti-viral developed was idoxuridine, which required early application and could cause inhibition of stromal healing, this is now rarely used in the United Kingdom.

The most popular and effective anti-viral for HSV keratitis remains acyclovir, this blocks the thymidine kinase enzyme of the virus and has been subject to very limited viral resistance. It is more effective against HSV than any other anti-viral. Treatment is required five times per day, but it is relatively non-toxic to healing epithelium. Acanthamoeba is fortunately relatively rare, although early work by Dart and others demonstrated that 90% of cases were associated with soft contact lenses, with the association occurring almost three times as frequently as RGP lenses. Fortunately the mean time to diagnosis has decreased dramatically in the last 10 years with the raised awareness in the ophthalmic and optometric community in regard to the presentation of acanthamoeba. However, late and misdiagnosis still occurs, with the disease commonly being mistaken for HSV keratitis.

Early disease often manifests with limbitis, perineural infiltrates, and superficial epithelial changes, whereas, late disease manifests with frank ulceration, ring infiltrates and severe uveitis. Treatment generally consists of dual therapy with either chlorhexidine or polyhexamethylbiguanide (PHMB) combined with brolene.

**Corticosteroids**

Corticosteroids, as a general rule, should not be used in the management of conjunctivitis or infective keratitis. As always there are exceptions to the rule, but it is an apposite maxim that corticosteroids constitute a two edged sword. Whilst these are important and often sight-saving anti-inflammatory drugs, adverse side-effects include steroid cataract, steroid-induced glaucoma, and exacerbation of microbial infections.

Corticosteroids inhibit the inflammatory response to noxious stimulus, such as mechanical chemical infectious and immunological agents. They act by reducing vasodilatation, stabilising mast cells to reduce histamine release, by maintaining normal blood vessel permeability and they reduce the production of prostaglandins.

Corticosteroids are commonly used for severe allergic conjunctivitis, to inhibit inflammation following cataract surgery, in the treatment of acute anterior and chronic posterior uveitis, for immunosuppression following, transplantation and in the acute management of giant cell arteritis. They have a very limited role in the management of ocular infections, and indeed are often misused in this role, leading to more severe infections and permanent ocular damage.

The advantages of local ocular corticosteroids administration are: targeted local delivery, lower total steroid dose, high local concentrations, and fewer systemic side-effects. The common topical steroids are listed below.

| Generic name | Product name |
As with all topical drugs, the ocular penetration of corticosteroids is dependent upon whether they are produced as lipid soluble drugs, and whether they are constituted as microsuspensions or solutions. In this regard prednisolone acetate, which is both lipid soluble and is marketed as a microsuspension, penetrates into the aqueous humour twenty times more than prednisolone phosphate, which is a polar compound. The graph below highlights the differences in penetration into human aqueous humour of two commonly used, commercially available, steroids.

One of the better-known complications of corticosteroids is that of raised intraocular pressure. Around 4-6% of the population demonstrate a high response, with intraocular pressure rising >15 mmHg usually within 4-12 weeks of commencing treatment. Approximately one-third have a moderate IOP response, and two-thirds of the population have a response that exhibits an IOP rise of less than 6 mmHg. Steroid responsiveness is higher in those with glaucoma, and an exaggerated response also occurs in subjects with myopia. In children, the maximum IOP response can actually occur within eight days!

An association between corticosteroids and cataract was first identified in 1960. Further studies have demonstrated that eighteen months of high potency topical steroid (Prednisolone Acetate) will produce cataract in one-third of individuals. In contrast, posterior subcapsular cataract has also been reported with as little as four months treatment with fluorometholone (FML Liquifilm), generally regarded as a weaker and poorly penetrating corticosteroid.

Corticosteroids are also associated with ocular infections, and herpes simplex virus can be reactivated by a single topical dose. In established HSV keratitis, the inadvertent use of corticosteroids can exacerbate the disease process significantly. A number of other studies have demonstrated that corticosteroids may mask or delay the presentation of severe keratitis, particularly acanthamoeba. A number of studies have also highlighted corticosteroids as a risk factor in severe keratitis leading to hospitalisation.

The list of complications associated with corticosteroids is extensive and is highlighted below.

1. Ocular surface toxicity 2. Delayed epithelial healing
3. Reduced wound strength 4. Keratocyte apoptosis
5. Corneal phosphate deposits 6. Exacerbation of microbial infections
7. Reactivation of HSV 8. Crystalline keratopathy
9. Steroid glaucoma 10. Steroid cataract
11. Lid ptosis 12. Dilated pupil
15. Intraocular penetration/injection 16. Systemic absorption

Conclusions

From the foregoing introduction I hope it will clearly be seen that a methodical approach to the pharmacokinetics and therapeutics of ocular drugs leads to a greater understanding of, as well as a practical approach to, the prescription of ophthalmic drugs. Local and systemic side-effects of
ocular drugs are important since they can masquerade as other disease processes or can result in exacerbation of existing disease processes. It is therefore incumbent upon the clinician using ocular drugs to not only be aware of the therapeutic actions of drugs in their armamentarium but also of the symptoms and signs of toxicity and side-effects.
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