Pharmacokinetics of ophthalmic corticosteroids

Corticosteroids have been used by ophthalmologists with increasing frequency over the past 30 years, with the concomitant development of a diverse range of drop, ointment, subconjunctival, and oral preparations. Though the clinical benefits and side effects of such corticosteroid preparations have been well documented, their basic pharmacokinetics in the human eye have yet to be fully established. Indeed most of our pharmacokinetic knowledge of these drugs has been elucidated by extrapolation of data obtained from rabbit experiments. These results can be significantly disparate from human data because of the thinner rabbit cornea, lower rabbit blink rate, effect of general anaesthetic, upright or recumbent position, vascularity of the rabbit orbital plexus, and small rabbit body mass. Thus, in general, measurements of steroid concentration in rabbit eyes tend to be significantly higher than those recorded in humans.

Topical ophthalmic drops/ointments

These are still the most common methods of administering steroids to the eye and following a single topical drop, steroid is measurable in human aqueous humour within 15–30 minutes. Not surprisingly, increased steroid concentration in topical preparations generally results in higher intraocular concentrations, but for prednisolone acetate the optimum dose response effect in experimental keratitis occurs at a 1% concentration, and is not improved by further increases in concentration. Increasing ocular contact time by preparing topical steroids in a microsuspension, gel, or viscous formulation can double the corneal and aqueous humour concentrations of steroid compared with the same drug applied as a solution. Other apparently minor changes in formulation, such as the addition of benzalkonium, can significantly alter the pharmacokinetics of topical steroids. For these reasons many workers chose to use commercially prepared 'off the shelf' steroids in an attempt to unravel differences in pharmacokinetic behaviour, which may be associated with clinical efficacy. In contradistinction, the preparation of different topical steroid derivatives in an identical base vehicle has demonstrated that the greatest barrier to intraocular penetration is the lipid rich corneal epithelium, which retards the ingress of polar, hydrophilic derivatives such as prednisolone phosphate, but is much less of a barrier to lipophilic derivatives such as the alcohol and acetate forms of dexamethasone and prednisolone. Interestingly, if this epithelial barrier is removed prednisolone phosphate penetrates the cornea in much higher quantities than the lipophilic, acetate derivative. These additive effects of increased concentration, lipophilic derivation, and the increased contact time afforded by a microsuspension have been demonstrated in humans, where a single drop of prednisolone acetate 1% microsuspension has been shown to produce intraocular steroid concentrations which were 20-fold those of a single drop of prednisolone phosphate 0.5% solution, and almost 100-fold those of a single drop of betamethasone phosphate 0.1% solution. In contrast, when dexamethasone, prednisolone, and fluorometholone are all formulated at a concentration of 0.1% in an identical vehicle, the aqueous humour concentrations of these steroids are almost identical. None the less it is essential when considering such empirical data, to recall that the systemic anti-inflammatory effect of both betamethasone and dexamethasone is five to seven times that of prednisolone. The local anti-inflammatory potency of ocular steroids has yet to be fully investigated and whilst early work suggested that prednisolone acetate 1% had the greatest anti-inflammatory effect in experimental keratitis, later studies demonstrated that fluorometholone acetate in a 1% formulation was equally efficacious in the same model. However, prednisolone acetate 0.5% drops have been shown to significantly inhibit the tear film polymorphonuclear leucocyte response to partial denudation of the corneal epithelium, whereas 0.1% concentrations of prednisolone acetate, dexamethasone, and fluorometholone are ineffective. As already noted, the absence of corneal epithelium can significantly affect the penetration of topical steroids, and it may also be relevant to the clinical situation that higher corneal concentrations of steroid may occur in the presence of intraocular inflammation, whereas the concomitant application of an antibiotic drop within 60 seconds of steroid application can reduce the bioavailability of the applied steroid by almost 70%. It has not been established which concentration of steroid is desirable for minor ocular inflammatory conditions such as postoperative uveitis, and whilst concentrations of 670 ng/ml of prednisolone have been recorded in human aqueous humour, perhaps a peak of 25 ng/ml might be sufficient to suppress inflammation and minimise side effects. For comparison, peak timolol concentrations of 2500 ng/ml have been recorded in rabbit aqueous humour following topical application, yet β receptor blockade can be obtained by as little as 9 ng/ml.

Preparation of prednisolone acetate as a gel provides a more prolonged release and higher peak aqueous concentration when compared with an equivalent topical solution. However, some viscous agents and ointments may actually produce lower peak ocular concentrations of steroid when compared with drops. Despite this, owing to prolonged release, a single application of a steroid ointment such as dexamethasone phosphate results in only 25% less overall absorption of steroid than a single drop of the same steroid.

