Systemic antimicrobials and the eye

When selecting an antimicrobial agent to treat infection, various considerations must be borne in mind. Susceptibility of the organism to the agent, the drug's safety in an individual patient and its ability to reach adequate concentrations in the infected tissue are all important factors. Some sites, such as the brain and the eye, have barriers that limit the access of certain drugs. Therefore any agent used must be able to penetrate these barriers and achieve therapeutic concentrations.

Bacterial endophthalmitis is an infection of the vitreous, retina and uveal coats of the eye. Acute endophthalmitis is a medical emergency as permanent visual loss may occur if it is not effectively treated. Visual loss occurs in 20% of patients and a vitrectomy may be required in some patients.

The bacteria are normally introduced exogenously as a result of ocular trauma, surgery or severe infections of the cornea. Such patients do not usually have systemic signs and symptoms of infection. However, endogenous seeding of bacteria to the eye may occur secondary to systemic infection, such as in bacterial endocarditis.

After cataract surgery, coagulase-negative staphylococci, Staphylococcus aureus, streptococci and Gram-negative bacilli are the most important pathogens. In post-traumatic endophthalmitis, Bacillus cereus is a major pathogen and may cause a fulminant infection, but all of the above bacteria may also be responsible.

Bacterial endophthalmitis must be treated with intravitreal injections (direct injections into the vitreous humour) of antimicrobials. This is because the blood-ocular barriers prevent the achievement of adequate intravitreal concentrations when the drug is used systemically, and the lack of vasculature of the vitreous makes it difficult for drugs to achieve high concentrations in this area.

Up to 96 hours of effective antimicrobial exposure can be achieved by intravitreal injection, depending on the properties of the drug injected. In order to assess intravitreal drug concentration, some vitreous is removed before injection and drug concentrations can be determined in these specimens. Recommended treatment is with intravitreal antimicrobials such as vancomycin in addition to cefazidime or amikacin.

What are the blood-ocular barriers?

These physiological barriers inhibit the entry of systemically administered drugs into the eye. The blood-aqueous barrier prevents water-soluble drugs from crossing the epithelium of the ciliary body into the aqueous humour (see Fig. 1). The blood-retinal barrier prevents water-soluble drugs from reaching the vitreous and consists of tight junctions between the cells of the retinal pigment epithelium and endothelial tight junctions around the retinal capillaries. Drugs may therefore reach high concentrations in the choroid but not enter the vitreous.

Lipid solubility of a drug is important in enabling penetration. Lipophilic drugs such as the fluoroquinolones and chloramphenicol are more likely to enter the aqueous and vitreous spaces.

Inflammation of the eye disrupts these barriers and permits greater permeability. The practical implication is that the systemic use of a highly lipophilic antimicrobial, such as chloramphenicol or a fluoroquinolone, may lead to adequate concentrations being achieved in the aqueous. However, drug concentrations achievable in the vitreous are lower and therefore systemic therapy alone is regarded as ineffective in the treatment of endophthalmitis.

Clearance of drugs from the vitreous

An active transport system exists for anionic drugs (such as penicillins, cephalosporins and quinolones) to be removed from the vitreous by endothelial and epithelial cells. This allows anionic drugs an elimination half-life of 8 hours in the vitreous after direct injection.

Inflammation of the eye reduces this active transport, thereby prolonging exposure. Probenecid inhibits the transport of organic acids across epithelial barriers and is therefore employed to inhibit renal secretion of penicillin. It raises the serum levels of beta-lactam antibiotics and quinolones and may also block their active transport out of the eye.

Passive elimination also occurs whereby all drugs are eliminated by diffusion into the aqueous humour.

What is the role of systemic antimicrobials in the treatment of endophthalmitis?

Systemic antimicrobials must be used when endophthalmitis has resulted from endogenous seeding, and are used in conjunction with intravitreal antimicrobials.
Concurrent use of the same antimicrobial by intravitreal injection and systemic administration reduces the gradient between the vitreous and circulation, decreasing the efflux of drugs from the vitreous. This results in prolongation of vitreous exposure.

The Endophthalmitis Vitrectomy Study (EVS) found that intravenous amikacin and ceftazidime did not improve outcomes when added to intravitreal antimicrobials in patients with postoperative endophthalmitis. However, this study has been criticised as amikacin displays poor penetration into the vitreous.

Recent studies suggest that the fourth-generation quinolones (gatifloxacin and moxifloxacin) may be superior regarding access to the vitreous. The methoxy side-chain of these quinolones is thought to be responsible for its improved penetration. These drugs also have the advantage of a wide spectrum of activity encompassing both Gram-positive and Gram-negative organisms, as well as high oral bioavailability.

In a study of 24 patients who were due to undergo vitrectomy for various indications, gatifloxacin concentrations were estimated in the vitreous after 2 oral doses. Roughly 26% of the serum concentration was detected in the aqueous humour and about 21% in the vitreous. The concentrations achieved were above the minimum inhibitory concentration (MIC) for many bacteria that are known to cause endophthalmitis. The study, however, utilised twice-daily doses of gatifloxacin before sampling, whereas a daily dose is recommended. Gatifloxacin has subsequently been withdrawn from the market after reports of serious metabolic adverse events.

A study using oral moxifloxacin demonstrated that only 6.7% of the serum concentration of moxifloxacin is achieved in the vitreous. The concentrations achieved were below the MIC for many common causes of postoperative endophthalmitis. This study used a dose-to-sampling time of 2 hours (the gatifloxacin study used 10 hours) based on the time to reach maximum serum concentrations for this drug. This may not have allowed sufficient time for vitreal uptake and therefore a delay in the maximum vitreous concentrations was achieved. The authors are planning further studies to address this issue.

Further studies are needed to define the role of systemic antimicrobials, particularly the newer quinolones, in endophthalmitis.

Recommended reading

In a nutshell
• Intravitreal antimicrobials are necessary in endophthalmitis because of the blood-ocular barriers.
• Systemic antimicrobials must be used when endophthalmitis occurs secondary to systemic infections.
• The value of systemic antimicrobials in the absence of systemic infections remains unclear.
• The fourth-generation quinolones may hold promise as add-on systemic therapy.

Single suture
Abstinence doesn’t work
Contrary to what the US government believes – and that belief directs their funding programmes – promotion of abstinence does not cut HIV infection rates. When Kirsten Underhill and her team from Oxford looked at the literature they found that almost all the evidence suggests that abstinence programmes are of very little value. In a study of 13 trials of US-based abstinence programmes they found that none helped to reduce the incidence of unprotected sex or cut the number of partners that young people slept with. A similar lack of success has been found in developing countries.

Another knock to US HIV/AIDS policy comes from research that shows that HIV prevention programmes targeting sex workers do cut infection rates. At present, the US government requires that the organisations it funds sign a pledge saying that they oppose prostitution – so stigmatising the groups that they are supposed to be helping.