It is generally believed that most of the topical and, indeed, subconjunctival steroid (see below), enters the eye via the cornea, thus radiolabelled hydrocortisone produces only 2-5% of the anticipated aqueous humour concentration when corneal penetration is prevented, compared with topical application with free access to the cornea. However, for other drugs such as pilocarpine and timolol, penetration into the iris and ciliary body via the non-corneal route may account for drug concentrations which reach almost 10% of the combined corneal and non-corneal route, and such trans-scleral penetration may be even more important for larger molecules, such as insulin.

Periorcular injections

Repeated subconjunctival injections of prednisolone (50 mg) have been shown to be inferior to hourly topical prednisolone acetate 1% drops (6·5 mg) in reducing the inflammatory
response in experimental keratitis. Early analytical techniques suggested that such subconjunctivally injected steroid entered the eye via the sclera. Indeed, the sclera is readily permeable to even relatively large molecules such as albumin, and therefore, not surprisingly, high levels of corticosteroid can be detected in the sclera underlying a subconjunctival injection site. However, the greater concentration of such steroid appears to enter the eye by diffusing through the puncture site in the conjunctiva into the tear film, and thence via the cornea into the intraocular milieu.

In this context it is not unexpected that sub-Tenon’s injections of methyl prednisolone in monkeys produced significant anterior segment steroid concentrations (approx 25 ng/ml) but could only produce peak vitreous concentrations of 2 ng/ml. In contrast, retrobulbar methyl prednisolone in the same model produced much higher posterior uveal/retinal concentrations and significant vitreous levels which persisted for up to 9 days. These discrepancies might be partly explained by the lack of post-equatorial diffusion of drug following subconjunctival and sub-Tenon’s injections. It is notable that, in contrast to the enhanced corneal penetration of topical steroid drops previously noted in intraocular inflammation, when a periocular injection is used, total ocular steroid levels may actually be lower in eyes with intraocular inflammation compared with uninfamed eyes.

The inherent risks of periocular injection of steroid (see below) and the availability of alternative, superior methods of application, suggest to the author, in the context of the preceding data, that the role of periocular injection is limited to the operating room and to a few other selected situations where frequent topical medication is not practicable. The short term local use of orbital floor steroids in non-necrotising scleritis may be such an exception to this, whereas the role of retrobulbar steroid in the treatment of persistent macular oedema remains unresolved.

Systemic administration

When one considers the bodywide distribution of a systemically administered steroid, it is easy to comprehend the dramatically larger steroid doses required to equal the previously noted aqueous humour concentrations produced by topical drops; however, the extent of this disparity is seldom fully appreciated. In the rabbit it has been shown that an intravenous dose of 25 mg dexamethasone (equivalent to 500 mg in a 70 kg man!) was required to produce aqueous humour levels which were comparable with those achieved following topical dexamethasone alcohol drops, whereas a similar intravenous dose of prednisolone only achieved 50% of the peak aqueous concentration obtained by four drops of methyl prednisolone 0.5%. Similarly, intramuscular methyl prednisolone in squirrel monkeys produced total ocular tissue concentrations, and vitreous concentrations in particular, which were less than 1% of those obtained by a similar dose given as a periocular injection. Indeed, maximal intraocular steroid concentration may actually represent as little as 0.5% of an intravenous dose. That systemic steroids have an important role in ophthalmic practice, such as the treatment of corneal graft rejection, is not in question, but they must be used in the knowledge that they act by primarily affecting the systemic limb of ocular disease and that there are superior, local, alternative methods of producing significant intraocular concentrations of steroid, if that is what is desired.

Collagen shields and contact lenses

Waltman and Kaufmann demonstrated that hydrophilic contact lenses could be presoaked in a drug solution and used as a form of delayed release vehicle. A few years later Hull et al established that hydrophilic contact lenses, presoaked in 1% prednisolone phosphate, produced an aqueous humour peak concentration that was three to fourfold that obtained by application of topical drops and this advantage was maintained at 4 hours. The search for a topically applied, slow release drug system in other areas led to the successful development of pilocarpine ocuserts, which though not widely used, and despite some limitations, have shown to be a viable alternative to topical drops in certain patients. Similarly, early soluble collagen inserts presoaked in gentamicin produced higher tear film and corneal concentrations of gentamicin than gentamicin administered in drop, ointment, or subconjunctival form. The development of dissolving collagen shields has rekindled interest in this method of delivering ophthalmic drugs and such shields presoaked in tobramycin have been well tolerated by patients and have been shown to produce higher aqueous and corneal concentrations of tobramycin than subconjunctival injections. Collagen shields have also been suggested as the optimum vehicle for poorly soluble drugs such as cyclosporin. Recently it has been demonstrated that collage shields presoaked in dexamethasone alcohol produce superior intraocular concentrations of dexamethasone than hourly drops over the first 4 hours: that combination of a presoaked shield and hourly topical drops doubles the cumulative delivery of steroid to the eye at 6 hours when compared with hourly drops alone. For those looking for the ideal short term sustained release vehicle, and a safe yet superior alternative to subconjunctival injections, collagen shields would appear to provide increased compliance, better 24 hour control, higher ocular drug concentrations than comparable methods of administration, and good patient tolerance. However, like pilocarpine ocuserts they have yet to gain wide acceptance by clinicians and whether, like ocuserts, they will fail to gain a regular place in our pharmacological armamentarium, owing to limitations yet to be identified, remains to be seen. In a note of caution, it has already been highlighted that certain antibiotic and steroid combinations in collagen shields may provoke adverse corneal reactions.

Intravitreal injection, liposomes, and iontophoresis

Whilst intravitreal injections of antibiotics have become a standard technique in the treatment of endophthalmitis the use of intravitreal steroids in ophthalmology is less well established. Ocular dialysis has demonstrated that after subconjunctival gentamicin, virtually no gentamicin is recorded in the vitreous, whereas intravitreal injection of gentamicin may produce significant levels with a half life of up to 22 hours. In contrast, intravitreally injected dexamethasone appears to have a half life of 3 hours with only 10% of the peak concentration remaining at 8 hours, although concentrations of 50 ng/ml may persist for up to 4 days.

The incorporation of drugs into liposomes has demonstrated an up to 10 times improvement in the intraocular penetration of hydrophobic drugs following topical application. However, possibly because the commonly used ophthalmic steroids such as dexamethasone alcohol, prednisolone acetate, and fluorometholone are already lipophilic, there has, as yet, been little utilisation of liposome delivery for steroids. Transcorneal and trans-scleral iontophoresis of polar drugs, which normally penetrate these structures poorly, remain largely experimental, though the trans-scleral iontophoresis of dexamethasone phosphate can produce higher vitreous concentrations than the retrobulbar, subconjunctival, or topical routes.
Side effects of ophthalmic steroids

The adverse effects of systemic steroids are well known to ophthalmologists, therefore local administration is often seen as a logical method of minimizing such side effects. Some local applications are not without obvious inherent risks such as bulbar perforation, choroidal injection, central retinal artery occlusion, muscle imbalance and persistently raised intraocular pressure following the pericocular injection of steroids. Additionally, systemic absorption of periorcular steroids in rabbits has been noted to decrease circulating lymphocytes and antibodies, and to reduce the total white blood cell count. Surprisingly, considering the small volume of steroid administered, topical drop application of steroid in rabbits produces significant liver, urine, and plasma concentrations and by 30 minutes almost a third of the applied steroid is distributed systemically, with less than 5% of the administered steroid being recoverable from the eye. Owing to this significant systemic dissemination of steroid, topical application inhibits corneal wound healing in both the treated and the untreated, contralateral eye in rabbits.

In larger experimental animals, following eight drops of prednisolone acetate 1.0% per day (4 mg of prednisolone per day), both small dogs and large dogs (27–41 kg) have exhibited adrenal suppression, though the adrenal axis is more rapidly suppressed than in dogs in humans. In humans, the systemic absorption of topically applied drugs such as β blockers is well established, whereas the systemic effects of topical ocular steroids is less clearly defined, and whilst Burch observed a 50% decrease in endogenous steroid production in male volunteers given hourly dexamethasone 0.01% drops (0.75 mg dexamethasone per day) for 6 days, Krupin demonstrated a reduction in endogenous plasma cortisol but no adrenal axis suppression following eight drops of dexamethasone 0.1% per day for 6 weeks. It seems reasonable, therefore, to suggest that the possibility of adrenal suppression should be considered when ophthalmologists employ intensive topical steroids such as prednisolone acetate 1.0% and dexamethasone 0.1%.

Conclusion

Although more information on ophthalmic corticosteroids in humans is becoming available, we still rely heavily on data derived from animal models. Fortunately, while some of the animal data are conflicting, the general trends appear to be similar in humans, though the magnitude of intraocular steroid penetration in humans appears less. The marked differences in bioavailability illustrated by identical concentrations of the same steroid, in different topical drop formulations, does mean that generic equivalency cannot be assumed between preparations merely on the basis of equivalent steroid content. Topical and local application of steroids appears preferable to systemic administration wherever possible; however, the limitations of, and alternatives to, subconjunctival injection should be carefully considered, as should the possibility of adrenal suppression following intensive ophthalmic corticosteroid drops in children and small adults.